Dear colleagues,

The 2nd of ESGO Textbook of Gynaecological Oncology was published in September 2011 and inaugurated at ESGO17 congress in Milano. The book is updated in accordance with the feedback following the 1st edition, has adapted, and increased the contents to reflect the needs of the society. ESGO is delighted to be associated with this exciting, ground breaking and innovative publishing venture. As a unique membership benefit of ESGO members, a full version will be available in DVD format in March 2012.

New authors and new topics are included and the whole book is up to date with the most recent literature and new illustrative figures. The authors of the book have been chosen from all around the world and include the pioneers and famous oncologists. Of course, this shows the humility of the contributing authors and we are grateful to their efforts in the creation of the Textbook.

ESGO would like to thank Boehringer Ingelheim GmbH for their support and educational partnership so that selected chapters featuring the ovarian cancer are now available at this E-book. This endeavour is also important for such a book and will supply an important resource for trainees in the emerging European nations.

ESGO is extremely grateful to the authors of these manuscripts. Without their efforts and permissions, this e-version should not be available.

Thanks to our partners, ESGO can contribute fulfilling its mission to improve the health of women suffering from the gynaecological cancers.

We hope you will find it useful for your clinical practice.

Textbook Editors

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Introduction

Pathologic evaluation of gynecologic tissue specimens is typically performed using tissue sections stained with hematoxylin and eosin (H&E stain). Occasionally, the diagnosis may not be straightforward because some diseases may demonstrate morphologic features that overlap with other diseases. Certain malignancies may mimic benign lesions. Similarly, certain subtypes of neoplasms may mimic neoplasms with different behavior or different response to therapy. In such settings, immunohistochemical stains may aid in differential diagnosis. Immunohistochemistry is a routine laboratory method that uses chromogen-linked antibodies to detect antigens in the cell membrane, cytoplasm, or nucleus. Because some antigen targets are specific to a particular cell type, cell content or tumor type, immunohistochemical antibodies to such antigens can be used in differential diagnosis. The staining is performed on slide-mounted sections of routinely formalin-fixed tissue. Presence of an antigen is typically heralded by a dark brown staining of the cell membrane, cytoplasm, or nucleus, depending on the particular antigen. The staining can be visualized using a standard light microscope. Interpretation of the staining can be challenging, especially since, in reality, the sensitivity and the specificity of a given immunostain may not be perfect. This review will focus on the following common clinical gynecologic scenarios in which a pathologist may use immunohistochemistry. Rather than provide details of test sensitivity/specificity and interpretation, this review is aimed at introducing the markers that are commonly used and their rationale. More extensive discussion can be found in several recent larger reviews (1-5).

Common Diagnostic Settings in which Immunohistochemistry May Be Valuable

- Cervical squamous dysplasia versus reactive/metaplastic epithelium
- Endometrial versus endocervical origin of adenocarcinoma
- Serous carcinoma versus endometrioid adenocarcinoma of uterus or ovary
- Uterine smooth muscle tumor versus endometrial stromal tumor
- Ovarian granulosa cell tumor versus adenocarcinoma
- Ovarian primary mucinous carcinoma versus metastatic carcinoma
- Ovarian serous carcinoma versus metastatic breast carcinoma
- Molar pregnancy versus hydropic abortus
- Mismatch repair protein status in endometrial adenocarcinoma

Cervical Dysplasia Versus Reactive/Metaplastic Epithelium: MIB-1, p16, ProEx C

Squamous metaplasia of the cervical transition zone can mimic squamous dysplasia, especially when acute or chronic inflammation is superimposed on the metaplastic epithelium. Enlarged irregular nuclei and an appearance of loss of epithelial maturation can occur in reactive or inflammatory squamous metaplasia, mimicking features seen in dysplasia. Immunostaining for MIB-1 (Ki67), p16, and/or ProEx C can be helpful. MIB-1 is a nuclear marker of cell proliferation. In normal cervical epithelium, MIB-1 expression is confined to the lowest layer (basal layer) of the epithelium. In dysplasia, MIB-1 expression will be present in the middle and upper layers of epithelium. Metaplasia will not show this pattern. ProEx C is a newer marker of altered cell-cycle regulation. It is a cocktail combination of antibodies against minichromosome maintenance protein 2 (MCM2) and DNA topoisomerase II alpha (TOP 2A) which are both involved in early steps of DNA replication and are overexpressed in HPV infection. ProEx C is a nuclear marker which is expressed and interpreted in the same way that is MIB-1 is expressed and interpreted in normal and in dysplastic squamous epithelium. In the cervix, p16 is a surrogate marker of HPV infection. In normal cervical epithelium, including metaplasia, p16 is absent but in dysplasia, particularly higher grade lesions, a diffuse, strong cytoplasmic and nuclear pattern of p16 expression is present. Either MIB-1 or p16 alone can be useful, although when used in tandem, diagnostic certainty is increased. These stains are not accurate in separating mild dysplasia from moderate/severe dysplasia (6-8). A final caveat is that MIB-1 and ProExC interpretation require that the specimen be oriented such that the maturation from basal layer of epithelium to the surface of the mucosa can be appreciated. In some cervical biopsies, particularly small biopsies, the specimen is not well-oriented and therefore these stains cannot be used. P16, however,
is still useful in this setting since the interpretation does not depend on evaluating what epithelial layers are involved.

**Endometrial Versus Endocervical Origin of Adenocarcinoma: ER, Vimentin, p16, mCEA**

The microscopic appearance of primary endometrial endometrioid adenocarcinoma may resemble primary endocervical adenocarcinoma. Thus, it may not be possible to determine the site of origin of adenocarcinoma in an endocervical sampling based only the H&E findings. The most accurate method to do so is to evaluate the clinical and radiologic features of the mass. Immunohistochemistry, however, can provide some adjunctive help, especially for more well-differentiated tumors. Most primary endometrial endometrioid adenocarcinomas will express estrogen receptors in a strong diffuse pattern as well as vimentin in a membranous pattern whereas most primary endocervical adenocarcinomas do not. In contrast, many primary endocervical adenocarcinomas will express p16 in a strong diffuse pattern as well as monoclonal CEA (carcinoembryonic antigen) whereas most primary endometrial tumors will not. When results of all four immunostains fit this profile, the results are usually concordant with the surgical and radiologic evidence of the tumor origin however these immunostains are not perfectly accurate. For example, some endometrial adenocarcinomas may express p16 in a patchy pattern. Although p16 expression can be a downstream result of HPV infection in the cell, there are non-HPV related mechanisms that may cause p16 expression (9-13). More direct methods of HPV detection, such as in situ hybridization, may be more helpful but these are not routinely available in a typical pathology laboratory.

**Serous Carcinoma Versus Endometrioid Adenocarcinoma of Uterus or Ovary: p53, WT1, ER, p16**

Serous carcinoma and endometrioid adenocarcinoma may resemble each other in the ovary or uterus. Both may demonstrate papillary, solid or tubuloglandular growth patterns. A host of morphologic features (e.g. nuclear grade, squamous differentiation) can often be used to distinguish these two tumors but occasionally such features are not present, especially in small endometrial biopsies. Because of the differences in management and prognosis, the distinction is important and immunohistochemistry can be useful. Most serous carcinomas of the gynecologic tract harbor a point mutation in the p53 gene, leading to strong, diffuse nuclear expression of p53. A minority of mutations are so-called truncating mutations that result in functional absence of protein expression; thus, a minority of serous carcinomas will be negative for p53. Most endometrioid adenocarcinomas do not express p53 or do not express it in a strong, diffuse pattern. Conversely, a well-differentiated endometrioid adenocarcinoma should express estrogen receptors in a strong diffuse pattern whereas serous carcinomas are either negative or show patchy heterogeneous expression. In the ovary, fallopian tube, and peritoneum, the urogenital transcription factor gene WT1 will be expressed in serous tumors but not in endometrioid adenocarcinoma. Recent studies suggest that strong diffuse p16 expression may distinguish serous carcinomas from its mimics (14-23).

**Uterine Smooth Muscle Tumor Versus Endometrial Stromal Tumor: CD10, Desmin, Caldesmon, Smooth Muscle Myosin**

Cellular leiomyoma of the uterus may resemble endometrial stromal tumor (either endometrial stromal nodule or low grade endometrial stromal sarcoma). Both are highly cellular spindle cell neoplasms though cellular leiomyoma tends to contain a background of thick walled blood vessels of varying sizes while endometrial stromal tumor contains a background of tiny thin walled uniformly small arterioles. CD10 expression is usually diffuse and strong in the spindle cells of endometrial stromal tumor, which generally lack expression of myoid markers (desmin, caldesmon, myosin). The converse applies for these stains in cellular leiomyoma. A panel approach of multiple myoid markers is advised since their sensitivity and specificity can vary from case to case. Rare examples of mixed endometrial stromal – smooth muscle tumors may produce confusing results; thus, integration of the immunostain results with morphologic details is particularly important in this setting (24-26).

**Ovarian Granulosa Cell Tumor Versus Adenocarcinoma: Calretinin, Inhibin, EMA, Steroidogenic Factor-1, FOXL2**

Granulosa cell tumor may exhibit a large spectrum of growth patterns, including microfolllicular, trabecular, pseudoglandular, solid, spindled, or mixed patterns. One of the more common diagnostic problems is distinction from ovarian endometrioid adenocarcinoma. Characteristic nuclear grooves or Call-Exner bodies are not always present in granulosa cell tumors. Calretinin and inhibin are markers of ovarian sex cord-stromal tumors, of which granulosa cell tumor is a subset. Neither marker should be expressed in endometrioid adenocarcinoma, which is characterized, instead, by markers of epithelial differentiation, such as keratin or epithelial membrane antigen (EMA). One common pitfall, however, is that granulosa cell tumor can occasionally show patchy keratin expression. Therefore it is best to use EMA rather than keratin, since EMA should be negative in granulosa cell tumor (27-30). Two novel markers have recently been reported to be of value in the diagnosis of granulosa cell tumor. Steroidogenic factor 1 (SF-1) is a transcription factor regulating steroidogenesis, sexual differentiation, gonadal and adrenal gland development, and metabolism. It is a highly sensitive marker for sex cord stromal tumors, including granulosa cell tumor. Since it is not expressed in adenocarcinoma or carcinoid tumor, SF-1 is an excellent marker to use along with calretinin and inhibit, particularly since it is a nuclear marker and therefore easy to interpret. Recently, the gene FOXL2 has been shown to be mutated in most adult granulosa cell tumors, FOXL2 is a transcription factor required for ovarian development. Immunostaining for FOXL2 has been reported in nearly all adult granulosa...
Ovarian Primary Mucinous Carcinoma Versus Metastatic Carcinoma: CK7, CK20, CDX2, DPC4, TTF-1

The vast majority of mucinous tumors in the ovary that are classified as mucinous carcinomas are metastases from non-ovarian sites such as colon, pancreaticobiliary tract, stomach, lung or endocervix. Primary ovarian mucinous carcinoma is uncommon. While some gross and microscopic features may be of diagnostic help to separate primary versus metastatic origin, immunohistochemical staining for cytokeratins CK7 and CK20 and CDX2, a marker of intestinal differentiation, is helpful. The profile of positive CK7/negative CK20 and CDX2 argues for a primary ovarian mucinous tumor rather than colonic metastasis, which should be positive for CK20 and CDX2 but negative for CK7. The nuclei of primary lung adenocarcinoma should express TTF-1 as opposed to primary ovarian mucinous carcinoma. About half of pancreatic adenocarcinomas will lose expression of the marker DPC4 whereas it remains intact in ovarian carcinoma. Diffuse strong p16 expression should raise concern for endocervical adenocarcinoma (34-40).

Ovarian Serous Carcinoma Versus Metastatic Breast Carcinoma: WT1, p53, CA125, Mammaglobin, GCDFP

Both breast cancer and ovarian serous carcinoma can grow in solid, papillary or tubular patterns that mimic each other, especially when tumor first presents in a distant metastatic site or in a lymph node. Serous carcinoma of ovarian, fallopian or peritoneal origin expresses WT1 and, in the majority of cases, p53 and CA125. It is rare for a breast carcinoma to express any of these markers. Mammaglobin and gross cystic disease fluid product (GCDFP) are relatively specific for primary breast origin in this particular differential diagnosis. The problem, however, with both mammaglobin and GCDFP is that their sensitivity is low and so negative results are not always helpful. Estrogen receptor is not helpful since both breast and ovarian carcinoma can be positive (41-43).

Early Complete Molar Pregnancy Versus Hydropic Abortus: p57

Early complete hydatidiform molar pregnancies are notoriously problematic for pathologists to recognize because the microscopic abnormalities can be subtle and can mimic hydropic non-molar abortus. The genetics of complete mole provide a basis for the useful immunostain p57. Complete moles have a diandric genome; that is, all of the nuclear DNA comes from the father and there is no maternal nuclear DNA present. This results from two sperm fertilizing an empty egg (or a single sperm that divides and fertilizes an empty egg). The p57 gene is an imprinted gene, meaning that the protein is only expressed from the gene from one of the parents. In the case of p57, it is only expressed by the maternal p57 gene. Since complete moles only have paternal genes and no maternal genes, this nuclear protein is not expressed in the villus cytotrophoblast nor villus mesenchyme of a complete mole. Hydropic abortus contains maternal genes, therefore p57 will be present. Since partial moles have a triploid genome (two genomic complements from the father and one from the mother), they will also express p57. Thus, p57 can distinguish complete versus partial mole but cannot distinguish partial mole versus hydropic abortus (44-47). For this latter issue, testing for DNA ploidy is needed. Partial moles are triploid whereas hydropic abortus is not. DNA ploidy can be performed on formalin fixed tissue in specialty laboratories.

Mismatch Repair Protein Status in Endometrial Adenocarcinoma

Recent progress in understanding the molecular biology of hereditary uterine cancer due to Lynch syndrome has led to two new tests that pathologists may use as screening tools. Lynch syndrome is defined as the presence of a germline mutation in one of the mismatch repair genes which are responsible for correcting errors in DNA. If one of the mismatch repair proteins is absent, DNA errors accumulate, rendering the cell susceptible to further alterations which may ultimately lead to malignant transformation. Immunostains have recently become available for 4 mismatch repair proteins: MLH1, MSH2, MSH6 and PMS2. Immunohistochemical presence of all 4 proteins in the tumor cells strongly suggests that there are no underlying germline mutations in these genes and therefore the patient is unlikely to have Lynch syndrome. Complete immunohistochemical absence of any one of these proteins in the tumor cells is an indication for further evaluation, including referral to a genetics counselor for consideration of germline mutation analysis. Because of protein dimerization, deficiency in MLH1 protein usually results in degradation of PMS2; likewise for MSH2 and MSH6 (48-51). Defining which uterine tumors should be screened for Lynch syndrome is still under study however limited early data suggests that several microscopic features of the tumor may be informative. Tumors with peritumoral lymphocytic aggregates or tumor infiltrating lymphocytes probably should be screened as should tumors with undifferentiated histology or origination in the lower uterine segment. A PCR based test for microsatellite instability is a complementary screening test for Lynch syndrome. Loss of the mismatch repair protein machinery leads to errors in microsatellite segments of the genome, which may increase or decrease in length due to such errors. PCR based detection of these microsatellite alterations can be performed on formalin fixed tissue sections of the tumor in specialty laboratories. Alteration in two or more microsatellites is considered “Microsatellite Instability-High” and this raises concern for germline mutation in mismatch repair genes. Such patients should be referred to a genetics counselor for further evaluation. Microsatellite stable tumors are unlikely to be Lynch syndrome tumors.

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Diagnostic Immunohistochemistry in Gynecologic Pathology: A Brief Review of Common Clinical Applications


Introduction

Carcinomas of the stomach, colon, appendix, and breast and lymphoma can occasionally involve the ovary. Metastases may occur by direct spread, the hematogenous route, or lymphatic drainage. Metastatic ovarian cancers are defined as neoplasms that grow originally in extra-ovarian locations and, subsequently, invade the ovaries. It is very difficult to differentiate primary ovarian cancers from metastatic tumors in the ovaries, which are likely to masquerade as the former. Occasionally, metastatic ovarian cancers are diagnosed simultaneously with primary malignancies. Optimal cytoreductive surgery combined with chemotherapy is the standard treatment for primary ovarian cancer; however, such treatment may be not helpful for metastatic ovarian cancer patients. In fact, misinterpretation of ovarian tumors can result in significant adverse effects from this treatment.

Metastatic ovarian cancers are not rare, with primary ovarian cancers in 5–30% of the patients found to be metastatic ovarian malignancies as noted in clinical and autopsy reports. In previous studies, the colon, breast, stomach, endometrium, and cervix have been reported as the common primary cancer sites for metastasis to the ovary. In addition, lymphoma, leukemia, and melanoma can affect the ovaries. A history of malignancy can provide a useful clue for diagnosing metastatic ovarian tumors, but symptoms due to these tumors can mask the primary neoplasm.

The prevalence of metastatic ovarian tumors appears to demonstrate the overall incidence and ethnic variances of primary malignancies. The incidence rate of metastatic ovarian tumors is slightly higher in Asian rather than Western countries. The global incidence of stomach cancer, the leading type of cancer in Korea and Japan, is concentrated in Eastern Asia. Worldwide, lung, breast, and colorectal cancers are the first, second, and third most common cancers, respectively. The incidence rates of breast and colorectal cancers are highest in developed Western countries and lowest in Africa and Asia.

The majority of metastatic ovarian tumors develop in patients aged between 40 and 60 years, with the mean age of these patients being approximately 10 years less than that of patients with primary ovarian cancer. Tumor metastasis to the ovaries can follow several routes such as through direct spread, lymphatic or hematogenous channels, or transcoelomic dissemination.

Metastatic tumors to the ovary commonly show bilateral involvement in 60% of the patients and, frequently, present a solid appearance in gross findings. They are usually small; however, primary ovarian tumors are very large in comparison with secondary ovarian tumors. Unsurprisingly, bilaterality, solid appearance, and a tendency towards smaller size can be helpful in the diagnosis of metastatic tumors to the ovary. However, these gross characteristics can also be noted in primary ovarian neoplasms, and so, cautious differentiation in diagnosis is advised.

Because serum CA 125 level is elevated in both primary and metastatic ovarian cancers, it is not useful for differentiation. Fortunately, preoperative levels of carcinoembryonic antigen (CEA) and tumor-associated trypsin inhibitor (TATI) are often higher in metastatic ovarian cancers. TATI is a 60-kD protein, which was first isolated from the urine of ovarian cancer patients, and is even elevated in pancreatic cancer. CEA is an oncofetal protein and is not used for the detection of primary ovarian cancers, due to its low detection sensitivity of 25%. Recently, CEA and TATI have been frequently used in the preoperative evaluation for metastatic ovarian tumors.

Imaging Findings

The radiological features of metastatic ovarian cancers demonstrate considerable variability. Unfortunately, there are no definite criteria for the diagnosis of metastatic ovarian tumors in radiology. In general, metastatic tumors present bilateral ovarian involvement and solidity, while primary ovarian malignancies exhibit unilaterality and a cystic nature. However, only 14% of ovarian metastases from endometrial cancer present bilateral ovarian involvement, and so, bilaterality cannot be the absolute standard of differentiation. Moreover, the manifestation of ovarian metastasis from colon cancer tends to be cystic, thus a solid and cystic nature cannot be the absolute milestone for the diagnosis of metastatic cancers either. The Radiology Diagnostic Oncology Group (RDOG) proposed that solidity on magnetic resonance imaging (MRI) and a high resistance index (RI) of the tumor on color Doppler ultrasonography (US) be used as the diagnostic features of a metastatic ovarian neoplasm. Multilocularity on MRI and US has been considered as a characteristic of primary ovarian cancer by the RDOG study. However, other groups reported little difference in the RI on color Doppler US, based on the premise that primary and metastatic ovarian cancers exhibit similar angiogenesis. Thus, diagnosticians should bear in mind that differential diagnosis of ovarian masses based
MUC2-positive expression pattern. The ovary has been reported to exhibit an MUC5AC-negative and MUC2-positive expression pattern. However, distinguishing between colon cancer metastasis to the ovary and primary ovarian carcinoma is challenging. Therefore, it is recommended that CDX2 be used in conjunction with CK7 and CK20 (Figure 1).

CDX2 is the protein encoded by Cdx2, a homeobox gene, and is expressed predominantly in colorectal adenocarcinoma. CDX2 is highly specific for the colon and demonstrates 83% sensitivity and 96% specificity. Unfortunately, CDX2 alone is insufficient as a marker for the differential diagnosis of metastatic ovarian cancer from primary mucinous tumors. Therefore, it is recommended that CDX2 be used in conjunction with CK7 and CK20 (Figure 1).

Recently, MUC5AC and MUC2 have been used to distinguish between colon cancer metastasis to the ovary and primary ovarian carcinoma; colon cancer involving the ovary has been reported to exhibit an MUC5AC-negative and MUC2-positive expression pattern.

Prognosis

Multivariate analysis to evaluate prognostic factors for metastatic ovarian cancer showed that the primary tumor site and tumor stage were the most significant factors. Ovarian metastases of gynecologic origin had a much better prognosis than those with non-gynecologic origins. The reason is that compared with metastases from a non-gynecologic malignancy, carcinomatosis of advanced gynecologic cancer is relatively confined to the intra-abdominal cavity without distant metastasis and shows superficial spreading patterns.

Metastatic cancer of colorectal origin had more favorable prognosis than other non-gynecologic cancers, but there was no significant prognostic difference in non-gynecologic metastatic cancers based on the primary tumor site.

Treatment

There are few clinical reports on tumor management or prognostic factors on metastatic ovarian cancer because it is not targeted in typical chemo- and radiotherapy. Following a review of previous reports, cytoreductive surgery in metastatic ovarian cancer may be beneficial for the initial diagnosis or symptom relief, but the survival benefit of surgery remains debatable. As described in previous studies, surgical resection should be considered as indicated by a patient's condition. In conclusion, it is very difficult to make simple generalizations of the characteristics of metastatic ovarian cancers. Therefore, for correctly differentiating heterogeneous ovarian tumors, these tumors should be evaluated using clinical information as well as laboratory techniques. Furthermore, large-scale data and long-term follow-up information will provide accurate knowledge about metastatic ovarian cancers and the outcomes of combined modality treatments.

Metastases from Gastric Cancer (Krukenberg Tumors)

A Krukenberg tumor is a well-known secondary ovarian tumor that was first described as a fibrosarcoma of the ovary and reported to arise from an adenocarcinoma of the gastrointestinal tract. Subsequently, the definition of a Krukenberg tumor was revised to include all metastatic tumors to the ovary irrespective of their origin. Many studies have reported that patients with a Krukenberg tumor are aged 20–70 years, with the average patient age being 40 years.

The World Health Organization has proposed the following criteria for diagnosing a Krukenberg tumor: (1) presence of signet-ring cells with mucin (Figure 2); (2) presence of stromal invasion; and (3) sarcomatoid proliferation of ovarian stroma. Bilaterality, slightly enlarged size, lobulation, and solidity are important radiological imaging findings. The solid area of the ovary can often be observed as a homogeneous enhancement on T1-weighted MRI and as heterogeneous intensity on T2-weighted MRI. Dense fibrous stroma and tubular formation are the key microscopic features of a Krukenberg tumor. Preoperative serum CA 125 level is frequently elevated. CK immunohistochemical analyses can be used to diagnose Krukenberg tumors, and cases with a combination of CK7 positivity and CK20 negativity are considered to be Krukenberg tumors.

**Figure 1.** The immunohistochemistry staining was performed on formalin-fixed, paraffin-embedded ovarian tissues. (A) The metastatic ovarian adenocarcinoma from colon exhibits cytokeratin 20 positivity diffusely. (B) Cytokeratin 7 negativity was noted on the cytoplasm of ovarian cancer tissues. (C) CDX-2 positive expression was demonstrated diffusely on the nucleus of cells.
Krukenberg tumor, which is less frequently positive for CK7 (55%) and more frequently positive for CK20 (70%). Unfortunately, the prognosis of a Krukenberg tumor is poor, and most patients die within 2 years. Some authors reported that the limited extent of disease and little residue following surgery are favorable prognostic factors; however, well-defined prognostic factors have not been elucidated.

**Metastases from Colon Cancer**

Colon cancer is one of the most common origins of metastatic ovarian tumors. A known history of colon cancer provides a clinical clue for the diagnosis, but ovarian tumors in the pelvic cavity without known primary origins are diagnosed as the first presentation in many cases.

Metastatic tumors to the ovary from colon cancer frequently exhibit a cystic nature and bilateral involvement (Figure 3). A stained glass appearance and multicystic chamber can be noted in computed tomography (CT) and MRI. Metastases from colon cancer are very similar to an ovarian mucinous adenocarcinoma in pathologic findings, which can confuse pathologists and gynecologists. Primary ovarian mucinous carcinomas frequently show up as a confluent glandular invasion, but a metastatic ovarian mucinous tumor displays superficial involvement of the cortex and nodular tendency in the ovarian parenchyma. “Dirty” necrosis of the glandular pattern is a characteristic of a metastatic tumor to the ovary from colon cancer (Figure 4).

In terms of prognosis, a 5-year survival rate is observed in 5.4% of patients with metastatic ovarian cancer originating from the gastrointestinal tract. Several studies have demonstrated that secondary ovarian tumors from colon cancer have a better prognosis than those from stomach cancer. Thus, location of the primary tumor can play a major role in the prognosis of metastatic ovarian cancers. The propensity of colon cancers to metastasize to the ovaries can justify the rationale to perform a prophylactic bilateral salpingo-oophorectomy during colon surgery.

**Metastases from Appendiceal Tumors**

Metastatic tumors to the ovary from the appendix are highly associated with pseudomyxoma peritonei, which was first defined in 1884 as an ovarian tumor producing a jelly-like material. In general, pseudomyxoma peritonei, characterized by exuberant gelatinous material and non-invasive mucinous implants in the peritoneum, is observed in metastatic
ovarian neoplasms from appendiceal tumors. The majority of metastatic ovarian tumors from appendiceal tumors feature bilateral involvement; however, tumors in the right ovary are more common due to its proximity to the appendix, such as in cases of unilateral involvement of the ovary. The mucinous epithelial tumor cells that spill out of the appendix due to increased intraluminal pressure are harbored in the ovary and are disseminated into the peritoneal cavity by peritoneal fluid flow. The increased density and prominently large amount of ascites compressing the bowels and liver can be observed on US and CT (Figure 5). Tumor markers such as CA 19-9 and CEA are reported to be useful for preoperative evaluations and postoperative follow-up. Repeated debulking surgeries, including appendectomy, have been adopted as the traditional treatment due to recurrence resulting in abdominal painful distension and bowel obstructions. Gough et al. have reported a 5-year survival rate in 53% of the patients. Recently, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy has been performed in many institutions and was found to be effective in preventing microscopic residuals, and a 5-year survival was reported in over 80% of the patients.

Metastases from Breast Cancer

Breast cancer is the most common non-cutaneous malignancy with a good prognosis. However, the prognosis for metastatic breast cancer to the ovary is very poor with a 5-year survival rate of less than 10%. Clinical symptoms involving the ovary are very rare when breast cancer metastasizes to the ovary, and bilateral involvement and small ovary size are the typical traits. Tumor metastasis to the ovary is not detected in approximately 50% of patients. Surprisingly, 10% of the patients who had undergone a prophylactic oophorectomy experienced microscopic metastasis to the ovary. Therefore, regular examinations should be conducted as a precaution for patients with familial history or BRCA mutation.

Metastases from Uterine Cancers

Metastasis from uterine cancer to the ovary is uncommon, and tumors in both locations often have a similar cell type, i.e., endometrioid adenocarcinoma. Consequently, cautious examination of clinical and pathologic findings is the most important step for accurate diagnosis. In general, early-stage and endometrioid adenocarcinoma of the uterus with tumors of 1 or both ovaries may indicate synchronous primary neoplasm of the genital tract. In contrast, deep myometrial invasion of the uterus with tumors of 1 or both ovaries may suggest a metastatic tumor to the ovary. Nodular growth of a tumor on the surface of an ovary and the preservation of ovarian stroma can also serve as clues for metastatic tumors to the ovaries.

Summary

In conclusion, bilateral involvement, solid appearance, elevated CEA, CK20 positivity, CDX2 positivity, and MUC2 positivity can be useful parameters for the diagnosis of metastatic ovarian cancer (Table 1). Particularly, history of stomach, colon, and breast cancer is an important clue apart from the primary symptoms of a patient. Many metastatic adenocarcinomas involving the ovary exhibit morphologically and clinically similar patterns. Therefore, multidisciplinary approaches, including radiological, serological, and pathological methods are required for accurate diagnosis.

| Table 1. The general characteristics of metastatic ovarian cancers and primary ovarian malignancies. |
|---------------------------------|-----------------|-----------------|
| Age                            | old             | young           |
| History of malignancy          | rare            | often           |
| Relationship with parity       | yes             | no              |
| Ovary involvement              | uni-laterality  | bi-laterality   |
| Solidity of ovary              | cystic and solid | solid          |
| Size of ovary                  | large           | small           |
| Frequency of ascites           | more common     | less common     |
| Multi-locularity on CT and MRI | more common     | less common     |
| Resistance index on color      | decreased       | increased       |
| Doppler US                     | more common     | less common     |
| CK 7 positive on immunostaining| more common     | less common     |
| CK 20 positive on immunostaining| less common     | more common     |
| CDX 2 positive on immunostaining| less common     | more common     |
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As with other solid tumors, chemotherapy is a key part of the armamentarium available to the gynecologic and medical oncologist charged with caring for patients with gynecologic malignancies.

**Ovarian Cancer**

**Epithelial Tumors**

The mainstay of ovarian cancer care remains surgical cytoreduction. Nevertheless, in 95% of patients, chemotherapy will be required. For these patients, treatment plays a vital role in effecting durable responses in the majority, as well as cures in up to 75% of those diagnosed with early stages disease, and 20% of those with advanced stage disease. The current standard of platinum and paclitaxel emerged following a sequence of phase III trials with one US and one Canadian/European study showing its superiority over cyclophosphamide and cisplatin. Subsequently, carboplatin with paclitaxel in non-inferiority trials was less toxic and had a similar outcome to the cisplatin combination, leading to its rapid adoption as the preferred reference initial treatment. More recently, a weekly (dose-dense) paclitaxel schedule is being tested in clinical trials based on superiority over the every 3-week schedule in a trial from Japan (see below).

**Early Stage Disease**

Certain patients with stage I or II disease have a risk of relapse of up to 25-45%. These include patients with stage IA, grade 3; stage IB grade 3; clear cell histology; stage IC any grade; stage II any grade. Despite the heterogeneous patient population represented in the ICON 1/ACTION trials, adjuvant chemotherapy was shown to reduce the risk of relapse. As a result, these patients are offered carboplatin and paclitaxel at standard dosing (Table 1). In a subsequent study by the Gynecologic Oncology Group (GOG) attempting to determine the optimal number of cycles for this patient population, there was no statistical improvement in outcome when six versus three cycles was administered. A related subgroup analysis showed that patients with serous histology may be more likely to benefit from six cycles.

**Advanced Disease**

Over 70% of patients with epithelial ovarian cancer present with advanced (stages III and IV) disease. Platinum-based chemotherapy has dramatically changed the course for these patients. Prognosis varies according to the amount of residual disease noted after primary cytoreductive surgery. The surgical outcome is generally classified in three ways: No gross residual disease (if no visible tumor remains after surgical staging); optimal cytoreduction (if any remaining tumor is <1 cm in diameter); or suboptimal cytoreduction (if any remaining tumor is >1 cm in diameter).

The backbone for adjuvant therapy in patients with advanced (stage III or IV) disease remains platinum with paclitaxel. However the preferred route of administration and timing has come into question. Standard intravenous treatment is carboplatin with paclitaxel every 21 days (Table 1). Although between six and eight cycles have been evaluated, no clear benefit has been shown by extending beyond 6 cycles. The paclitaxel may be dosed over three hours when given with carboplatin. The Calvert formula is the accepted method to dose carboplatin, and is represented by the following formula:

$$\text{Carboplatin dose (mg)} = \text{AUC} \times (\text{GFR (ml/min)} + 25)$$

The patient’s GFR is usually estimated by creatinine clearance, for which there are multiple methods for calculation, including Cockcroft-Gault, Jeliffe, and Chatelut.

For patients with either no gross residual disease or an optimal cytoreduction, intraperitoneal chemotherapy has been shown to have an advantage over standard intravenous carboplatin and paclitaxel. Protocol 172 of the GOG compared an intravenous regimen (IV paclitaxel day 1, IV cisplatin d2) to an intravenous and intraperitoneal regimen (IV paclitaxel day 1, IP cisplatin d2, IP paclitaxel d8) (Table 1) in patients with stage III disease following optimal cytoreduction. This intraperitoneal regimen showed a significant benefit in both overall and progression free survival when compared to the intravenous only treatment, that was also shown in two prior IP versus IV trials by the GOG as well as a meta-analysis of all such trials. The intraperitoneal arm of GOG 172 was also associated with increased toxicity, including pain, myelosuppression, gastrointestinal events and neurologic effects, with only 42% of patients on the IP arm finishing the six prescribed cycles. When evaluated using an intention to treat basis, the patients on the intraperitoneal regimen had an overall survival of 65.6 months, as compared to 49.7 months for patients on the intravenous regimen. The improved survival has led to the adoption of IP chemotherapy for all optimally debulked stage III patients in many centers. However, investigations are ongoing with modifications designed to reduce toxicity such as 1) Reduction of cisplatin dose from 100 mg/m² to 75 mg/m², 2) Substitution of carboplatin for...
cisplatin, 3) Omission of day 8 IP paclitaxel, and 4) Shortening IV paclitaxel from 24 hours to 3 hours.

The Japanese Gynecologic Oncology Group published their results comparing standard IV paclitaxel with carboplatin vs. dose-dense paclitaxel with carboplatin (Table 1). The dose-dense arm had improved overall survival (72.1% alive at 3 years vs. 65.1% HR 0.75, 0.57 – 0.98; p=0.03) and progression free survival (28 months vs. 17.2 months, HR 0.71, 0.58 – 0.88; p=0.0015) when compared to the standard arm. Severe neutropenia and anemia were more likely in the dose dense group. A recently activated GOG study (GOG 262) will seek to confirm these results.

The GOG compared IV carboplatin and paclitaxel with bevacizumab to carboplatin and paclitaxel alone, including randomization to a maintenance phase of bevacizumab. A recently activated GOG study (GOG 262) will seek to confirm these results.

The GOG compared IV carboplatin and paclitaxel with bevacizumab to carboplatin and paclitaxel alone, including randomization to a maintenance phase of bevacizumab. A recently activated GOG study (GOG 262) will seek to confirm these results.

Recurrent Disease

Several drugs have activity against ovarian cancer as single agents: Paclitaxel, pegylated liposomal doxorubicin, gemcitabine, topotecan and bevacizumab are amongst the most often used because of favorable therapeutic indices. When a recurrence is first documented, treatment is dictated by the length of the platinum-free interval. Patients who received bevacizumab during therapy as well as maintenance had an additional 5.3 months increased progression free survival (the study’s primary endpoint) when compared to patients receiving no bevacizumab or those who received bevacizumab during chemotherapy only. Based on these results, bevacizumab has been added to all of the treatment options for the most recent GOG trial evaluating adjuvant therapy for advanced ovarian cancer. The GCIG activated a similar trial, ICON 7, to evaluate the effect of the addition of bevacizumab in the adjuvant setting. Although survival analysis is pending, preliminary results have shown an increase in progression free survival for patients receiving bevacizumab during cycles 2 through 6 of chemotherapy and continuing for 12 additional cycles of maintenance. However the median progression free survival advantage reported to date is 1.7 months. While this is the second positive trial for bevacizumab, the clinical significance of this degree of improvement remains unclear. As a result, incorporation of bevacizumab into front-line adjuvant treatment regimens for ovarian cancer has not been embraced.

### Table 1. Ovarian cancer protocols.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Schedule</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard intravenous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>IV</td>
<td>AUC 5 or 6</td>
<td>d1 of 21d</td>
<td>Given in 30 minutes</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>IV</td>
<td>175 mg/m²</td>
<td>d1 of 21d</td>
<td>Should be administered first; premedications required to avoid hypersensitivity to cremophor, the diluent.</td>
</tr>
<tr>
<td><strong>Dose-dense intravenous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>IV</td>
<td>AUC 6</td>
<td>d1 of 21d</td>
<td>Each dose given over 1 hour; should be administered prior to carboplatin with premedications as above</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>IV</td>
<td>80 mg/m²</td>
<td>d1, d8, d15 of 21d</td>
<td></td>
</tr>
<tr>
<td><strong>Intraperitoneal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>IV</td>
<td>135 mg/m²</td>
<td>d1 of 21d</td>
<td>Given over 24 hours</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>IP</td>
<td>100 mg/m²</td>
<td>d2 of 21d</td>
<td>Administered via intraperitoneal port; requires strong antiemetic therapy as well as hydration prior to and following cisplatin</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>IP</td>
<td>60 mg/m²</td>
<td>d8 of 21d</td>
<td>Administered via intraperitoneal port; premedications required as above</td>
</tr>
<tr>
<td><strong>Second-line regimens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegylated liposomal doxorubicin</td>
<td>IV</td>
<td>40 mg/m²</td>
<td>d1 of 28d</td>
<td></td>
</tr>
<tr>
<td>Topotecan</td>
<td>IV</td>
<td>15 mg/m² OR 4 mg/m²</td>
<td>d1-d5 of 21d</td>
<td>Recent evidence suggests that daily may be more efficacious than weekly schedule of administration.</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>IV</td>
<td>AUC 5</td>
<td>d1, 8, 15 of 28d</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>IV</td>
<td>1000 mg/m²</td>
<td>d1, 8 of 21d</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>IV</td>
<td>80 mg/m²</td>
<td>weekly</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>PO</td>
<td>50 mg</td>
<td>daily of 28d</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>IV</td>
<td>10 mg/kg</td>
<td>weekly for 3 wks, then every 2 wks/28d</td>
<td></td>
</tr>
</tbody>
</table>
doxorubicin has been shown to have superior PFS compared to retreatment with carboplatin and paclitaxel, and may be preferable to the prior standard given its toxicity profile.

In those patients who either did not respond to their initial platinum therapy (platinum refractory) or who recur within 6 months (platinum resistant), evidence-based protocols dictate treatment with either pegylated liposomal doxorubicin or topotecan. Other active agents/combinations in ovarian cancer include: Carboplatin/gemcitabine; single agent taxol (both monthly and weekly regimens); and bevacizumab/cyclophosphamide. Table 1 reviews common protocols for chemotherapeutics in the recurrent setting. In addition, combinations of these agents with other biologic agents, including bevacizumab, receptor tyrosine kinase inhibitors, PARP inhibitors and others are increasingly included in phase I and II studies.

Neoadjuvant Chemotherapy

Although primary surgical cytoreduction has been the preferred initial treatment option, for patients too sick to undergo primary surgery, neoadjuvant chemotherapy has been a useful adjunct. While no standard protocol exists, our practice is to administer three to four cycles of intravenous carboplatin and paclitaxel. If a clinical response is documented and the patient is amenable, surgery is undertaken, with further treatment dictated by the surgical findings.

There is data to suggest that the standard of optimal cytoreduction is insufficient and that patients’ outcomes stratify based on the presence of any gross residual disease. According to Vergote et al., patients with no gross residual disease following initial staging surgery achieve the best outcomes, followed by those who are able to achieve no gross residual disease following neoadjuvant treatment and cytoreductive surgery. Neoadjuvant therapy may eventually play a larger role, as it may be offered to patients as a mechanism to ensure that a cytoreductive surgery leaving no significant gastrointestinal toxicity. In this setting, overall response rates exceeding 95% have been documented.

Two notable toxicities attributed to this regimen bear mention: Pulmonary fibrosis (bleomycin) and secondary leukemias (etoposide). Although we generally believe that the platinum is the most important player in this regimen, both the omission of bleomycin or substitution of cisplatin by carboplatin have been related to worse outcomes in testes protocols. Given the high percentage of cure with BEP, it should remain as frontline therapy despite the low risk for life threatening adverse events.

Reproductive outcomes, an important index for this young patient population, have been good in long term follow up of survivors, with over 90% resuming normal menstrual function soon after completing BEP.

Cisplatin, vinblastine and bleomycin (PVB) is an alternate regimen which may be used in those patients in whom etoposide is not feasible, however vinblastine also carries significant gastrointestinal toxicity.

Sex Cord Stromal Tumors

Platinum-based combination chemotherapy should be utilized as adjuvant therapy in cases with stage I disease with high risk factors, as well as more advanced stage disease. BEP has been the standard regimen, with a cooperative trial showing an over 80% response rate, however favorable retrospective data and early phase trials have promoted the use of carboplatin with paclitaxel.

Endometrial Cancer

Surgery and radiation therapy have long been the mainstays for treatment in endometrial cancer, however the role of chemotherapy continues to evolve and plays an ever important role.

Early Stage, Low Risk Histopathologic Types

The majority of these patients will be cured with surgical resection +/- radiation therapy. In patients with high-intermediate risk features on pathology, there may be a role for adjuvant chemotherapy. This is currently under review by several large cooperative groups, with the optimal regimen not yet established.

Early Stage, High Risk Histopathologic Subtypes

Patients with either papillary serous or clear cell endometrial cancers have an increased risk for distant metastases, even with early stage disease. These patients are routinely offered adjuvant chemotherapy. Active agents have included doxorubicin (alone or in combination with platinum and taxane) as well as carboplatin and paclitaxel. No consensus exists at the current time regarding the optimal regimen for these patients.

Late Stage, All Histopathologic Subtypes

Standard of care for patients with advanced stage disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>IV</td>
<td>20 mg/m²</td>
<td>d1-d5 of 21d</td>
</tr>
<tr>
<td>Etoposide</td>
<td>IV</td>
<td>100 mg/m²</td>
<td>d1 d5 of 21d</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>IV</td>
<td>30 u</td>
<td>weekly</td>
</tr>
</tbody>
</table>

Table 2. BEP regimen for ovarian germ cell tumors.
following surgical resection includes adjuvant systemic chemotherapy. The most active agents include doxorubicin (Adriamycin), cisplatin and paclitaxel. The GOG evaluated the combination of paclitaxel (Taxol), adriamycin, and cisplatin (TAP) in a phase III trial (Table 3), and reported an improvement in progression-free and overall survival when compared to the doublet of adriamycin and cisplatin. These results remain limited, however, with a response rate of 22% and median progression free survival of 9 months. Many phase II trials have reported high response rates with the combination of carboplatin with paclitaxel in this patient population. The results of a phase III trial comparing TAP to carboplatin and paclitaxel by the GOG has completed accrual, and we await the results.

Patients with low-grade disease and receptor positive tumors may also respond to hormonal treatments. These protocols include progestins as well as anti-estrogens, including tamoxifen, and aromatase inhibitors.

Cervical Cancer

The treatment of locally advanced cervical cancer requires systemic cisplatin chemotherapy given weekly, in conjunction with pelvic radiotherapy. Other radiosensitizers to add in addition to cisplatin, including gemcitabine, have shown promise as potentially synergistic combinations. In addition, the addition of adjuvant chemotherapy following curative intent chemoradiation has led to improved progression free and overall survival in a handful of trials, although this has not led to widespread adoption.

For distant (stage IVB) or recurrent disease, systemic chemotherapy plays an important role. The combination of cisplatin with topotecan was the first regimen to show an improvement in overall survival when compared to cisplatin alone in this patient population. However, a follow-up trial designed to determine the optimal partner for cisplatin (including topotecan, gemcitabine, paclitaxel and vinorelbine) was stopped early given an inability to show superiority over the reference arm. Current phase III protocols include evaluation of both platinum and non-platinum based doublets with and without the benefit of bevacizumab. At the current time, cisplatin with either topotecan or paclitaxel should be considered the standard of care.

In the recurrent setting, multiple agents have activity, including single agent cisplatin, paclitaxel (particularly for adenocarcinoma histologies), and single agent vinorelbine. Although gemcitabine has demonstrated activity with cisplatin, as a single agent it has had disappointing results. It should be remembered, however, that the goal is only palliation in this setting, making the toxicity profile paramount when choosing a drug.

Gestational Trophoblastic Neoplasia

Gestational trophoblastic neoplasia involves a spectrum of diseases including malignant hydatidiform mole, choriocarcinoma and placental site trophoblastic tumor (PSTT). With the exception of PSTT, these tumors are highly sensitive to chemotherapeutics, which is the cornerstone of their management.

In order to determine which patients will benefit from chemotherapy, a combined scoring system utilizing both the World Health Organization and FIGO criteria is commonly utilized (Table 5). Patients scoring 6 or less are low risk, and are treatable with single agent chemotherapy. Two agents, methotrexate (MTX) and actinomycin-D, have good activity.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>IV</td>
<td>45 mg/m²</td>
<td>d1 of 21d</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>IV</td>
<td>50 mg/m²</td>
<td>d1 of 21d</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>IV</td>
<td>160 mg/m²</td>
<td>d2 of 21d</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>SQ</td>
<td>5 μg/kg</td>
<td>d3 - d12 of 21d</td>
</tr>
</tbody>
</table>

Table 3. TAP regimen for advanced endometrial cancer.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined chemoradiation</td>
<td>IV</td>
<td>40 mg/m²</td>
<td>weekly, to start concurrently with first day of pelvic radiotherapy</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>IV</td>
<td>40 mg/m²</td>
<td>weekly, to start concurrently with first day of pelvic radiotherapy</td>
</tr>
</tbody>
</table>

Table 4. Cervical cancer protocols.
Due to its side effect profile, most centers start with MTX. The failure rate, which is between 10 – 30%, is dependent on the dosing schedule, with more failures reported with weekly vs. daily protocols (Table 6). Patients who fail MTX, either due to toxicity or insufficient decline in hCG levels, are routinely switched to actinomycin-D. Over 90% of these patients will be successfully treated with one of these two agents; less than 5% will need multiagent chemotherapy.

For those patients who either fail single agent treatment, or who fall into a high-risk category on initial scoring (score greater or equal to 7), multiagent chemotherapy should be initiated. Several protocols have been developed, the most widely used being EMACO: Etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine. The EMA is given on days 1 and 2, while the CO is given on day 8, all on a 15 day schedule. Success rates for this regimen generally range between 70 and 75%. In cases of failure, the CO portion of the protocol is replaced with etoposide and cisplatin, which will generally produce successful treatment in three-fourths of previously resistant patients. Other regimens which have yielded success in resistant patients include PVB and ICE. Cisplatin from the outset, often with etoposide, should be considered in patients with the highest WHO/FIGO scores such as those with brain metastases or recurrences after prior treatments.

Dose density is important in this treatment regimen, and patients should be dosed unless toxicity is unduly prohibitive. Treatment should continue for several cycles beyond reaching

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**Table 6.** Gestational trophoblastic neoplasia protocols.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single agent chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>IM</td>
<td>0.4 mg/kg</td>
<td>d1 - d5 of 15d</td>
</tr>
<tr>
<td>Methotrexate with leucovorin rescue</td>
<td>IM</td>
<td>1.0 mg/kg</td>
<td>Alternating days x 4 doses with leucovorin 0.1 mg/kg 24 hrs after each MTX dose</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>IM</td>
<td>50 mg/m²</td>
<td>weekly</td>
</tr>
<tr>
<td>Actinomycin-D</td>
<td>IV</td>
<td>1.25 mg/m²</td>
<td>d1 of 15d</td>
</tr>
<tr>
<td>Actinomycin-D</td>
<td>IV</td>
<td>12 μg/kg</td>
<td>d1 - d5 of 15d</td>
</tr>
<tr>
<td><strong>Combination chemotherapy - EMACO</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actinomycin-D</td>
<td>IVP</td>
<td>500 μg</td>
<td>d1 of 15d</td>
</tr>
<tr>
<td>Etoposide</td>
<td>IV</td>
<td>100 mg/m²</td>
<td>d1 of 15d</td>
</tr>
<tr>
<td>Methotrexate 1 hr infusion</td>
<td>IV</td>
<td>100 mg/m²</td>
<td>d1 of 15d</td>
</tr>
<tr>
<td>then MTX over 12 hrs</td>
<td>IV</td>
<td>200 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Actinomycin-D</td>
<td>IVP</td>
<td>500 μg</td>
<td>d2 of 15d</td>
</tr>
<tr>
<td>Etoposide</td>
<td>IV</td>
<td>100 mg/m²</td>
<td>d2 of 15d</td>
</tr>
<tr>
<td>Folinic acid</td>
<td>IVP</td>
<td>15 mg q 6 hrs x 8</td>
<td>start d2</td>
</tr>
<tr>
<td>OR</td>
<td>PO</td>
<td>15 mg q 12 hrs x 4</td>
<td>start d2</td>
</tr>
<tr>
<td>Vincristine</td>
<td>IV</td>
<td>1 mg/m²</td>
<td>d8 of 15</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>IV</td>
<td>600 mg/m²</td>
<td>d8 of 15</td>
</tr>
<tr>
<td><strong>Combination chemotherapy - EPIEMA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>IV</td>
<td>80 mg/kg over 12 hrs</td>
<td>d1 of 15</td>
</tr>
<tr>
<td>Etoposide</td>
<td>IV</td>
<td>100 mg/m²</td>
<td>d1 of 15</td>
</tr>
<tr>
<td>Actinomycin-D</td>
<td>IVP</td>
<td>500 μg</td>
<td>d8 of 15</td>
</tr>
<tr>
<td>Etoposide</td>
<td>IV</td>
<td>100 mg/m²</td>
<td>d8 of 15</td>
</tr>
<tr>
<td>Methotrexate 1 hr infusion</td>
<td>IV</td>
<td>100 mg/m²</td>
<td>d8 of 15</td>
</tr>
<tr>
<td>then MTX over 12 hrs</td>
<td>IV</td>
<td>200 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Folinic acid</td>
<td>IVP</td>
<td>15 mg q 6 hrs x 8</td>
<td>start d9</td>
</tr>
<tr>
<td>OR</td>
<td>PO</td>
<td>15 mg q 12 hrs x 4</td>
<td>start d9</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>SC</td>
<td>5 mg/kg</td>
<td>start 24 hours after therapy, and discontinue 24 hours prior to next dose of chemotherapy</td>
</tr>
</tbody>
</table>
a negative hCG level. Due to the rarity of these tumors and their heterogeneous behavior, referral to centers of excellence in the disease should be initiated whenever possible.

References
Introduction

For several reasons there has been considerable interest within the gynecologic oncology community for the therapeutic potential of a variety of targeted therapies in disease management.

First, it had been hoped that targeted anti-neoplastic drug delivery might reduce the toxicity of treatment by specifically impacting cancer-related molecular targets, and avoiding non-cancerous tissues (or at least reducing the risk of producing a clinically-relevant negative impact on normal cellular function).

Second, it was anticipated that by defining relevant targets it might be possible to determine which tumors did not contain these targets, such that one could prospectively delineate which patients (and their cancers) should not be treated with a particular anti-neoplastic agent.

Third, since pre-clinical data has suggested that certain molecular targets may play an important role in chemotherapy drug resistance, it has been speculated that by combining specific targeted agents with cytotoxic drugs it may be possible to enhance the biological activity of already established management approaches.

Finally, it was hoped that targeted therapeutics would permit the establishment of personalized cancer medicine, where the development of a management strategy would be based more on well characterized molecular and genetic features within an individual patient and specific malignancy rather than having treatment administrated based solely on the tumor’s site of origin (e.g., ovary) and histologic type (e.g., adenocarcinoma).

Definition of “Targeted Therapy”

Before proceeding with a discussion of the current status of targeted therapy of gynecologic malignancies, it is important that we attempt to clearly state what is meant by this term, for (in fact) all anti-cancer agents produce their biological effects (both favorable and unfavorable) by impacting a “target” (e.g., DNA, mitotic spindle formation). Thus, the fundamental difference between targeted and non-targeted anti-neoplastic drug therapy is the attempt by researchers to prospectively and accurately determine the specific target(s) being influenced by the agent, as well as the subsequent consequences resulting from such interactions.

It is important to note here that the process of defining “targets” remains in its infancy, and considerable existing data reveal that establishing molecular targets within relatively simple pre-clinical in vitro model systems may have limited (or no) relevance when the drugs are delivered to patients.

It is also relevant to acknowledge that while there has much recent attention to this evolving drug development paradigm, the concept of “targeted therapy” of malignancy is actually quite old, as hormonally-based approaches to the management of cancers of the breast, prostate, and endometrium have been routinely employed in standard patient management for several decades in individuals who possessed the appropriate biological “target” (e.g., estrogen/progesterone receptors).

Status of Targeted Therapy in the Non-Gynecologic Cancer Setting

Over the past decade much has been learned regarding the general principles of targeted therapy of human malignant disease. First, it is reasonable to conclude that as a therapeutic group such agents are certainly not non-toxic (1). However, it is also fair to state that the side effect profiles observed with targeted therapies are often quite different from the more “routine” established toxicities of most cytotoxic anti-neoplastic drugs (e.g., emesis, hair loss, myelosuppression). For example, rashes are commonly observed following the administration of epidermal growth factor receptor (EGFR) inhibitors and hypertension is frequently noted after treatment with anti-angiogenesis agents (1).

To date, only a few of the new targeted anti-neoplastic drugs have been shown in randomized phase 3 trials to substantially improve overall survival (e.g., imatinib in chronic myelogenous leukemia), although a much larger number of drugs have demonstrated a more modest (but clinically meaningful) impact on this outcome of therapy (e.g., trastuzumab in metastatic breast cancer; bevacizumab in metastatic colon cancer).

Of considerable interest, data are beginning to emerge regarding specific molecular signatures that define cancers within individual patients that are completely (or almost completely) resistant to a particular targeted therapeutic intervention. Perhaps the best recent example of this phenomenon is the finding that patients with metastatic colon cancer whose tumors possess a mutant K-ras (versus wild-type K-ras) essentially never respond to the administration of EGFR inhibitors (e.g., cetuximab) (2). Similarly, patients whose breast cancers do not over-express the HER-2/neu receptor are highly unlikely to respond to treatment with
trastuzumab.

Again, it is relevant to note that it has long been established that patients whose breast cancers fail to demonstrate the presence of estrogen and/or progesterone receptors very rarely (if ever) respond to hormonal manipulations (medical or surgical), so the concept of employing predictive tests in determining ineffective therapies is in reality not a novel concept.

One of the most important lessons learned through the conduct of trials in this arena is the profound complexity of human cancer and the likely fact that the ultimate success of a personalized medicine approach to cancer management may require the delivery of a minimum of several targeted agents, each directed toward those molecular targets that have been revealed in an individual patient's malignancy during pre-treatment laboratory evaluation to be at least partially responsible for the progression of the tumor in this specific cancer. This statement appears to be particularly relevant in those settings where it is not possible to define a single molecular abnormality that appears to be responsible for the progression of a cancer; for example, where the cancer may have become dependent upon (or "addicted" to) the presence of this receptor/pathway to remain viable.

Status of Targeted Therapy of Gynecologic Cancers

A number of approaches (e.g., EGFR-inhibitors; anti-HER-2; tyrosine kinase inhibitors) have been explored with an inadequate "signal" for evidence of biological activity being generated in phase 2 studies to suggest that further clinical exploration would be appropriate. Several reasons can be advanced to explain these disappointing results (Table 1).

The GOG experience with anti-HER-2 therapy is particularly informative as only 10% of screened patients were revealed to over-express this biological marker and within the population ultimately treated a 7% response rate was observed (3). Thus, of the total population initially screened, <1% achieved a measurable level of objective benefit. Clearly, this is a highly inefficient strategy to define a very small subset of patients ("personalized medicine") with gynecologic malignancies who may achieve benefit from a particular targeted management strategy.

**Anti-Angiogenesis Agents in Gynecologic Malignancies**

In contrast to the overall experience with targeted neoplastic therapy, data regarding a potential for anti-angiogenic therapy is far more promising. Several published phase 2 trials have revealed that approximately 15% of women with platinum-resistant ovarian cancer will be anticipated to achieve an objective response to single agent bevacizumab (4,5), and approximately 11% of individuals with previously treated metastatic/recurrent cervix cancer may experience tumor regression (6). Of potential considerable importance, existing data suggest that a higher percentage of ovarian cancer patients may achieve "stabilization" of their disease process for an extended period of time (e.g., >6 months) than are documented to attain an objective measurable response (4).

Preliminary results of two phase 3 randomized trials examining a role for bevacizumab as a component of primary treatment of ovarian cancer reveal the addition of this agent improves progression-free survival (compared to the use of cytotoxic chemotherapy alone) (Table 2), but the limited existing data have not suggested the approach will impact overall survival (7,8).

In addition to the now well-characterized toxicity profile for anti-angiogenic agents in multiple tumor types (e.g., hypertension), studies in ovarian cancer have revealed that as many as 10% of women treated in the second-line setting may experience a bowel perforation. The risk of this potentially serious toxicity appears to be greatest in the setting of substantial intra-peritoneal cancer, particularly when it is felt the tumor is intimately involved with the bowel wall (e.g., thickened bowel wall on CT scan, or air-fluid levels seen on a plain radiograph of the abdomen), where it is suggested that the anti-angiogenic effect interferes with the body's normal

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**Table 1.** Possible reasons targeted anti-neoplastic agents may not favorably impact outcome

<table>
<thead>
<tr>
<th>Reason</th>
<th>Possible Negative Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The target may not be present on the cancer cells, or present on only a small (even if measurable) subset of such cells</td>
<td></td>
</tr>
<tr>
<td>2. The target may not be relevant to the progression of the cancer</td>
<td></td>
</tr>
<tr>
<td>3. The agent may be unable to reach the target (e.g., inadequate blood flow to the site of tumor; the receptor is not adequately exposed on the cell surface)</td>
<td></td>
</tr>
<tr>
<td>4. Even if a target/pathway is effectively inhibited alternative survival pathways may be utilized by the tumor</td>
<td></td>
</tr>
<tr>
<td>5. Impacting a target may actually activate a pathway, rather than inhibit the process (at least in a proportion of cells)</td>
<td></td>
</tr>
<tr>
<td>6. Inhibition of a target/receptor may result in a malignant cell increasing the number of receptors/targets on that cell, or favor the survival of a population with a pre-existing concentration of receptors/targets requiring inhibition</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2.** Phase 3 trials combining bevacizumab (B) with standard carboplatin/paclitaxel (C/P) in the primary chemotherapeutic management of ovarian cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>PFS (median)</th>
<th>Overall Survival (1-year)</th>
<th>Overall Survival (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICON 7 (8)</td>
<td>C/P (&quot;control arm&quot;)</td>
<td>10.3 months</td>
<td>90.6%</td>
</tr>
<tr>
<td></td>
<td>C/P + B (only during chemotherapy)</td>
<td>11.2 months</td>
<td>90.4%</td>
</tr>
<tr>
<td></td>
<td>C/P + B (both during chemotherapy and a single agent &quot;maintenance&quot;)</td>
<td>14.1 months (p=0.001)</td>
<td>91.3%</td>
</tr>
<tr>
<td></td>
<td>C/P (&quot;control arm&quot;)</td>
<td>17.3 months (p=0.0041)</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>C/P + B (both during chemotherapy and a single agent &quot;maintenance&quot;)</td>
<td>19.0 months</td>
<td>95%</td>
</tr>
</tbody>
</table>
processes of wound healing.

**PARP Inhibitors in Epithelial Ovarian Cancer**

Highly provocative phase 2 trial data have revealed that approximately one-third of ovarian cancer patients with a known BRCA 1 or BRCA 2 mutation (5-10% of women with the malignancy) will achieve an objective response to a PARP inhibitor (9,10). This strategy is based on the hypothesis that individuals with these genetic abnormalities have a defect in DNA repair which will be enhanced by inhibition of a second repair mechanism (PARP). Ongoing research is exploring the combination of PARP inhibitors with cytotoxic chemotherapy.

Researchers are also exploring the potential of employing PARP inhibition in individuals whose cancers possess **somatic mutations** that closely resemble those found in patients with the germline defects (“**BRCAness profile**”) (11). Thus, the potential exists that a larger patient population may be able to benefit from treatment with this class of targeted anti-neoplastic agents.

**Future Directions**

It is important to acknowledge that ongoing research efforts are providing a clearer understanding of molecular pathways that may be highly relevant in the development, progression, and “inherent or acquired” chemotherapy-resistance of advanced gynecologic cancers. As a result, it can reasonably be anticipated that over the next decade a number of novel targeted biological agents will be shown to be active in gynecologic malignancies and these drugs will “find a place,” along with cytotoxic agents, in the standard-of-care management of this group of diseases.

Well-designed clinical trials, in most settings phase 3 randomized studies will be required to document the utility of such drugs. This is a particularly relevant point as it can be predicted that this class of agents will be very expensive. Further, to achieve optimal benefit it may be necessary to deliver such drugs over prolonged periods of time (e.g., “maintenance approach”).

However, in view of the fact that the strategy of **personalized medicine** may necessitate treating quite limited subsets of patients who may benefit, it is essential that acceptably valid novel trial designs be developed to accelerate the evaluation of individual targeted agents, and various combination regimens. Importantly, international collaboration in the conduct of studies designed to efficiently, yet critically, examine innovative strategies will benefit gynecologic cancer patients throughout the world.

**References**

Over the last 30 years, substantial progress has been made in the treatment of ovarian cancer, both in the primary and recurrent settings. Though early detection has remained an elusive goal, improvements in systemic treatment for patients have resulted in a nearly two year improved survival for women who are afflicted with this disease (1). Unfortunately, despite these achievements, the proportion of patients who achieve a “cure” remains low, and the vast majority of patients who present with advance stage disease eventually succumb to this cancer. For this reason, the development of novel therapeutics that can both improve overall survival and cure rates remains an imperative. Rapid advances in our understanding of the molecular biology of ovarian cancer have enabled researchers to develop an increasing array of targeted therapies that have the potential to achieve the aims listed above while exposing patients to less toxicity. This chapter will discuss recent clinical trials involving cytotoxic as well as targeted therapeutics in frontline and recurrent ovarian cancer. In addition, several novel cytotoxic agents that are also being studied in the recurrent disease setting will be presented as well.

Novel Therapeutics in Ovarian Cancer

Arguably, one of the most exciting developments in ovarian cancer therapeutics has been the emergence of agents targeted to the biological processes of tumor growth and survival.

Investigation has proceeded down several different identified mechanisms of carcinogenesis and has fostered the discovery and invention of a broad portfolio of interventional strategies. A number of these new compounds are undergoing Phase II study and have the potential to vie for position in management of epithelial ovarian cancer.

Vascular Targeting Agents (VTAs)

Development of a sufficient blood supply is required for cancer growth to extend beyond 1 mm³ (2). Angiogenesis occurs by either sprouting (branching of new blood vessels from pre-existing blood vessels) or non-sprouting (enlargement and splitting of pre-existing blood vessels) (3). Tumor vasculature within the microenvironment is phenotypically different from its normal counterparts and is characterized by vessels that are irregular in shape, dilated, tortuous, and disorganized. Initiation of this process is dependent on a shift in balance toward pro-angiogenic factors (such as vascular endothelial growth factor and its receptor, VEGF/VEGFR, platelet derived growth factor and its receptor, PDGF/PDGFR, and the Ephrins/Eph), which, given their critical role in this regard are appealing therapeutic targets (4). In addition, endothelial cells, unlike tumor cells, are generally genetically stable, providing another potential angiogenesis-related therapeutic avenue.

Strategies to exploit tumor angiogenesis have resulted in the development of two broad classes ofvascular targeting agents (VTAs), namely angiogenesis inhibitors (AI) and vascular disrupting agents (VDA) (5). They differ in that AIs affect primarily the establishment of new blood vessel development, and VDAs are known to more effectively damage established tumor vasculature. While the development and clinical use of AIs are well ahead of VDAs, there is significant enthusiasm regarding VDAs, as they have been shown activity in both pre-clinical and clinical studies (monotherapy and in combination therapy with AIs and cytotoxic chemotherapy) (6-10).

Angiogenesis Inhibitors

Vascular Endothelial Growth Factor (VEGF) ligand and receptor targeting

Based on the clinical significance of the VEGF pathway, several strategies for targeting VEGF signaling have been developed including anti-VEGF antibodies, genetically engineered VEGF-binding proteins, VEGF receptor tyrosine kinase inhibitors (TKIs), and vascular disrupting agents (Table 1). Bevacizumab (Avastin®, Genentech), the first FDA-approved drug targeting tumor angiogenesis, is a humanized monoclonal antibody directed against human VEGF ligand (11). In patients with ovarian carcinoma the agent has shown promise. The Gynecologic Oncology Group (GOG) initiated a phase II trial with single-agent bevacizumab in patients with persistent or recurrent epithelial ovarian carcinoma, which reported 13 of 62 eligible patients (21%) experiencing clinical response. Twenty-five patients (40.3%) had a progression free survival of at least 6 months and the median number of cycles per patient was 7. The regimen was reasonably well tolerated and no bowel perforations were registered (12). A separate but similarly structured trial of patients receiving third- or fourth-line bevacizumab demonstrated a 16% response rate with a median progression-free survival (PFS) of 4.4 months. However, in contrast to the former study, 5 women (11.4%) had spontaneous bowel perforation leading to premature study closure and issuance of an action letter by the FDA.
to alert clinicians and patients of the potential risk. Risk factors for GI perforation in ovarian cancer patients receiving bevacizumab are unclear and controversial; however, this study suggested increased risk was present in patients who had received multiple prior regimens and in whom impending bowel obstruction was suspected (13,14). 86 Contemporary trials of bevacizumab in ovarian cancer include additional single-agent studies, chemotherapy combinations, and dual biological therapies in the primary, maintenance and recurrent disease settings (6). In primary treatment, GOG Protocol 218 (GOG 218, *NCT00262847), and ICON7 (NCT00483782) were presented in 2010 and are currently available in abstract form; their schema are compared in Table 2. Both trials demonstrated significant improvements in progression-free survival (PFS).

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**Figure 1.** Treatment schema for Gynecologic Oncology Group Protocol 218. The study’s initial eligibility included only those patients with residual disease following primary surgery of greater than 1 cm. Currently, the protocol allows participation for those women left with visible but residual disease of no greater than 1 cm. Patients are randomized once with a primary and maintenance treatment phase, which is placebo-controlled. The primary endpoints are overall survival and progression-free survival. This trial is now closed to new patient accrual.

**Figure 2.** Trial schema of International Collaborative Ovarian Neoplasm protocol 7 (ICON7). Like GOG 218, this trial is planning a primary and maintenance phase of administration. The primary endpoint of ICON7 is PFS.
free survival (PFS) (+3.8 months (GOG 218); +2.3 months (ICON-7)) with the addition of bevacizumab to paclitaxel + carboplatin followed by a maintenance phase of 12 cycles (15-17). Though a PFS advantage was validated for both studies, the use of bevacizumab in the setting of primary disease has been criticized by some due to its cost (particularly during maintenance therapy) relative to the PFS advantage of 2–4 months (17).

In the recurrent setting, GOG 213 (NCT00565851) and ICON-6 (NCT00544973) are enrolling patients. GOG 213 is near enrollment completion designed to evaluate the role of secondary cytoreduction as well the addition of bevacizumab to paclitaxel and carboplatin in the setting of platinum sensitive first recurrence. As such, GOG 213 has two potential randomization sequences (Figure 3). The first is based on the investigator’s assessment that secondary cytoreduction for a patient will result in no gross residual disease at the completion of the case. Patients who are deemed surgery candidates are randomized to surgery or not.

The second randomization is performed either after a surgery candidate is randomized to no surgery or after secondary cytoreduction; it involves the addition (or not) of bevacizumab to standard treatment with paclitaxel + carboplatin, followed by maintenance bevacizumab (bevacizumab patients only).

Finally, a third randomized, phase III, double-blind, placebo-controlled trial (OCEANS trial, NCT00434642, Figure 4) is designed to evaluate the addition of bevacizumab to combination gemcitabine and carboplatin in women with platinum sensitive first recurrence; it has completed accrual and preliminary results were recently presented. A four month improvement in PFS was observed within the treatment arm (12.4 vs 8.4 month, HR 0.484). This represented a 52% reduction in the risk of progression in comparison to the control arm. These results measure favorably when compared to other trials in platinum sensitive recurrent ovarian cancer. In addition, the toxicity profile of bevacizumab in combination with chemotherapy was similar to what is described in previous reports and no new toxicities were observed. Bowel perforations were not observed in patients on trial which suggest a significant benefit in PFS. The doublet of gemcitabine and carboplatin is already FDA-approved for platinum-sensitive recurrent ovarian cancer (18).

While the aforementioned trials have focused on platinum-sensitive patient cohorts, bevacizumab has shown activity as a single agent and in combination with metronomic cyclophosphamide, gemcitabine and weekly paclitaxel in platinum resistant patients (19,20). The AURELIA trial (NCT009769911) is evaluating the addition of bevacizumab to a number of cytotoxic agents in platinum-resistant patients. The active comparators include, weekly paclitaxel, topotecan (weekly and daily times 5 schedules) and pegylated liposomal doxorubicin. This trial should provide important safety and efficacy information for a number of treatment standards in patients with recurrent disease.

One other VEGF ligand targeted agent has been engineered and is being investigated in ovarian cancer patients. Aflibercept (VEGF Trap, Sanofi-aventis) is a potent, high-affinity VEGF blocker constructed by fusing the second domain of VEGFR-1 with the third domain of VEGFR-2 to produce a decoy VEGF receptor (21). Preliminary results from a large randomized, phase II, single-agent, multicenter study of aflibercept in patients with platinum-resistant epithelial ovarian cancer have revealed activity for this drug.
Additional single-agent and chemotherapy combination studies are underway, including a planned phase III study in platinum-resistant recurrent ovarian cancer patients.

**VEGF Receptor Targeting**

Modalities for targeting the VEGF receptor family include monoclonal receptor antibodies and tyrosine kinase inhibitors (TKIs) (23). The vast majority of compounds being developed clinically in ovarian cancer patients are TKIs, however, one fully humanized monoclonal antibody (IMC-1121B, Imclone), which targets VEGFR-2, the primary receptor mediating the angiogenic effects of VEGF ligand, is in phase II investigation in ovarian cancer patients. Cediranib (Recentin), is VEGFR-2 TKI that has shown tolerability and activity in phase I and II clinical trials in ovarian cancer (24). As a result, it is the subject of evaluation in ICON 6, which randomizes patients with a platinum sensitive first recurrence to standard re-treatment with paclitaxel + carboplatin + either cediranib or placebo, followed by a maintenance phase with either cediranib or placebo (Figure 5).

Table 1 presents a partial list of the multiple TKIs under study in ovarian cancer. Because TKIs have variable affinity for different receptor systems, nearly all function to some degree as multi-kinase inhibitors. The functional relevance of this is that while multi-kinase inhibitors, via blockade of multiple signaling pathways, offer potentially increased tumor killing ability, they also frequently are found to have problematic "off-target" adverse effect profiles that vary substantially from one drug to another. New studies/agents are entering the clinical domain with dizzying regularity, however, the vast majority of these agents are still in early clinical trials (phase I/II). One TKI, intedanib (BIBF-1120) has entered phase III investigation in the front-line setting in combination with paclitaxel and carboplatin. This agent, which targets VEGFR, PDGFR and FGFR demonstrated delay in progression with placebo controlled primary and maintenance phases. ICON6 is evaluating cediranib (AZD 2171), which has multiple targets for the VEGF receptor. Unlike GOG 213, ICON6 is only addressing a chemotherapy question.

**Novel Anti-angiogenesis Agents**

In addition to the classic VEGF pathways of angiogenesis, there are other pathways involved in later stages of neovascularization which hold promise for targeted therapy. Ang-1 and Ang-2 bind the receptor Tie-2 to activate pathways that stimulate endothelial cell proliferation, motility, and survival. In addition, the angiopoietins recruit pericytes to support vascular maturation (26). AMG-386 is a peptibody, a peptide fusion protein, that selectively binds Ang-1 and Ang-2 preventing interaction with Tie-2. In phase I studies of solid tumors, this compound was well tolerated, without many of the classic toxicities associated with anti-angiogenic agents (27). A phase II study comparing two different dose levels of AMG-386 (3 mg/kg, 10 mg/kg) versus placebo in combination with weekly paclitaxel (80 mg/m²) demonstrated a trend toward improved progression free survival in patients who achieved higher steady state concentrations of AMG-386. These results lead to the dose selection for TRINOVA-1 which is a study comparing AMG-386 versus placebo plus weekly paclitaxel in recurrent ovarian cancer. AMG-386 (10 mg/kg) is also being explored in combination with liposomal doxorubicin (50 mg/m²) or topotecan (4 mg/m²) for recurrent ovarian cancer in a Phase Ib trial. Interim results have demonstrated acceptable toxicity, however, efficacy data are not yet mature. AMG-386 is also to be evaluated as a single agent treatment for recurrent uterine cancer as part of a GOG study.

**Vascular Disrupting Agents (VDA)**

As mentioned above, VDAs target existing tumor vasculature. As a result, they are associated with rapid tumor ischemia and cell death (28). There are several types, of VDAs, namely ligand based therapies, which deliver toxins, procoagulant, or pro-apoptotic effectors to disease associated vessels, and small molecular VDAs, which do not specifically localize to
tumor vasculature, but exploit the known differences between them to induce selective vascular dysfunction (5). Between these two broad classes of VDAs, small molecule VDAs have shown more promise to date, and several have been studied clinically in ovarian cancer (9).

The agent most studied in ovarian cancer is Combretastatin A4 phosphate (CA4P; fosbretabulin), which is a water soluble prodrug of the tubule-binding VDA combretastatin A4 (CA4), derived originally from the African bush willow (29). It functions as tubulin de-polymerizing agent, disrupting the cytoskeleton of proliferating endothelial cells, resulting in endothelial cell shape changes and detachment, ultimately leading to vascular collapse and tumor necrosis. It’s tumor specificity stems from the increased growth and division of tumor endothelial cells (30). A phase II non-randomized trial in patients with platinum resistant ovarian cancer was recently reported. 44 patients with platinum resistant ovarian cancer were treated with CA4P 63 mg/m2 in combination with q 3 week paclitaxel (175 mg/m2) and carboplatin (AUC = 5). The therapy was relatively well tolerated, with predictable grade 2 toxicities of neutropenia (75%) and thrombocytopenia (9%). Grade 2 hypertension was also notable (23%), requiring anti-hypertensive treatment in most patients. A RECIST response rate of 13.5% was observed.

**PARP Targeting**

Poly-ADP ribose polymerase (PARP) is an enzyme complex super family, which consists of seventeen members. Among these, PARP-1 and PARP-2, which are important for DNA repair, are the best characterized subtypes. Their utility as a target for anti-neoplastic therapy is based on the concept of synthetic lethality, which exploits the fact that BRCA-1 and BRCA-2 deficient tumor cells are, at baseline, deficient in double stranded DNA (dsDNA) repair (31). In contrast to normal cells, which have redundant dsDNA repair mechanisms, exposure of BRCA-1 and BRCA-2 deficient tumor cells to PARP-inhibition makes them incapable of dsDNA repair, resulting in apoptosis and tumor cell death. PARP inhibitors are relatively unique among currently biologics in ovarian cancer in that their cytotoxic effects are largely trophic to tumor cells.

There are a number of PARP-inhibitors in different stages of pre-clinical and clinical trials, however the most well described agent is Olaparib, an oral PARP-inhibitor that has been evaluated in phase I and II trials in doses ranging from 100–600 mg twice daily. In one phase I trial which treated 19 patients with BRCA-related ovarian cancer, nine of nineteen patients (47%) achieved a RECIST partial response (PR) (32). In a phase II study treating BRCA positive ovarian cancer patients with olaparib at multiple doses (mostly 400 mg twice daily), fourteen of fifty (28%) women achieved a RECIST PR. Toxicities were reversible with only 12% of patients experiencing grade 3/4 toxicities, primarily nausea, fatigue and anemia. As might be expected, responses were highly correlated with disease free interval and platinum sensitivity (33).

Clinical efficacy of single agent olaparib has fostered evaluation of chemotherapy combinations of several of the available PARP inhibitors, as well as, comparison to chemotherapy in patients carrying BRCA mutations. A recently reported randomized phase II study of olaparib (two dose levels: 200 mg BID and 400 mg BID) and pegylated liposomal doxorubicin (50 mg/m2) addressed this latter hypothesis. The trial was designed to address a 45% reduction in the hazard for disease progression (median 4 to 7.3 months) with equal randomization of the 3 arms (N=30/arm). The trial was well balanced for known prognostic factors and was weighted approximately 5:1 for BRCA1 vs. BRCA2. The median number of prior therapies administered was 3 in each arm. Overall the PFS was 6.5 months vs. 8.8 months vs. 7.1 months, respectively for olaparib (200 mg BID), olaparib (400 mg BID) and pegylated liposomal doxorubicin (P=NS). Response rates were highest in the high dose olaparib arm but not significantly. The PARP inhibitor was well tolerated and while not superior to chemotherapy in this context, clearly offers a non-chemotherapy option for these patients.

Although only 10–15% of ovarian cancers are related to a BRCA mutation, it is estimated functional loss of homologous DNA repair proteins may be present in as many as 50% of patients with sporadic ovarian cancer, making these patients phenotypically similar to women with a known BRCA mutation. There are multiple proposed techniques for assessment and quantification homologous recombination deficiencies – termed “BRCAiness”; as would be expected, an individual’s degree of BRCAiness correlates with disease free interval and platinum sensitivity (31). Since tumoral dysfunction in homologous recombination may be innate or induced by cytotoxic agents, several trials are now being launched to address chemotherapy combinations with PARP inhibitors in unselected recurrent ovarian cancer patients. The chemotherapy agents of choice appear to be those that induce DNA strand breaks, such as, platinummates, alkylators and anthracyclines. For instance, two recently completed single-arm phase II studies reported on gemcitabine and cisplatin in combination with iniparib (platinum-sensitive and platinum-resistant cohorts). In both trials, activity from the first stage of accrual supported further development (34,35).

Finally, there is interest in whether PARP inhibitors can effectively keep tumors from growing following an induced response. This latter hypothesis was the focus of a recently reported randomized placebo-controlled study of olaparib (400 mg po BID) in patients with recurrent ovarian cancer. Eligible patients were to have achieved a partial or complete response to a second- or third-line platinum-based regimen. BRCA mutation was not required for entry. In the both arms, agent or placebo was administered until progression. In all 265 patients were registered; PFS by RECIST criteria was 8.4 months in the olaparib arm and was favorable to placebo (median PFS 4.8 months, HR: 0.35; 95% CI 0.25-0.49, p<0.00001). Overall survival data are immature, however, the impact is notable particularly in light of the favorable adverse event profile (36).
Alpha Folate Receptor Targeting

Folate receptor alpha (FRA) binds folic acid with high affinity and is involved in folate transport. This is quite relevant in ovarian malignancy, as this receptor is over-expressed in greater than 90% of ovarian cancers (37). Furthermore, there is minimal expression of this target in normal tissues, making this an attractive target for anti-cancer therapy. There are a number of new agents being developed to take advantage of these findings. Farletuzumab (MORAb-003), a humanized monoclonal antibody to folate receptor alpha, demonstrated inhibition of cellular proliferation and stimulation of cell death in preclinical models. A phase II trial of this agent (100 mg/m²) in platinum-sensitive ovarian cancer was designed as a single agent study with subsequent addition of traditional chemotherapy (carboplatin and paclitaxel) at the time of disease progression. In the single agent arm, 24 of 28 patients remained on therapy at least 9 weeks. With combination therapy, 90% of patients achieved normalization of their CA125 and 70% had complete or partial response (38). This drug is now under further exploration in combination with a variety of cytotoxic chemotherapies (Phase III trial of Paclitaxel and Carboplatin with or without Farletuzumab in platinum-sensitive recurrent ovarian cancer and Randomized phase II study of weekly paclitaxel with or without farletuzumab in patients with platinum resistant ovarian cancer) and as a single agent in ovarian cancer.

A second agent, EC-145, uses folate and its affinity for the FRA to bring drug conjugates selectively to expressing tumor cells. In the case of EC-145, the cytotoxic payload is desacetylvinblastine monohydrazide (DAVLBH), a vinca alkyloid. In the proof of concept randomized phase II trial, pegylated liposomal doxorubicin (PLD, 50 mg/m²) was administered alone or with EC-145 to women with platinum-resistant ovarian cancer and no more than 2 prior regimens. The mature PFS data demonstrated a significant reduction in the hazard for progression (HR: 0.626) with a difference at the medians of 21.7 weeks vs. 11.7 weeks (39). Remarkably, there was no additional toxicity in the combination arm relative to the control, confirming the selective targeting afforded by the FRA and the lack of payload dislodgement in the drug-conjugate. A phase III version of this trial (PROCEED) is underway and is evaluating a radiotracer form of the drug conjugate, EC-20, to identify patients for whom EC-145 may work best.

Phase III Trials of Novel Cytotoxic Agents

There are a number of cytotoxic agents that have completed or are the subject of ongoing phase III investigation: trabectedin, patupilone, BNP 1530. Each of these are being or were studied in the recurrent setting but have addressed different cohorts of patients, including those with platinum-sensitive first recurrent disease and those with multiple lines of prior therapy. Necessarily, these trials have been large and as a matter of process, include “standard of care” control arms for their relevant population. The ultimate goal of each of these studies is to provide a measured performance advantage in either progression-free survival or overall survival. The most recently reported is trabectedin, which was combined with the currently FDA approved drug pegylated liposomal doxorubicin (PLD), and compared against this agent in women with first recurrent ovarian cancer.

Trabectedin

Although it was known in the late 1960’s that this agent, isolated from an extract of the sea squirt, Ecteinascidia turbinata, had anti-cancer properties, it wasn’t until the mid 1980’s that the active moiety was characterized. Even so, it was some years later until the compound, termed ET-743, could be produced in sufficient quantities to be formally investigated in the clinic (40). Trabectedin works principally by binding to the minor groove of DNA, interfering with transcription-coupled nucleotide excision repair machinery, inducing lethal DNA strand breaks and blocking the cell from entering the G2 phase of the cell cycle (40). Preclinical data supports the synergistic interaction with platinum without overlapping toxicity (41). The compound is currently approved by European Medicines Agency (EMEA) as a single agent for advanced soft tissue sarcoma. In ovarian cancer, 2 recent phase II studies in platinum-resistant patients revealed modest clinical efficacy (42,43). Data in platinum-sensitive patients was more encouraging (37% response rate). Two infusion schedules (weekly – 3 of 4 weeks, and 3 hour bolus and 24 hour infusion, every 3 weeks) have demonstrated differing rates of non-hematological toxicity, principally reversible liver function tests and myelosuppression (44).

Nevertheless, the feasibility of combining this novel agent with PLD provided the rationale to proceed with a phase II trial of trabectedin and PLD versus PLD in women with recurrent ovarian cancer. The combination was dosed PLD 30 mg/m² + trabectedin 1.1 mg/m² over 3 hours every 3 weeks and the control arm, PLD was dosed at 50 mg/m² every 4 weeks. Patients with measurable and evaluable disease were included, although only one prior regimen for primary therapy was allowed. Patients could be platinum-sensitive or resistant, which formed a stratum for analysis. The trial’s primary endpoint was initially overall survival but was later changed to progression-free survival when this endpoint was accepted following a consensus conference of biomarkers and endpoints for recurrent ovarian cancer. In order to provide 90% power (2-sided test) to detect a 37.5% increase in the median PFS (16 weeks to 22 weeks) with the combination, 650 patients (415 events) were required. At study closure, 672 patients were enrolled and evaluable for assessment: approximately 60% of the patient population in both arms of the trial were considered platinum-sensitive (treatment-free interval of greater than 6 months). Eighty percent of patients in both arms had also been exposed to a platinum and taxane combination as part of their primary therapy. Table 3 summarizes the outcomes in this trial as recently presented. The primary objective was met demonstrating superiority of the combination. The effect was greatest in the platinum-sensitive cohort. Response as adjudicated by independent...
review (both radiologists and a board of oncology specialists) was also superior for the combination. Overall survival are now mature at a median follow-up of 47.4 months, where 522 events (78%) have been recorded. The median overall survival for patients receiving PLD and trabectedin was 22.2 months compared to 18.9 months in the PLD alone arm (HR: 0.89, 95% CI: 0.72-1.02, P = 0.08, ASCO 2011, Abstr#5045). Toxicity assessment demonstrated that both regimens were well tolerated and dose intensity was able to be maintained. There were, however, more severe neutropenic episodes in the combination arm, as well as a higher rate of reversible grade 3/4 transaminase abnormalities. In the single agent arm, there was more hand-foot syndrome (19% vs. 4%) and stomatitis (12% vs. 3%), consistent with the higher dose of PLD (45).

**Epothilone Analogues**

Agents targeting the mitotic apparatus have generally fared well in ovarian cancer, notably the taxanes. Paclitaxel, the only taxane to be approved for ovarian cancer is joined by docetaxel as the two most intensively studied in this disease. However, mechanisms of resistance including the efflux pump, P-Glycoprotein and tubulin mutations, plague long-term cancer susceptibility to this class of agent. This challenge has provided an opportunity for new classes of taxanes and the epothilones. The epothilones are microtubule-targeting cytotoxics isolated and synthesized from the mycobacterium Sorangium cellulosum (46-48). Patupilone (EPO906) and ixabepilone are two epothilones in phase III investigation in ovarian cancer. Both agents induce mitotic cell cycle arrest and apoptosis by promoting tubulin polymerization and inhibiting depolymerization, leading to microtubule stabilization and suppression of microtubule dynamics. The mechanism is similar to paclitaxel and docetaxel but the class is far more potent, intrinsically active in paclitaxel-resistant cells and is less vulnerable to multidrug resistance genes such as, P-glycoprotein, BCRP, LRP and MRPs’s 1-5 and retains activity in the presence of β-tubulin mutation. Phase I/II data from each of these candidates have demonstrated promising anti-tumor activity in patients with recurrent ovarian cancer, including those with taxane-resistant disease (49-51). The most mature, in terms of clinical investigation is patupilone, which was investigated in an 829 patient trial against PLD (EXTEND trial, NCT00262990). The trial was reported via press release in May 2010 - reported demonstrating no significant benefit between the arms. Eligible patients for this trial included women with primary or secondary platinum-resistant (treatment-free interval of 6 months or less) ovarian cancer, considered measurable or evaluable. Overall survival is the primary endpoint.

**Kareinitecin**

The topoisomerase I inhibitors, such as topotecan and irinotecan, are active and commonly used compounds in patients with recurrent epithelial ovarian cancer. Topotecan is currently approved for use in this setting. However, unlike these water-soluble camptothecin analogues, Kareinitecin, a highly lipophilic demonstrates superior oral bioavailability and increased lactone stability (52). In addition, this compound was demonstrated preclinically to be more active than its hydrophilic cousins and less susceptible to tumor-mediated drug resistance, including P-glycoprotein/ MRPs and the BRCP. A phase II study conducted by the GOG in women with mixed chemo-sensitivity and up to 2 prior regimens of therapy demonstrated a response rate of 12% in 26 evaluable patients (53). Toxicity was mild (Grade 3 or 4 neutropenia, 19% and gastrointestinal 15%) compared to historical controls receiving topotecan. In light of these observations, a phase III trial has been launched in women with platinum and taxane resistant ovarian cancer with up to two prior regimens. All patients in this trial are required to have measurable disease. The study is randomizing 1:1 Kareinitecin (1.0 mg/m² IV, daily times 5, every 21 days) versus topotecan (1.5 mg/m² IV daily times 5, every 21 days). The primary endpoint of this 500 patient trial is PFS (NCT00477282). The study opened to accrual in February 2008.

**Other Novel Agents Under Investigation**

**Novel Cytotoxic Chemotherapy Trials in Ovarian Cancer**

There are several new compounds in development, which are modifications or enhancements of existing classes of cytotoxics. For instance, NKTR-102 (PEG-irinotecan) is a polyethylene glycol (PEG) conjugated camptothecin that inhibits topoisomerase I, an enzyme critical to successful DNA replication in tumor tissue. NKTR-102 is currently in Phase 2 development for the treatment of platinum-resistant ovarian cancer, metastatic breast cancer and kras mutant colorectal cancer. The agent was specifically engineered to provide a sustained release of irinotecan thereby providing a flatter, more continuous exposure to SN38. By reducing peak concentration and markedly prolonging half-life and overall exposure, it is possible that anti-tumor activity can be enhanced without a significant increase in dose limiting toxicity (DLT). In Phase 1 testing, NKTR-102 produced a confirmed RECIST n overall confirmed response rate by RECIST of 11% in patients with solid refractory tumors. A recently reported multi-institution, single agent, open label study of NKTR-102 accrued 71 heavily pretreated recurrent

**Table 3.** Primary and secondary endpoints in the Phase III trial (OVA-301) comparing Pegylated Liposomal Doxorubicin (PLD), the control group, to combination PLD + Trabectedin.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PLD</th>
<th>PLD + Trabectedin</th>
<th>HR (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS overall</td>
<td>5.8 mos</td>
<td>7.3 mos</td>
<td>0.79 (0.019)</td>
</tr>
<tr>
<td>PFS platinum-sensitive</td>
<td>7.5 mos</td>
<td>9.2 mos</td>
<td>0.73 (0.017)</td>
</tr>
<tr>
<td>PFS platinum-resistant</td>
<td>3.7 mos</td>
<td>4.0 mos</td>
<td>0.95 (0.75)</td>
</tr>
<tr>
<td>Response, platinum-sensitive</td>
<td>33%</td>
<td>47%</td>
<td>(0.0022)</td>
</tr>
<tr>
<td>Response, platinum-resistant</td>
<td>16%</td>
<td>23%</td>
<td>(0.26)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>19.4 mos</td>
<td>20.9 mos</td>
<td>0.85 (0.15)</td>
</tr>
</tbody>
</table>
ovarian cancer patients, who were randomized on one of two infusion schedules (36 on the q14d and 35 on the q21d schedule). Approximately 71% of patients with platinum-resistant disease had a platinum-progression free-interval of less than 3 months, with approximately half of the patients with platinum refractory disease (platinum-free interval less than 1 month). The median platinum treatment free interval in patients with platinum resistant/refractory disease was only 4 weeks. Overall RECIST response rates were observed in 24% and 29% of patients treated on the 2 dosing schedules. Toxicity was more favorable on the 21-day schedule. Common related grade 3/4 toxicities were diarrhea (14%), dehydration (6%), hypokalemia (9%), fatigue (14%), nausea (3%), and neutropenia (9%) (54). A Phase 3 study has been designed to further investigate the efficacy of this agent.

In addition, more than a dozen taxanes are being developed including those with properties to improve efficacy by overcoming drug resistance mechanisms, enhance tumor delivery and increase dose intensity or density. Other modification targets in this important drug class are toxicity (hypersensitivity, alopecia, neuropathy, fluid retention) and convenience. Taxanes, such as paclitaxel polyglumex (OPAXIO™, Cell Therapeutics, Inc.) and albumin-bound nanoparticle paclitaxel (nab-paclitaxel, Abraxane®, Abraxis Oncology) are being investigated in ovarian cancer therapy as maintenance and recurrence therapy, respectively. However, two emerging classes of therapeutics deserve discussion: anti-folate compounds and the Aurora kinase inhibitors.

Pemetrexed is an antifolate that inhibits multiple enzymes in the DNA synthesis pathway, and synergy between platinum and pemetrexed has been documented. To estimate the anti-tumor activity of pemetrexed in patients with persistent or recurrent platinum-resistant epithelial ovarian or primary peritoneal cancer who have failed on higher priority treatment protocols and to determine the nature and degree of toxicity of pemetrexed in this cohort of patients, a multicenter cooperative group phase II trial was conducted by the Gynecologic Oncology Group (GOG) (55). Pemetrexed 900 mg/m² was administered as an IV infusion over 10 minutes every 21 days and continued until disease progression or unacceptable adverse effects. A total of 51 patients were enrolled and received 259 cycles (median: 4; range 1 to 19) of pemetrexed. 40% of patients received 6 or more cycles. There was 1 complete response (CR) and 9 partial responses (PR) (21% overall response rate) with a median duration of response of 6.8 months. An additional 35% had stable disease for 4.1 months. Thirty-eight percent had progressive disease. The median PFS was 3+ months with OS 11.4+ months. The treatment was well tolerated; grade 3/4 toxicities included neutropenia (42%), leukopenia (25%), anemia (15%), and constitutional symptoms (15%). No treatment-related deaths were reported. A second trial in platinum-sensitive recurrent ovarian patients was recently reported. Matulonis and colleagues conducted a phase II study of carboplatin AUC 5 with pemetrexed 500 mg/m² both administered IV on day 1, with dexamethasone, B12, and folate premedication, and given every 21 d for 6-8 cycles (56). The primary objective was response rate. Other endpoints included toxicities, time to progression (TTP), and survival. Forty-five patients were enrolled with 41 evaluable for response, 27 of which completed at least 6 cycles. ORR was 51%, all PRs; there were also 2 unconfirmed PRs. Median TTP was 4.7 months with PFS of 7.6 months. Mean overall survival was 20 months.

Toxicity was evaluated in 44 patients. Grade 3/4 toxicities observed included the following: neutropenia (19 patients), thrombocytopenia (11), leukopenia (7), anemia (4), fatigue (4), nausea, diarrhea, and dizziness (2 each), and hypokalemia, vomiting, constipation, anorexia, memory impairment, and pulmonary embolism (1 each). The combination appears well-tolerated with significant activity in platinum-sensitive recurrent ovarian cancer.

The Aurora kinases (A, B and C) are a family of serine/threonine kinases that play an important role in both normal and aberrant cell division. Aurora A functions primarily in the G2/M phase of cell division and is associated with centrosome maturation, mitotic entry, spindle assembly, and microtubule organization (57,58). Overexpression of Aurora A is linked to tumorigenesis, resulting in tumor growth and metastases (58). The Aurora A kinase gene is located on chromosome 20q13, which is often amplified in malignancies including melanoma and cancers of the breast, colon, pancreas, ovaries, bladder, liver and stomach (57). Specifically, Aurora A activity is over-expressed in up to 83% of human epithelial ovarian cancers, and this over-expression has been identified as a negative prognostic marker in cancers such as breast and ovary, where such over-expression is common (59,60). In addition to promoting tumor growth, Aurora A over-expression is linked to resistance to common anti-mitotic agents used to treat ovarian cancer, such as paclitaxel and cisplatin (59, 60). Responses to the Aurora kinase inhibitors have been observed in patients with advanced solid tumors. Therapeutic development has included combination therapy, particularly with a taxane, where additive or synergistic effects have been observed. Studies have demonstrated that Aurora A activity can help to protect cells from taxane-induced apoptosis through activation of Akt (59,60). Inhibiting Aurora A activity may mitigate the protective effect Aurora A may have on taxane-induced apoptosis. In addition, Aurora A kinase inhibition can re-sensitize resistant ovarian cancer cell lines to taxane therapy. Off-target effects, including cardiotoxicity, have challenged non-selective inhibitors of the Aurora kinases. Nevertheless, specific Aurora A inhibitors, such as MLN8237, are entering the ovarian cancer portfolio.

Summary

While most drug development in ovarian cancer currently is centered on combining cytotoxic and biological agents to attack currently known targets, work continues in earnest to identify novel targets that can produce a direct apoptotic response in cancer cells. The need for such therapy is apparent given the current fact that even the best currently available agents are unable to produce a universal response. And even...
in patients who are fortunate enough to achieve complete clinical remission, the durability of that remission is frequently short. It is hoped the recently completed and ongoing clinical trials will produce an important step in improving cancer care for this population of patients.

References

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18. Aghajanian C. OCEANS: A randomized, double-blinded, placebo controlled phase III trial of chemotherapy with or without bevacizumab (BEV) in patients with platinum-sensitive recurrent epithelial ovarian cancer (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC). J Clin Oncol 2011;29:18s abstract LBA 5007


In 2008, the incidence of ovarian cancer in the European Union was as high as 45,299 and deaths from ovarian cancer numbered 28,840. Despite the advances in surgical therapy and expanding choices for adjuvant therapy, most women will likely relapse. For these women, treatments must be carefully considered, particularly given that treatment for recurrence is palliative, not curative.

In order to discuss treatment, one must have specific definitions of these populations. **Recurrent disease** refers to women who had a period of clinical remission followed by the unequivocal diagnosis of relapsed disease. If the interval from last treatment with platinum to recurrence (the **platinum-free interval**) is at least six months or longer, women are considered to have **platinum-sensitive** recurrent disease. An interval of less than six months defines those with **platinum-resistant** disease, which can also include those with persistent or progressive disease during front-line platinum based therapy, also called **primary refractory disease**. Another group of women to consider in this population is those women who develop a rising CA-125 without evidence of clinical or radiologic disease, termed **serologic relapse**.

Therapy for recurrent ovarian cancer can best be described along a disease-states model for ovarian cancer (Figure 1). In this model, the intent of treatment segregates into adjuvant therapy (with curative intent) and treatment for palliation (for chronic disease). The latter population is further divided into more homogenous groups of women, such as those with platinum-resistant and those with platinum-sensitive disease. The model gives probability estimates of entering each of these disease states based on prospective randomized trials, and the median amount of time expected for women to remain in these states. As one can see, ultimately women enter platinum-resistance, which predicts a poor prognosis and heralding death from disease.

Thinking of the population of women with recurrence in terms of their platinum-free interval has proven to be useful in several ways. First, it is used clinically to help determine the therapeutic options in this heterogenous population. Second, as noted in the disease-states model, it can also be used to render prognosis to those with platinum-resistance fairing not as well as those with platinum-sensitive disease. Finally, the interval is used in clinical research to develop new treatments and to test novel agents in women with recurrent ovarian cancer. In this section we will discuss the management and definitions of platinum-sensitivity, as well as the therapeutic options available to women diagnosed with recurrent disease.

**Serologic Relapse**

Women under follow-up for a diagnosis of ovarian cancer are routinely followed every 3-4 months at the end of treatment, at which time a complete examination is performed and CA-125 obtained. While sporadic but isolated rises in the CA-125 are not uncommon, one that is confirmed by repeat measurement can reliably predict the onset of recurrence which can be radiologically apparent within several months. The value of early diagnosis is unclear however, as recent data does not support treatment for a rising marker in the absence of radiologic or clinical symptoms. The MRC OV05/EORTC 55955 figure 1. Disease States Model for Ovarian Cancer

directly looked at the value of treatment for relapse based on CA-125 versus measurable disease recurrence. It enrolled 1442 women who had achieved a clinical complete response after adjuvant platinum-based chemotherapy. At the time of CA-125 relapse, patients were then randomly assigned to treatment based on serologic progression versus delayed treatment until clinical or symptomatic progression was noted. Ultimately 37% were randomized to early treatment (n=265) versus delayed treatment (n=264). Time to second chemotherapy was significantly shorter in the early versus the delayed treatment group (0.8 vs. 5.6 months, respectively; p<0.0001) but despite this, there was no difference in overall survival (median, 26 months; absolute difference at 2 years of -0.1%).

For women who relapse serologically, endocrine therapy may play a role. The Gynecologic Oncology Group evaluated the use of tamoxifen 20 mg twice a day for this population and demonstrated an objective response rate of 18%. Another trial from the Harvard Comprehensive Cancer Center enrolled 53 women with asymptomatic but recurrent mullerian cancers and demonstrated an overall response rate of 2% with stable disease of at least 6 months in 15%. In the absence of data suggesting benefit, the use of chemotherapy in serologic relapse is not recommended.

**Platinum Sensitive Disease**

Women whose platinum-free interval (PFI) is 6 months or longer can expect to respond to further chemotherapy with response rates to platinum re-treatment ranging from 27% for a PFI of 12 months to 72% after 24 months. Several randomized trials have confirmed platinum-based combination therapy as the preferred regimen of choice in this group of women (Table 1). The ICON4/AGO-OVAR2.2 evaluated single agent platinum versus platinum plus paclitaxel. Combination therapy was associated with a PFS of 13 months which was statistically significant to single agent cisplatin, where the PFS was 10 months. In addition, median survival was also prolonged with the combination compared to single agent cisplatin, 29 versus 24 months, respectively. Gemcitabine and carboplatin was also evaluated against carboplatin in an international trial lead by the AGO (Arbeitsgemeinschaft Gynaekologische Onkologie). Again, gemcitabine plus carboplatin was associated with a longer progression free survival than single agent carboplatin, 8.6 versus 5.8 months (Hazard ration (HR) 0.72 (95% CI, 0.58 to 0.90). Recently, Pujade-Lauraine et al reported results of the CALYPSO study, which evaluated the combination of carboplatin with either pegylated liposomal doxorubicin (PLD) or paclitaxel in a non-inferiority design. Overall 976 women participated in this trial and with median follow-up of 22 months, the progression free survival for the carboplatin with PLD was statistically non-inferior to carboplatin and paclitaxel; progression free survival was 11 months versus 9 months, respectively. In addition, carboplatin with PLD had a better toxicity profile with less alopecia, neuropathy, hypersensitivity, and nonhematologic toxicity leading to discontinuation.

While re-treatment with platinum analogs remains the preferred treatment, re-challenging patients with either cisplatin or carboplatin carries a risk for hypersensitivity, which can prove to be fatal. For the allergic patient, however, one may re-treat with platinum using published desensitization protocols in an inpatient supervised setting. One such protocol from the Dana Farber Cancer Institute is illustrated in Figure 2. It is essential that nursing is familiar and comfortable with the signs and symptoms of a drug allergic reaction and the proper rescue medications be readily available to treat hypersensitivity reactions.

For patients who are either not candidates or would rather not proceed with platinum re-treatment multiple options are still available and women deemed to be platinum-sensitive are far more likely to respond to non-platinum treatments, compared to those with platinum-resistant disease. Monk et al

<table>
<thead>
<tr>
<th>Citation</th>
<th>Randomization</th>
<th>Clinical Benefit (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tr>
<td>ICON-4/AGO-OVAR2.2</td>
<td>Carboplatin vs. Carboplatin/Paclitaxel</td>
<td>54</td>
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<td>24</td>
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<tr>
<td>AGO/NCIC/EORTC</td>
<td>30</td>
<td>39</td>
<td>5.8</td>
<td>17</td>
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<tr>
<td>Pfisterer et al. J Clin Oncol 2006;24:4699-707.</td>
<td>47</td>
<td>38</td>
<td>8.6</td>
<td>18</td>
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<tr>
<td>SWOG S0200</td>
<td>Carboplatin vs. Carboplatin/Gemcitabine</td>
<td>32</td>
<td>8</td>
<td>18</td>
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<tr>
<td>Alberts et al. Gynecol Oncol 2008; 108:90-4.</td>
<td>67</td>
<td>NR</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>CALYPSO</td>
<td>Carboplatin vs. Carboplatin/PLD</td>
<td>NR</td>
<td>9</td>
<td>NR</td>
</tr>
</tbody>
</table>
report a randomized trial of pegylated liposomal doxorubicin (PLD) versus PLD with the novel biologic agent ecteinascidin (ET-743, Trabectedin) where over 60% of women treated had platinum-sensitive disease. The primary objective was progression-free survival. The combination of ET-743 and PLD was associated with a statistically significant advantage in PFS over PLD alone (7.3 vs. 5.8 months, p=.019). However, this survival advantage appeared restricted to women with platinum-sensitive relapse where the PFS was 9.2 months with combination versus 7.5 months with single agent PLD (p=.017). In the platinum-resistant cohort, the PFS was essentially unchanged at approximately 4 months.

Beyond this, single agents are active in platinum-sensitive recurrence. As an example, topotecan 1.5 mg/m² administered daily for 5 days and repeated every 3 weeks has an overall response rate of 33% with a stable disease rate of 48. The agents with phase II or III data supporting their activity in recurrent ovarian cancer are listed in Table 2.

In summary, the agents of choice for women who relapse beyond six months from end of platinum-based treatment remain quite extensive. The standard option consists of a platinum-based combination, but one must acknowledge the risks of re-treatment in this cohort and balance this consideration with the potential benefits. For those not candidates for platinum re-treatment, one would expect benefits with the use of any one of the standard agents available for the treatment of relapsed disease. An algorithm for the management of platinum-sensitive relapse is presented in Figure 3.

### Platinum Resistant Disease

Platinum resistant ovarian cancer, defined as progression within six months of completing a platinum-based therapy, presents a therapeutic dilemma as response rates and survival are universally poor with complete response the rare exception rather than the rule. This makes the attention to quality of life far more important in any decisions regarding further treatment. Retrospective data suggests that patients with malignant bowel obstructions related to recurrent ovarian cancer will not regain function with chemotherapy. In addition, patients experiencing a significant functional decline manifest either as a poor performance status, anorexia, hypoalbuminemia, and/or refractory ascites or pleural effusions, may be at greater risk of treatment-related toxicity than any potential for benefit. As such, patients approaching the end-of-life should not be offered further treatment and instead managed symptomatically in the terminal phases of their illness.

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**Figure 2.** Protocol for carboplatin desensitization.

1. Calculate total Carboplatin dose using Calvert or Cockroft-Gault formula (Total dose = X).
2. Prepare three infusion solutions diluted in 250 ml of D5 water using gradually increasing concentrations of Carboplatin: Solution A = X/100; Solution B=X/10; Solution C=X.
3. Premedicate patient with diphenydramine 25 mg and famotidine 20 mg intravenously, 30 minutes prior to initiation of infusion.
4. Starting with Solution A: Begin at a rate of 2 ml/hr. Gradually increase rate of infusion every 15 minutes to 5 ml/hr, then 10 ml/hr, then to 20 ml/hr. At completion, discard bag.
5. Go to Solution B: Begin at a rate of 5 ml/hr. Gradually increase rate of infusion every 15 minutes to 10 ml/hr, 20 ml/hr, then 40 ml/hr. At completion, discard bag.
6. Go to Solution C: Begin at a rate of 10 ml/hr. Gradually increase rate of infusion every 15 minutes to 20 ml/hr then 40 ml/hr. If tolerated, infuse remaining solution at 75 ml/hr for a total of 184.4 minutes.

Adapted from CW Lee, et al. Gyencol Oncol 2004; 370-76.

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**Figure 3.** Management algorithm for recurrent ovarian cancer.
The overall response rate to chemotherapy in this cohort varies considerably but range from 6-20% in most trials. Gemcitabine (800-1000 mg/m² on a 2-3 week on/1-week off schedule) has shown a response rate of 18% in single agent use. Its toxicity profile is mild with no neurotoxicity, reversible myelosupression, and infrequent alopecia. Taxanes, either paclitaxel or docetaxel, have also been used in the platinum resistant. Weekly paclitaxel (60-80 mg/m² on a 3-on/1-off schedule) is also an effective regimen with a reported 20% response rate. Side effects of these drugs are usually manageable although pre-existing neuropathy may be exacerbated. PLD is active in platinum resistance and is well tolerated in terms of toxicity and multiple prior lines of chemotherapy. Long-term use has not been associated with cardiotoxicity that can be seen with doxorubicin, although cardiac function should still be monitored with MUGA scans. Gordon et al., conducted the randomized phase III trial of PLD and topotecan in recurrent ovarian cancer. The overall response rates were 20% and 17% respectively (p=0.393). Complete responders constituted <5% in either treatment arm. Within the platinum-resistant subgroup, overall response was 12.3% and 6.5%, respectively. Re-treatment with a platinum may be of some benefit though one retrospective from Memorial Sloan-Kettering Cancer Center suggests that it may be reasonable in selected patients who had a response to initial platinum-based therapy and had received no more

### Table 2. Cytotoxic agents with activity in recurrent ovarian cancer reported in phase II or III trials.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Schedule</th>
<th>Platinum-Sensitive</th>
<th>Platinum-Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ORR (%)</td>
<td>SD (%)</td>
</tr>
<tr>
<td>Etoposide 50 mg/m²</td>
<td>Daily for 21 days every 4 weeks</td>
<td>34</td>
<td>NR</td>
</tr>
<tr>
<td>Topotecan 1.5 mg/m²/daily</td>
<td>Days 1-5 every 21 days</td>
<td>29</td>
<td>38</td>
</tr>
<tr>
<td>Pegylated Liposomal</td>
<td>Every 4 weeks</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>Doxorubicin 50 mg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinorelbine 30 mg/m²</td>
<td>Days 1,8 every 3 weeks</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>Gemcitabine 1000 mg/m²</td>
<td>Days 1,8, [15] followed by one week rest</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>Paclitaxel poliglumex 175 mg/m²</td>
<td>Every 21 days</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>Topotecan 4 mg/m²</td>
<td>Weekly</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>nAb-paclitaxel 260mg/m²</td>
<td>Every 3 weeks</td>
<td>64</td>
<td>32</td>
</tr>
<tr>
<td>Ifosfamide 1.2 g/m²</td>
<td>Daily for 5 days every 21 days.</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td>Docetaxel 75-100 mg/m²</td>
<td>Every 3 weeks</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>Hexamethylmelamine 260 mg/m²</td>
<td>Daily for 2 weeks every 28 days</td>
<td>10</td>
<td>31</td>
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<tr>
<td>Paclitaxel 80 mg/m²</td>
<td>Weekly</td>
<td>21</td>
<td>46</td>
</tr>
<tr>
<td>Capecitabine 2000 mg/m²</td>
<td>PO 21-days every 4 weeks</td>
<td>8</td>
<td>61</td>
</tr>
</tbody>
</table>

ORR=Overall Response Rate; SD=Stable Disease; PFS=Progression Free Survival. NR=not reported.

*Trial population in Ferrandina study had a platinum-free interval up to 12 months.*
than three intervening regimens. The notion that prolonging the platinum-free interval with the use of non-platinum agents may improve response rate upon re-treatment has not been validated; one retrospective study conducted by the SOCRATES and MITO investigators showed lower response rates among women who received subsequent platinum therapy after non-platinum treatment.

Complete responses and greater response rates in general are seen with multi-agent treatment. However, multi-drug treatment often has more toxic side effects, is more expensive, and has a less convenient dosing schedule. Several phase II trials have evaluated combination therapy in the context of platinum-resistant disease. In one conducted by the GOG, Brewer et al. reported that cisplatin and gemcitabine had a response rate of 16% with a median progression-free survival of 5 months, which approximates what has been reported in single agent trials. Another phase III trial reported by Vergote et al compared PLD with or without canfosfamide. Unfortunately the study was closed before completion, however interim analysis showed a positive trend for the PLD/canfosfamide cohort although no statistically different progression-free survival.

A very promising agent for this population is bevacizumab. This is a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF) receptor to inhibit tumor growth by blocking angiogenesis. The Gynecologic Oncology Group evaluated bevacizumab as a single agent in women with relapsed or refractory ovarian cancer, having received up to two prior regimens. While stratification by platinum-sensitivity is difficult, the results were quite promising with an overall response rate of 21% noted and a six month progression-free survival of 40%. Since then, two further studies appeared to confirm the activity seen in this trial. Garcia et al. combined bevacizumab with metronomically dosed cyclophosphamide at 50mg daily and demonstrated a 28% response rate with a 57% six month progression-free survival. Finally, Cannistra et al. reported the results of a corporate sponsored phase II trial in recurrent ovarian cancer as well showing a 16% overall response rate with a 6-month progression-free proportion of 27%.

Having acknowledged that bevacizumab is one of the most promising agents for the treatment of relapsed disease, this enthusiasm must be tempered by its toxicity profile. In addition to well-documented side effects such as hypertension, difficulties with wound-healing, bleeding, and vascular thromboembolic events, women with relapsed ovarian cancer appear to be at risk for bowel perforations with an incidence that has yet to be truly defined, but in trials have ranged from 0-13%. Studies are underway to characterize the patients deemed at increased risk for this event, but to date, the risk profile is not fully understood. Still, patients with tumor implants along bowel, prior or current history of bowel obstruction, or treated with multiple lines of therapy have been used to define a high-risk subset.

In summary, women with platinum-recurrent disease must be approached with thoughtful deliberation. The treatment intent here is palliative and equal consideration should be given to quality of life as it is to treatment effectiveness. Patients with rapidly advancing disease, poor performance status, or nutritionally compromised are as likely to die from treatment-related complications as they are from disease, and may be best served by discontinuing active therapy in favor of hospice or supportive care. For those who are candidates for further treatment, single agents should be employed and evaluation for effectiveness be performed at regular intervals to reduce the chances of delivering futile therapy. Treatments should continue in the absence of disease progression as long as the therapy remains tolerable. As options continue to expand, it is likely that patients with advanced disease can continue to be treated along a paradigm of chronic illness. An algorithm for the management of the patient with platinum-resistance is given in Figure 3.

Conclusions

Optimal treatment in recurrent ovarian cancer still poses unanswered questions. There are many reasonable options including single and combination agents with or without a platinum. Performance status, co-morbidities, previous toxicities, and symptoms are important considerations in choosing a chemotherapeutic regimen in the recurrent setting. Treating to disease stabilization or disease progression is still controversial. Data suggests that continuing tolerated chemotherapy that provides disease stabilization yields survival benefits similar to therapy that produces partial responses. It should be remembered that treatment is palliative and toxicities should not outweigh the benefit to quality of life.

References

Cytoreductive surgery followed by intravenous (iv) paclitaxel/platinum-based chemotherapy is the standard treatment of advanced ovarian cancer, able to achieve a clinical complete response rate of approximately 50%, a pathological complete response rate of 25 to 30%, a median progression-free survival (PFS) of 14 to 21 months, and a median overall survival (OS) of 26 to 57 months (Table 1) (1). The role of neoadjuvant chemotherapy (NACT) followed by interval debulking surgery has been long debated. In a large multicenter trial comparing primary surgical cytoreduction followed by chemotherapy versus NACT followed by interval debulking surgery in 670 patients with stage IIIC - IV ovarian cancer, the hazard ratio (HR) of death for women assigned to NACT compared with those assigned to primary cytoreduction was 0.98 (90% confidence interval (CI), 0.84-1.13) and the HR of progression was 1.01 (90% CI, 0.89-1.15) (2). Complete resection of all macroscopic disease either at primary or interval surgery was the strongest independent prognostic variable for OS. No significant advantages of NACT or primary debulking surgery were observed with respect to adverse effects, quality of life, or postoperative morbidity or mortality. Primary cytoreductive surgery followed by chemotherapy remains the standard treatment. However, NACT followed by interval debulking can represent a valid alternative option for selected patients with stage IIIIC-IV disease.

Randomized studies comparing paclitaxel plus cisplatin versus paclitaxel plus carboplatin have shown that the two regimens are equally effective, with the carboplatin combination being well tolerated. In 2005, a Gynecologic Cancer Intergroup (GCIG) consensus meeting stated that the standard systemic treatment for advanced ovarian cancer was iv carboplatin dosed to an area under the concentration–time curve (AUC) of 5–7.5, in combination with iv paclitaxel at a dose of 175 mg/m² (3-hour infusion) every 3 weeks for six cycles (3). Two recent randomized phase III trials, Gynecologic Oncology Group (GOG) 218 and International Collaborative Ovarian Neoplasm (ICON) 7, reported promising results with the addition of iv bevacizumab to standard first-

### Table 1.

Randomised trials assessing paclitaxel/platinum-based regimens in advanced ovarian cancer.

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>pts</th>
<th>RD</th>
<th>Regimen</th>
<th>Median PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGuire (1996)* (GOG111)</td>
<td>410</td>
<td>&gt;1cm</td>
<td>CTX 750 mg/m² + CDDP 75 mg/m²</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TAX 135 mg/m² (24-h) + CDDP 75 mg/m²</td>
<td>18 (p&lt;0.001)</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CTX 750 mg/m² + CDDP 75 mg/m²</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Piccart (2000)* (OV 10)</td>
<td>680</td>
<td>any</td>
<td>TAX 175 mg/m² (3-h) + CDDP 75 mg/m²</td>
<td>16 (p=0.0005)</td>
<td>36</td>
</tr>
<tr>
<td>Neijt (2000)*</td>
<td>213</td>
<td>any</td>
<td>TAX 175 mg/m² (3-h) + CDDP 75 mg/m²</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TAX 175 mg/m² (3-h) + CBDCA AUC 5</td>
<td>p=ns</td>
<td>32</td>
</tr>
<tr>
<td>Muggia (2000)* (GOG132)</td>
<td>648</td>
<td>&gt;1cm</td>
<td>CDDP 100 mg/m²</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TAX 200 mg/m² (24-h)</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>Ozols (2003)* (GOG 158)</td>
<td>792</td>
<td>&lt;1cm</td>
<td>TAX 135 mg/m² (24-h) + CDDP 75 mg/m²</td>
<td>14 (p=ns)</td>
<td>26</td>
</tr>
<tr>
<td>DuBois (2003)* (AGO-OVAR-3)</td>
<td>798</td>
<td>any</td>
<td>TAX 135 mg/m² (24-h) + CDDP 75 mg/m²</td>
<td>**</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TAX 175 mg/m² (3-h) + CBDCA AUC 7.5</td>
<td>21 (p=ns)</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TAX 185 mg/m² (3-h) + CDDP 75 mg/m²</td>
<td>19 (p=ns)</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TAX 185 mg/m² (3-h) + CBDCA AUC 6</td>
<td>17 (p=ns)</td>
<td>43</td>
</tr>
</tbody>
</table>

(*papers cited in ref. 1) ; **CDDP vs TAX + CDDP, p=ns; TAX vs CDDP, p <0.001).
Legend: pts, patients; RD, residual disease; CTX, cyclophosphamide; CDDP, cisplatin; TAX, paclitaxel; CBDCA, carboplatin; AUC, area under curve.
line IV chemotherapy in this clinical setting (4,5) (Table 2). The GOG 218 study showed that the use of bevacizumab 15 mg/kg during and after paclitaxel/carboplatin-based therapy improved PFS compared with chemotherapy alone (p<0.0001) (4). Grade 3-4 hypertension and > grade 3 gastrointestinal perforation, hemorrhage or fistula occurred in 10% and 2.3% of the patients who received concurrent and maintenance bevacizumab. Similarly, ICON-7 trial demonstrated that concurrent bevacizumab 7.5 mg/kg and paclitaxel/carboplatin-based chemotherapy followed by maintenance bevacizumab for 12 additional cycles improved PFS with respect to standard chemotherapy alone (p=0.0041) (5). Adverse events were consistent with previous bevacizumab studies.

Table 2. Randomised trials assessing paclitaxel/carboplatin-based regimens + bevacizumab in ovarian cancer.

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>pts</th>
<th>Stage</th>
<th>Regimen</th>
<th>median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burger (2010)</td>
<td>1873</td>
<td>III-IV</td>
<td>Arm 1: TAX 175 mg/m² + CBDCA AUC6 for 6 cycles + placebo cycles (2-22)</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm 2: TAX 175 mg/m² + CBDCA AUC6 for 6 cycles + concurrent BEV 15 mg/kg (cycles 2-6) + placebo maintenance (cycles 7-22)</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm 3: TAX 175 mg/m² + CBDCA AUC6 for 6 cycles + concurrent BEV 15 mg/kg (cycles 2-6) + maintenance BEV 15 mg/kg (cycles 7-22)</td>
<td>14.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm 3 vs Arm 1, HR= 0.717 (95% CI, 0.625-0.824), p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm 2 vs Arm 1, HR= 0.908 (95% CI, 0.795-1.04), p=ns</td>
<td></td>
</tr>
<tr>
<td>Perren (2010)</td>
<td>1528</td>
<td>I-IIa **</td>
<td>Arm 1: TAX 175 mg/m² + CBDCA AUC6 for 6 cycles</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm 2: TAX 175 mg/m² + CBDCA AUC6 + concurrent BEV 7.5 mg/kg for 6 cycles + maintenance BEV 7.5 mg/kg for 12 cycles or until progression</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIb-IV*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*any residual disease
**grade 3, clear cell histology;
Legend: pts, patients; PFS, progression-free survival; TAX, paclitaxel; CBDCA, carboplatin; AUC, area under curve; BEV, bevacizumab; HR= hazard ratio; 95% CI, 95% confidence interval

Some randomised phase III trials revealed that intraperitoneal chemotherapy improved the clinical outcome of patients who had small residual disease (RD) when compared with standard IV treatment and these results were confirmed by a Cochrane meta-analysis (6-8) (Table 3 and Table 4). This meta-analysis enrolling 1819 patients showed that women who received an intraperitoneal component of chemotherapy experienced a better PFS (HR, 0.79; 95% CI, 0.69-0.90) and a better OS (HR, 0.79; 95% CI, 0.70-0.90) (8). There was greater serious toxicity as for gastrointestinal effects, pain and fever but less otoxicity with the intraperitoneal treatment, whereas the meta-analysis could not draw conclusions on haematological, renal, neurological and lung toxicity, as the data were too heterogeneous and largely depended on the regimen used. In 2006 the improved survival data resulting from GOG 172 trial led to a National Cancer Institute (NCI) Clinical Announcement recommending that consideration should be given to a regimen containing intraperitoneal cisplatin and a taxane in patients with optimal stage III ovarian cancer (http://ctep.cancer.gov/highlights/ovarian.html). The International Consensus Conference on intraperitoneal chemotherapy in ovarian cancer patients in Innsbruck, Austria, 17–18 February, 2006, provided the first worldwide consensus following the publication of the NCI announcement, and stated that, due to specific problems and complications, this treatment modality cannot be considered as the new standard although it should be proposed to patients as a valid alternative (9). This therapy should be anyway administered only in referral centres experienced with the management of typical side-effects and complications.

Data from meta-analysis are not completely convincing as for the superiority of intraperitoneal chemotherapy in patients with small RD, also because this systematic review has inappropriately pooled results from confounded trials in which different drugs and different doses of drugs were given in the control and intraperitoneal treatment arms (10-13). Therefore, it is not possible to assess which component of treatment is responsible for improving clinical outcome. In addition, none of the trials has used the internationally accepted standard of care, i.e IV paclitaxel plus carboplatin, as control arm. For instance in the study of Markman et al. (6), the experimental arm differed in many ways from the control arm. Indeed, in the experimental arm the first two cycles of IV carboplatin were administered at a high dose (AUC 9) and the dosages of intraperitoneal cisplatin (100 mg/m²) were higher than intravenous cisplatin (75 mg/m²) (11). The toxicity of experimental arm was very high, and the authors concluded that intraperitoneal chemotherapy used in this study could not be recommended as standard of care. In the GOG 172
trial (7) the benefit in term of OS for intraperitoneal arm was weak (p=0.03), and the advantage in term of PFS was of borderline significance (p=0.05) (11). The OS curves differed only after 15 months, which could be caused by salvage treatment. The authors of GOG 172 trial should present details of second-line therapy and should show that there was no meaningful imbalance that could have been responsible for the observed OS differences. Moreover, the number of intraperitoneal versus retroperitoneal recurrences was not different between the two groups. In the experimental arm, a higher dose of cisplatin (100 mg/m² versus 75 mg/m²) was given and paclitaxel was administered both on day 1 and on day 8, and these differences could have influenced the OS results. A Japanese trial (14), showing the superiority of systemic dose dense weekly paclitaxel (80 mg/m² week 1, 8, and 15) plus carboplatin AUC 6 (day 1) versus conventional paclitaxel (180 mg/m² week 1) plus carboplatin AUC 6 (day 1), further supports the possibility that the schedule of paclitaxel administration in the GOG 172 experimental arm could be relevant to explain the better OS of this arm, other than the intraperitoneal route of administration. The patient population of the GOG trial 172 was similar to that of the GOG 158 trial, and to the patient collectives with RD < 1 cm who were treated in the trials AGO-OVAR 3 (see Table 1, cited in ref. 10), AGO-OVAR 5 (cited in ref. 10), and AGO-OVAR 7 (cited in ref. 10). Each of these four trials randomised more patients than those enrolled in the GOG 172 study. Even if direct data comparison is not possible, it is worth noting that in all of the four trials significantly longer median OS was observed with standard iv paclitaxel/ carboplatin than with control arm of GOG 172 study (57.4, 59.5, 57.0, and 56.5 months , respectively, versus 49.7 months) (10). The paclitaxel/ carboplatin combination has shown more favourable toxicity profile and better quality of life compared with paclitaxel/cisplatin regimen used in GOG 158 and AGO-OVAR 3 study. Furthermore, in both trials paclitaxel/ carboplatin showed a nonsignificant trend for better clinical

## Table 3. Intra-peritoneal chemotherapy in advanced epithelial ovarian cancer: randomised trials .

<table>
<thead>
<tr>
<th>Authors (year )</th>
<th>pts</th>
<th>RD</th>
<th>ip arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zylberberg (1986)</td>
<td>20</td>
<td>not reported</td>
<td>iv. DOX 20 mg X2</td>
<td>iv. DOX 35 mg X2</td>
</tr>
<tr>
<td>Kirmani (1994)</td>
<td>87</td>
<td>any</td>
<td>ip. CDDP 200 mg/m²</td>
<td>iv. CDDP 100 mg/m²</td>
</tr>
<tr>
<td>Alberts (1996)</td>
<td>654</td>
<td>≤2 cm</td>
<td>ip. CDDP 100 mg/m²</td>
<td>iv. CDDP 100 mg/m²</td>
</tr>
<tr>
<td>SWOG-GOG 104</td>
<td></td>
<td></td>
<td>iv. CTX 600 mg/m²</td>
<td>iv. CTX 600 mg/m²</td>
</tr>
<tr>
<td>Markman (2001)</td>
<td>523</td>
<td>≤1 cm</td>
<td>iv. CBDA AUC9</td>
<td>iv. TAX135 mg/m² (24-h)</td>
</tr>
<tr>
<td>GOG 114</td>
<td></td>
<td></td>
<td>every 4 weeks x 2 cycles then</td>
<td>iv. CDDP 75 mg/m²</td>
</tr>
<tr>
<td>SWOG, ECOG</td>
<td></td>
<td></td>
<td>every 3 weeks x 6 cycles</td>
<td>every 3 weeks x 6 cycles</td>
</tr>
</tbody>
</table>

The authors reported a significant increase in the number of pts alive and disease-free in the ip. arm (p<0.05), but no further statistics were given.

No significant difference in PFS and OS between the two arms

<table>
<thead>
<tr>
<th>Authors (year )</th>
<th>pts</th>
<th>RD</th>
<th>ip arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG-GOG 104</td>
<td>654</td>
<td>≤2 cm</td>
<td>ip. CDDP 100 mg/m²</td>
<td>iv. CDDP 100 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>iv. CTX 600 mg/m²</td>
<td>iv. CTX 600 mg/m²</td>
</tr>
<tr>
<td>Markman (2001)</td>
<td>523</td>
<td>≤1 cm</td>
<td>iv. CBDA AUC9</td>
<td>iv. TAX135 mg/m² (24-h)</td>
</tr>
<tr>
<td>GOG 114</td>
<td></td>
<td></td>
<td>every 4 weeks x 2 cycles then</td>
<td>iv. CDDP 75 mg/m²</td>
</tr>
<tr>
<td>SWOG, ECOG</td>
<td></td>
<td></td>
<td>every 3 weeks x 6 cycles</td>
<td>every 3 weeks x 6 cycles</td>
</tr>
</tbody>
</table>

Legend: RD, residual disease; ip, intraperitoneal; iv, intravenous; DOX, doxorubicin; 5-FU, 5-fluorouracil; CDDP, cisplatin; BLEO, bleomycin; VBL, vinblastine; IFO, ifosfamide; VP-16, etoposide; CTX, cyclophosphamide; SWOG, South West Oncology Group; CBDCA, carboplatin; AUC, area under curve; TAX, paclitaxel; GOG, Gynecologic Oncology Group; ECOG, Eastern Cooperative Oncology Group.
outcome in optimally debulked patients. These favourable data led the GCIG Ovarian Cancer Consensus Conference to state that any new regimen should be compared with the actual standard iv paclitaxel/ carboplatin (15). Moreover, it should be taken into account that, in advanced ovarian cancer, retroperitoneal lymph node and pleural metastases are often present, and that intraperitoneal chemotherapy offers no advantage in these metastatic sites.

The potential for catheter related complications, abdominal pain, and toxicities needs to be taken into consideration for decision making in each individual woman potentially candidate for intraperitoneal chemotherapy (8,12). Data from the studies included in the Cochrane meta-analyses showed that catheter blockage occurred in 9 to 13%, catheter-related infections in 5 to 26%, and severe abdominal pain in 18 to 22%, respectively, of the patients enrolled in intraperitoneal arm. Moreover, only 25% to 77% (42% in the GOG 172 trial) of these latter completed the planned six cycles of chemotherapy, and catheter-related complications were the primary reason for discontinuation of intraperitoneal treatment. A detailed evaluation of intraperitoneal catheter-related outcomes in the GOG 172 trial showed that patients who had a left colonic or rectosigmoid resection were less likely to receive all planned doses of intraperitoneal chemotherapy (16). It is well known that procedures such aggressive upper abdominal surgery, radical pelvic surgery and bowel resection are commonly required to achieve optimal surgical cytoreduction. An aggressive upper abdominal surgery may cause extensive adherences preventing an adequate fluid diffusion in supramesocolic spaces and diaphragmatic surfaces. A pelvic retro-peritoneal approach often including recto-sigmoid resection is able to achieve a complete pelvic cytoreduction with acceptable morbidity in almost all patients with a frozen pelvis. Recto-sigmoidal surgery can be associated with a gross contamination of the operative field, postoperative infections, fistulas, and leaks at anastomotic sites, and in this case the catheter for intraperitoneal treatment should not be inserted during primary surgery. Catheter placement should be performed after 3 weeks at least, with not negligible psychological and organizing problems. Toxicity profile appears to be similar for women who receive intraperitoneal chemotherapy after optimal primary cytoreduction and for those who undergo this treatment after NACT and interval debulking surgery (17). There are limited data regarding long-term complications following intraperitoneal paclitaxel and cisplatin. Recently., Chan et al (18) reported the case of a patient who developed bowel obstruction secondary to peritoneal fibrosis attributed to prior intraperitoneal chemotherapy. Surgical exploration revealed an obliterated peritoneal cavity with multiple sclerotic adhesions encasing

### Table 4. Intraperitoneal chemotherapy in advanced epithelial ovarian cancer: randomised trials.

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>pts</th>
<th>RD</th>
<th>ip arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyzos (1999)</td>
<td>90</td>
<td>any</td>
<td>ip.CBDA 350 mg/m² iv.CTX 600 mg/m² every 3-4 weeks for 6 cycles</td>
<td>iv.CBDA 350 mg/m² iv.CTX 600 mg/m² every 3-4 weeks for 6 cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>median PFS median OS</td>
<td>18 months 26 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19 months (p=ns) 25 months (p=ns)</td>
</tr>
<tr>
<td>Gadducci (2000) (GONO)</td>
<td>113</td>
<td>&lt;2 cm</td>
<td>ip. CDDP 50 mg/m² iv. EPIDOX 60 mg/m² iv. CTX 600 mg/m² every 4 weeks for 6 cycles</td>
<td>iv. CDDP 50 mg/m² iv. EPIDOX 60 mg/m² iv. CTX 600 mg/m² every 4 weeks for 6 cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>median PFS median OS</td>
<td>42 months 67 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25 months (p=ns) 51 months (p=ns)</td>
</tr>
<tr>
<td>Yen (2001)</td>
<td>132</td>
<td>&lt;1 cm</td>
<td>ip. CDDP 100 mg/m² iv. DOX/EPIDOX 50 mg/m² iv. CTX 500 mg/m² every 3 weeks for 6 cycles</td>
<td>iv. CDDP 50 mg/m² iv. DOX/EPIDOX 50 mg/m² iv. CTX 500 mg/m² every 3 weeks for 6 cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>median OS</td>
<td>43 months 48 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48 months (p=ns)</td>
</tr>
<tr>
<td>Armstrong (2006) GOG 172</td>
<td>429</td>
<td>&lt;1 cm</td>
<td>iv. TAX 135 mg/m² (24-h) d1</td>
<td>iv. TAX 135 mg/m² (24-h) d1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ip. CDDP100 mg/m² d2 ip. TAX 60 mg/m² d 8 every 3 weeks for 6 cycles</td>
<td>iv. CDDP 75 mg/m² d2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>median PFS median OS</td>
<td>24 months 66 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18 months (p=0.05) 50 months (p=0.03)</td>
</tr>
</tbody>
</table>

Legend: pts, patients; RD, residual disease; ip., intraperitoneal; iv., intravenous; CBDA, carboplatin; CTX, cyclophosphamide; CDDP, cisplatin; EPIDOX, epirubicin; DOX, doxorubicin; TAX, paclitaxel
the small bowel and no evidence of ovarian cancer recurrence.

Based on these considerations, the iv paclitaxel/ carboplatin-based chemotherapy should be still considered as the standard of care for patients with advanced ovarian cancer, and intraperitoneal chemotherapy should be used only in the context of properly designed clinical trials. The addition of bevacizumab to iv paclitaxel/ carboplatin-based chemotherapy could represent a new standard in this clinical setting. As far as intraperitoneal chemotherapy is concerned, it remains unclear which group of patients will really benefit from this treatment, which is the optimal drug, dose and combination, and what is the real benefit of intraperitoneal treatment alone. The future trials must either assess intraperitoneal therapy in combination with the standard treatment or address the issue of route of administration for equivalent dosages and schedules of the same drugs, and not a mosaic of these questions. In addition, these trials should investigate intraperitoneal regimens that are less toxic than those used in the GOG trials, and which could be combined with molecular targeted therapies. The GOG 252 phase III trial is currently comparing bevacizumab in combination with paclitaxel and intraperitoneal cisplatin or carboplatin versus bevacizumab in combination with iv paclitaxel and carboplatin (19).

References

Review of Major Gynecologic Oncology Group Trials in the Management of Gynecologic Cancer

Matthew F. Kohler, MD
William T. Creasman, MD

Introduction
Gynecologic Cancer affects millions of women worldwide. In the early 1970’s, the Gynecologic Oncology Group (GOG) was established as a collaborative, multidisciplinary organization devoted to the rigorous development of clinical trials centered around the treatment of gynecologic cancer. With the commencement of activities, five protocols were approved, all phase III, with three of these being in ovarian cancer, both early and late stage, one in advanced cervical disease, and the fifth was a surgical pathological study of stage IA cervical cancer. It was not until the late 1970’s that the first article was published. Interestingly enough, it did not involve one of the first five protocols approved. Subsequently, hundreds of protocols have been approved, and over one thousand articles have been published on the research that the GOG has accomplished on gynecological malignancies. The following review is presented as an overview of some of the important Gynecologic Oncology Group trials in carcinoma of the cervix, ovary, endometrium, vulva and gestational trophoblastic disease. The scope of this review does not permit a comprehensive listing of all trials completed to date, nor of those currently ongoing, but instead attempts to provide an historical framework of important GOG trials, upon which an understanding of the evolution of modern therapy for gynecologic cancer can be based.

This review will attempt to highlight those studies which the authors feel are probably the most important and carry the most significant in regards to everyday practice. They will be divided into the organ sites.

Carcinoma of the Cervix
Surgical-Pathologic Risk Factors in Early-Stage Disease
In 1989 and 1990, Delgado et al published the long-term results of GOG protocol 49, a prospective study of surgical-pathologic risk factors in patients with stage IB carcinoma of the cervix undergoing radical hysterectomy with pelvic and para-aortic lymphadenectomy (1,2). Between 1981 and 1984, 1125 patients were enrolled on the study, of whom 732 had squamous cell carcinoma. 87 patients (12%) did not undergo radical hysterectomy because of gross disease beyond the uterus or microscopic aortic node involvement documented at laparotomy. Of the remaining 645 patients who underwent radical hysterectomy and node dissection, five risk factors were significantly associated with microscopic pelvic lymph node metastases: depth of invasion (P = 0.0001), parametrial involvement (P = 0.0001), capillary-lymphatic space (CLS) invasion (P = 0.0001), tumor grade (P = 0.01) and gross vs. occult primary tumor (P = 0.009). In a multivariate analysis, CLS, depth of invasion, parametrial involvement and age remained independent risk factors for pelvic node metastases. The three-year disease-free interval (DFI) for 545 patients with negative pelvic nodes was 85.6%, and 74.4% for the 100 patients with positive pelvic nodes. Depth of tumor invasion, clinical tumor size, and CLS were independent prognostic variables for disease-free survival. In a separate report, we did not find CLS to be independently prognostic (3).

Postoperative Adjuvant Radiation for Intermediate Risk Early Stage Disease
Patients with early stage (stage I and early stage II) carcinoma of the cervix may be offered definitive therapy either with chemoradiation (as for advanced disease), or with primary radical surgery. The survival rates for patients undergoing radiation or radical surgery are historically nearly identical. While the presence of metastatic disease in the pelvic lymph nodes, particularly multiple pelvic lymph nodes, is arguably the most predictive of treatment failure after radical surgery, the fact remains that fully half of patients who relapse after radical surgery have negative pelvic lymph nodes. Therefore, the Gynecologic Oncology Group initiated a randomized trial (GOG-92) to investigate the role of postoperative external beam radiotherapy following radical surgery for node-negative cervical cancer patients with intermediate risk factors. Patients were eligible if they had one of four combinations or risk factors: Positive capillary lymphatic space invasion and deep cervical stromal invasion for any tumor size, positive capillary lymphatic space invasion and middle one-third stromal invasion in tumor diameter ≥2 cm, positive capillary lymphatic space invasion with superficial one-third stromal invasion and tumor size ≥5 cm, and finally, deep or middle one-third stromal invasion and tumor size ≥4 cm, in the absence of capillary lymphatic space invasion. Two hundred and seventy seven patients were entered into the trial, 137 of whom were randomized to receive pelvic radiotherapy and another 140 who were randomized to no further treatment. The study resulted in two peer reviewed articles, although seven years apart (3,4).

In the first report, the authors reported 21 (15%) recurrences in the radiation therapy group, and 39 (28%) in the no further therapy group (3). This translated into a 47% reduction of the risk of recurrence (relative risk = 0.53, P = 0.008) amongst
those receiving postoperative radiation therapy (survival at two years was 88% and 79% in the radiation therapy versus no further therapy groups, respectively). Significance level was not provided as the survival data were not yet mature. As expected, toxicity was higher in the radiation therapy group (7% of the patients who received radiation therapy experienced severe life threatening adverse effects compared to 2.1% in the no further therapy group). One patient died of complications from a fistula after receiving radiation. The authors concluded that “adjunctive radiotherapy is beneficial for stage I cervical cancer patients with clinical pathologic risk factors for recurrence other than positive nodes”.

As mentioned above, a followup study was published in 2006 by the same authors (4). The authors again noted a statistically significant reduction in the risk of recurrence (hazard ratio = 0.54, P value of 0.007) as well as a statistically significant improvement in progression-free survival in the radiation therapy group (P = 0.008). However, despite many years of additional followup, no improvement in overall survival could be demonstrated. Moreover, the benefit of postoperative radiation was distributed unequally amongst patients with different histopathologic tumor subtypes and study eligibility categories. Much, if not nearly all, of the treatment benefit was concentrated on patients with adenocarcinomas or adenosquamous carcinomas. No statistical benefit could be established for patients with negative capillary and lymphatic space involvement, middle-third stromal invasion, and a tumor diameter of 4 cm or more, and for patients with positive capillary lymphatic space involvement, middle-third stromal invasion and a tumor diameter of 2 cm or more. Because the eligibility criteria for this adjuvant study were so heterogeneous, reduction in recurrence risk largely was confined to the adenocarcinoma/adenosquamous histology, and life-threatening complications clearly were increased in the adjuvant radiation group, many are hesitant to interpret this study as a broad mandate in support of prescribing radiation for node-negative patients with squamous cell carcinoma after radical hysterectomy.

**Postoperative Cemoirradiation for High Risk Early Stage Disease**

Concurrent with the publication of randomized trials in advanced cervix cancer showing an advantage for the addition of platinum-containing chemotherapy (see below), Peters, et al. in 2000 reported results of GOG protocol 109 (5). Patients with high risk early stage carcinoma of the cervix were randomized postoperatively to receive either radiation alone or radiation chemotherapy (7). Patients who had undergone radical hysterectomy for stages IA2, IB and IIA carcinoma of the cervix and demonstrated high risk histopathologic features (defined here as positive pelvic lymph nodes and/or positive surgical margins and/or microscopic involvement of the parametrium) were eligible for the study. Patients were randomized to receive either 4930 cGy of pelvic radiation therapy alone, or in combination with cisplatin (70 mg/m²) and a 96-hour infusion of fluorouracil (1000 mg/m² day) every three weeks for four cycles with first and second cycles concurrent with our radiation therapy. Two-hundred and sixty eight patients were entered into the trial, of whom 243 were assessable. Progression free and overall survival were statistically improved in the group receiving both radiation and chemotherapy. Projected overall survival at four years was 71% with radiation, 81% with radiation and chemotherapy. This publication concurrent with four other randomized trials of chemotherapy in cervical cancer, confirmed that the addition of platinum-based chemotherapy to radiation significantly improves outcome.

**Management of Bulky Stage IB (IB2) Carcinoma of the Cervix**

The management of large or bulky stage I carcinoma of the cervix remains controversial. Historically, a number of treatment options have existed, including radical hysterectomy, pelvic lymphadenectomy, primary radiation or chemotherapy, administration of preoperative radiation therapy with or without chemotherapy followed by extracavitary hysterectomy, or the administration of preoperative neoadjuvant chemotheraphy, followed by radical hysterectomy and pelvic lymphadenectomy and/or postoperative radiation or chemotherapy. Regardless of treatment strategy, the fact remains that large tumor volume often correlates with other adverse prognostic variables (especially higher incidence of pelvic lymph node metastasis) is associated with worse treatment outcome than smaller lesions.

In 2001, Keys, et al. reported the results of a phase III randomized trial comparing radiation therapy with and without extracavitary hysterectomy for bulky stage IB cervical cancer (6). As accrual in this trial was completed prior to the routine use of cisplatin radiosensitizing chemotherapy, patients in this trial were not given chemotherapy. There were 256 patients with lesions ≥4 cm, 25% had tumors with a maximum diameter ≥7 cm, were randomized either to external beam added to external and intracavitary irradiation or attenuated radiation following by extracavitary hysterectomy. Hysterectomy did not increase the frequency of reported grade 3 and 4 adverse effects. There was cumulative incidence of local relapse in the radiation followed by hysterectomy group at five years (14% versus 27%, respectively), there was no statistically significant improvement in survival in the patients undergoing hysterectomy after completion of radiation.

Alternative approach to the management of bulky stage IB cervical cancers utilizes neoadjuvant chemotherapy prior to radical hysterectomy and pelvic lymphadenectomy. In theory, such chemotherapy might facilitate surgical dissection by reducing tumor volume, and might improve outcome by sterilization tumor micrometastases. Pilot study by the GOG, demonstrated an 88% response rate and a 12% complete clinical response rate in 34 evaluable stage IB patients with lesions ≥4 cm who received preoperative vincristine or cisplatin chemotherapy (7).

A followup phase III randomized trial was conducted by the GOG to investigate the strategy further (8). After 291 patients were enrolled, the study was closed prematurely because...
of slow accrual. Two hundred and eighty-eight patients were randomized to either radical hysterectomy or neoadjuvant chemotherapy with vincristine and cisplatin followed by radical hysterectomy and pelvic lymphadenectomy. Patients with positive pelvic or aortic lymph nodes with disease in the parametria were treated with postoperative external beam radiotherapy. Approximately half of both treatment arms received postoperative radiation therapy and no statistically significant differences in recurrence rates in survival were observed. The authors conclude that there was no evidence that neoadjuvant chemotherapy offered any additional objective benefit to patients undergoing radical hysterectomy for bulky cervical carcinoma.

Curative Intent Primary Chemoradiation for Advanced Disease

Over the past century, the treatment of choice of advanced carcinoma of the cervix has consisted of the administration of pelvic radiotherapy. It was postulated decades ago that the addition of chemotherapy to radiation therapy might improve overall cure both by enhancing the efficacy of pelvic radiotherapy to control central disease, but also the potential to sterilize microscopic metastatic disease, which if untreated could manifest later as disease relapse.

The first prospective randomized trial of chemoradiation in cervical cancer performed by the Gynecologic Oncology Group was reported by Hreschyshyn et al. in 1979 (9). In that study, a statistically significant improvement in survival was noted with patients treated with radiation therapy and hydroxyurea compared to those undergoing radiation alone. GOG performed a followup study randomizing patients with advanced (stages IIB, III, or IVA) cervical cancer undergoing radiation therapy to receive in addition either hydroxyurea or the nitroimidazole/misonidazole (10). In this trial, 296 patients with advanced disease who had undergone clinical radiographic surgical staging were randomized to receive hydroxyurea (139 patients) or misonidazole (157 patients). Seventy-nine percent of the patients had negative pelvic lymph nodes pretreatment. Those treated with hydroxyurea had a longer progression-free interval bordering on statistical significance than those treated with misonidazole (P = 0.08). No statistical difference in survival was noted. The results of this trial were updated in a publication in 1993 (11).

In 1986, the Gynecologic Oncology Group and the Southwest Oncology Group activated a second randomized trial in the treatment of advanced cervical cancer involving hydroxyurea (12). The protocol compared primary radiation therapy plus hydroxyurea to radiation therapy plus 5-fluorouracil and cisplatin. In 388 randomized patients, 368 were eligible, 177 were randomized to cisplatin and 5-fluorouracil and another 191 to hydroxyurea. Severe life threatening leukopenia was more common in the hydroxyurea group (24%) than in the cisplatin and 5-FU group (4%). There was a statistically significant improvement in progress free survival in the cisplatin and 5-FU group (P = 0.033), as well as a significant improvement in overall survival in the platinum containing group (13).

Given these results, as well as the myelosuppressive and gastrointestinal toxicities of hydroxyurea, the Gynecologic Oncology Group and other investigators turned their emphasis to the study of cisplatin as a radiosensitizer in the treatment of advanced cervix in the ensuing decade, publishing a series of groundbreaking articles in the late 1990's that redefined the standard of care for the treatment of advanced cervical cancer.

In GOG 120, 526 patients with advanced cervical cancer were analyzed (13). All patients received external radiotherapy and were randomized to receive one of three different chemotherapy regimens: cisplatin 40 mg/m² per week for six weeks, cisplatin 50 mg/m² on days 1 and 29, followed by 4 grams of fluorouracil/m² with a 96-hour infusion on days 1 and 29, the addition of oral hydroxyurea 2 grams/m² twice weekly for six weeks, or finally, oral hydroxyurea 3 grams/m² twice weekly for six weeks. Both groups that received cisplatin had significantly improved progression-free survival and the overall survival group compared to hydroxyurea alone. There were no treatment related deaths. The authors recommended cisplatin as “the standard drug for radiotherapy and chemotherapy for locally advanced cervical cancer.”

The GOG also reported in 1999 results of radiosensitizing cisplatin in the treatment of bulky stage IB2 carcinoma of the cervix (14). In this trial, 169 women were randomized to receive either radiotherapy alone or in combination with cisplatin 40 mg/m² per week prior to type 1 extrafascial hysterectomy. Patients were prescribed 4500 cGy of external beam radiotherapy, to be followed by low dose brachytherapy in one or two applications, for a cumulative dose of 7500 cGy to point A and 5500 cGy to point B. Extrafascial hysterectomy was performed three to six weeks following the completion of radiotherapy. The progression-free and overall survival were improved in the treatment arm receiving cisplatin, both of which were highly statistically significant (P value < 0.001 and 0.008, respectively). As expected, in the chemoradiation arm, there was a higher frequency of stage III and IV adverse hematologic and gastrointestinal adverse effects. The authors concluded that there was a “compelling reason to consider cisplatin therapy in combination with radiation therapy as the new standard of care for patients with bulky stage IB, stage IIB through IVA, and high risk cervical cancers.”

When taken together, randomized trials of the GOG and other groups demonstrated substantial survival advantage for patients receiving platinum-based radiosensitizing chemotherapy in addition to radiation therapy for advanced carcinoma of the cervix. While analyses have demonstrated approximately 30% improvement in cure rate when platinum is incorporated into radiation therapy, that as a reference, weekly cisplatin is probably considered the standard of care in the current era.
Chemotherapy for Relapsed or Incurable Disease

Evolution of platinum-based chemotherapy for relapse during curable disease.

Except for central recurrence, patients with relapsed cervical cancer of the central pelvis who are salvaged with pelvic exenteration, cannot be cured. For those individuals, all therapy is essentially palliative in nature. More than 25 years ago, data from early phase II GOG trials (15) established cisplatin as the most active single agent in the treatment of these patients. Subsequent trials involving longer followup and larger number of patients showed response rates more in line with 20 or 30%.

In 2004, the GOG reported a phase III trial with cisplatin with or without paclitaxel for stage IVB recurrent or persistent squamous cell carcinoma of the cervix (16). Two hundred and eighty patients were entered, and 264 were eligible. Thirty-four received cisplatin alone (50 mg/m²) q3 weeks for six cycles, versus cisplatin plus paclitaxel (cisplatin 50 mg/m² plus paclitaxel 135 mg/m²) every three weeks for six cycles. Response rate for patients receiving the cisplatin and Taxol combination was significantly higher than for cisplatin alone (36% versus 19%, P value = 0.002), there was a two month improvement in progression-free interval (2.8 to 4.8 months), for the cisplatin and paclitaxel combination as compared to cisplatin alone. There is no statistically different improvement in immediate survival or in patient quality of life scores. There was more grade 3-4 anemia and neutropenia in the combination chemotherapy arm.

A phase III trial investigated platinum and ifosfamide with or without bleomycin for advanced recurrent squamous cell carcinoma of the cervix (17). Three hundred and three women were enrolled in the trial, of whom 287 were assessable. Patients were randomized to receive either cisplatin at 50 mg/m², ifosfamide 5 grams/m² over 24 hours and mesna 6 grams/m² during and after the ifosfamide infusion, versus bleomycin 30 units over 24 hours on day 1 followed by cisplatin 50 mg/m², ifosfamide and mesna. No difference was found between the two regimens with respect to response rate (32 versus 31.2%, respectively) in progression-free survival or overall survival, it was concluded that the addition of bleomycin to cisplatin and ifosfamide did not improve outcome in patients with advanced cervix cancer.

Cisplatin-containing combination chemotherapy regimens in advanced cervical cancer were further investigated by the GOG. In 2005, Long et al. reported results of a randomized phase III trial of cisplatin with or without topotecan for advanced carcinoma of the cervix (18). Actually, the trial started out with three treatment arms, the first (CPT) being cisplatin at 50 mg/ m² every three weeks, the second being cisplatin 50 mg/m² on day plus topotecan 0.75 mg/m² on day 1-3 q3 weeks, and the third arm utilizing methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), this arm being closed by the Data Safety Monitoring Board after four treatment-related deaths. Of the 294 patients enrolled into the remaining treatment regimens, 146 were treated with cisplatin and another 147 with cisplatin and topotecan. Grade 3 and 4 hematologic toxicity was more common with cisplatin and topotecan. There was a statistically increased survival in patients receiving cisplatin and topotecan (9.4 versus 6.5 months, P value = 0.017), as compared to cisplatin alone. This was the first randomized phase III trial that demonstrated a survival advantage for patients receiving platinum-based combination chemotherapy for advanced cervical cancer.

A randomized phase III trial (GOG 204) compared four cisplatin containing doublet combination in Stage IVB, recurrent or persistent cervical cancer was reported by Monk et al. There were 513 patients randomized to cisplatin 50 mg/m² day 2 and paclitaxel 135 mg/m² over 24 hours day 1 every 3 weeks (CP); vinorelbine 30 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks (VC); gemcitabine 1000 mg/m² day 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks (GC) or topotecan 0.75 mg/m² day 1, 2, and 3 plus cisplatin 50 mg/m² day 1 every 3 weeks (TC). Survival was primary endpoint. VC, GC, TC were not superior to PC in terms of overall survival; however the trend in RR, PFS and OS favors PC. Median survival was 12.8 months for PC, 9.9 months for VC, 10.2 months for GC and 10.2 months for TC. Severe adverse events (grade 4 and 5) of leucopenia for the GC was less than the other arms and alopecia was greater in the PC arm (54).

In summary, patients with relapsed or metastatic carcinoma of the cervix have an abyssal prognosis, with the vast majority surviving under one year. Cisplatin remains the most active regimen, with one recent GOG trial demonstrating a survival advantage for patients receiving both cisplatin and topotecan in combination. Nonetheless, the fact that almost all of these patients will eventually succumb to their disease in a short timeframe suggests that much further research remains to be done.

Carcinoma of The Ovary

Adjuvant Therapy for Early Stage Disease

Approximately one-third of epithelial ovarian cancers are confined to one or both ovaries at initial diagnosis (stage I or stage II). Despite presenting with early stage disease, it was realized many years ago that patients with certain subgroups of stage I and II disease still manifested a significant risk of treatment failure and relapse. It was thought that certain high risk early stage subgroups could therefore benefit from the administration of postoperative adjunctive therapy. In this regard, in 1990, the Ovarian Cancer Study Group (OCSG) and the Gynecologic Oncology Group (GOG), reported simultaneously the result of two randomized clinical trials in patients with early ovarian cancer. In the first trial, 81 patients with grade 1 or grade 2, stage IA and stage IB ovarian cancer were randomized to receive no further treatment or oral melphalan (0.2 mg/kg/day for five days, repeated every four to six weeks for up to twelve cycles) (19). All patients underwent comprehensive surgical staging. After a median of six years of followup, no significant differences were observed in the patients who received chemotherapy versus no further treatment (five year disease-free interval and overall survival
rates were 91 and 94%, respectively). Based on these early favorable results, it is now recognized that patients with stage IA and stage IB, grade 1 or 2 disease do not require adjuvant therapy.

In the second trial, 141 patients with grade 3, stage I tumors, or patients with stage II disease (any grade) were randomly assigned to treatment with either melphalan or a single intraperitoneal dose of P32 radiocolloid. After more than six years of median followup, the outcome for the two treatment arms was similar. Five-year disease-free survival was 80% in both groups, with overall survival being 81% and 78%, respectively, for those treated with melphalan versus P32.

The development of cisplatin-based therapy for advanced ovarian cancer in the late 1970's and early 1980's, led naturally to the investigation of the inclusion of cisplatin into treatment regimens for the adjuvant treatment of early stage disease. In 2003, Young, et al. reported the results of the large GOG trial (GOG-95) comparing intraperitoneal P32 or cisplatin (100 mg/m² IV on day 1) and cyclophosphamide (1 gram/m² IV on day 1, cycled every three weeks for three cycles) (20). This phase III randomized trial, begun in 1986, was conducted by the GOG, the North Central Cancer Treatment Group (NCCTG) and the Southwest Oncology Group (SWOG). A total of 251 patients were randomly assigned to treatment, of whom 229 patients remained eligible, 110 who were treated with P32 and 199 who received cisplatin and cyclophosphamide. Patients with stage I and stage II ovarian cancer were eligible if they were thought to have high risk disease (stage IA or stage IB, grade 3, or stage IC, or stage II). Cumulative incidence of recurrence in 10 years was 35% and 28%, respectively, for those receiving P32 and cisplatin and cyclophosphamide. Though it did not reach statistical significance, patients receiving cisplatin-based therapy had a 29% lower risk of recurrence than those receiving P32. Both regimens were reasonably well tolerated. While there was no statistically significant difference in survival with the lower cumulative recurrence rate with cisplatin-based therapy, it was suggested chemotherapy was the preferred adjuvant treatment for early ovarian cancer patients at high risk for recurrence.

The GOG next investigated an optimal number of treatment cycles in the adjuvant treatment of early stage disease. The results of GOG protocol 157 were reported in 2006 (21). This trial compared three versus six cycles of carboplatin (AUC = 7.5) and paclitaxel (175 mg/m² over three hours), patients with high risk early stage ovarian cancer, as previously defined. Four hundred and fifty seven patients were randomly assigned to treatment, of whom 427 were eligible. Six cycles was found to be more toxic than three, resulting in significantly more anemia and granulocytopenia. Recurrence risk for six cycles of chemotherapy was 24% lower than for three cycles, although this difference did not reach statistical significance. Estimated probability of recurrence at five years was 20.1% versus 25.4%, respectively, for patients receiving six cycles versus three cycles. The study authors concluded that compared to three cycles, six cycles of carboplatin and paclitaxel do not significantly alter the recurrence rate in high risk early stage epithelial ovarian cancer but is associated with more toxicity.

**Evolution of Cytotoxic Chemotherapy for Primary Treatment of Advanced Disease**

GOG has been instrumental over the last 30 years in developing chemotherapy treatment protocols for advanced ovarian cancer. GOG protocol 22 compared melphalan versus melphalan plus hexamethylmelamine versus cyclophosphamide plus doxorubicin in bulky stage III and stage IV ovarian cancer (21). Cyclophosphamide and doxorubicin produced a significantly higher complete clinical response rate than melphalan alone (32% versus 20%). Melphalan plus hexamethylmelamine was not significantly better than melphalan alone. Improvement in survival was observed.

Cyclophosphamide plus doxorubicin was then compared to cyclophosphamide plus doxorubicin plus cisplatin in GOG protocol 47 (22). The three-drug regimen of cyclophosphamide plus doxorubicin plus cisplatin produced a statistically significant improvement in complete clinical response rate, response duration and progression-free interval compared with cyclophosphamide and doxorubicin alone. While there was no statistical improvement in survival for the platinum-containing three-drug regimen, it is clear that platinum was a highly active agent in the treatment of advanced ovarian cancer.

The GOG next investigated whether doxorubicin, associated potentially with serious cardiac and other toxicities, contributed significantly to the activity of the platinum-containing regimens. Three hundred and forty nine patients were enrolled comparing cyclophosphamide and cisplatin to cyclophosphamide, cisplatin and doxorubicin (23). One hundred and seventy six patients received the two-drug regimen while 173 received the three-drug regimen. Hematologic toxicity was virtually identical. There was no significant improvement in progression-free survival, negative second look laparotomy or survival for the Adriamycin-containing three-drug regimen. It was concluded that “it seems clear that the addition of doxorubicin in minimal residual disease cases using dose schedules would equal hematologic toxicity as no significant advantage”.

For all intents and purpose, the use of Adriamycin in multiagent cytotoxic chemotherapy regimens for ovarian cancer ceased subsequent to this 1989 publication.

Given the significant activity of cisplatin in treating ovarian cancer, the question naturally arose as to whether if modifying the dose intensity (mg of drug administered per week) would impact outcome in treating advanced ovarian cancer. In this regard, in 1995, the GOG reported the results of a randomized trial discussing dose intensive cisplatin-based therapy in the suboptimally debulked ovarian cancer versus conventional therapy (24). A total of 485 patients with suboptimally debulked stage III and stage IV ovarian cancer were randomized to receive eight cycles of conventional dose
cisplatin and cyclophosphamide (50 mg/m² and 500 mg/m², respectively) versus dose intense therapy (cisplatin 100 mg/m² and cyclophosphamide 1000 mg/m²) for four cycles. Doubling of the dose intensity in the experimental arm showed no discernible improvement in patient outcome and was associated with more severe toxicity. According to the study authors, there was "no evidence to support the hypothesis that modest increases in dose intensity without increasing total dose is associated with significant improvement in overall survival.

In the mid 1980’s, paclitaxel emerged as clearly an active agent in the treatment of refractory and recurrent carcinoma of the ovary. A 37% response rate was observed in a phase II clinical trial by the GOG in patients with recurrent carcinoma of the ovary, making it the most active single drug ever evaluated by the Gynecologic Oncology Group (25). Assessment of phase I trial demonstrated that paclitaxel and cisplatin could be safely combined, with paclitaxel given over 24 hours followed immediately by the cisplatin (26).

A randomized trial of cyclophosphamide and cisplatin versus paclitaxel and cisplatin was reported in 1996 by McGuire, et al. (27). In this trial, 410 women with advanced suboptimally debulked ovarian cancer (residual disease greater than 1 cm) randomized to receive cisplatin (75 mg/m²) with either cyclophosphamide (750 mg/m²) or paclitaxel (35 mg/m² over 24 hours). Three hundred and eighty six women met eligibility criteria. A 73% response rate was observed in the cisplatin and paclitaxel arm versus 60% in the cisplatin and cyclophosphamide group (P = 0.01). Progression free survival and overall survival was significantly improved in the cisplatin and paclitaxel group versus 24 months in the cisplatin and cyclophosphamide group. This study defined a combination of cisplatin and paclitaxel as the standard of care for patients with advanced carcinoma of the ovary.

GOG next investigated whether cisplatin or paclitaxel, administered as a single agent, as effective as cisplatin and paclitaxel in combination in patients with suboptimally debulked stage III or IV ovarian cancer. Reported in the year 2000, the study randomized 648 patients on cisplatin alone (100 mg/m²) versus 24-hour infusion paclitaxel (200 mg/m²), or the combination of paclitaxel (135 mg/m²) and cisplatin (75 mg/m²) (28). Interestingly, cisplatin monotherapy was discontinued more frequently because of toxicity, and paclitaxel monotherapy continued more often because of progression of disease, compared with combination therapy. Response rates to paclitaxel monotherapy were significantly lower compared to the platinum-containing regimens (42% versus 67%, respectively, P<0.001); however, no survival differences were observed amongst the three treatment arms. Because the cisplatin regimens had a superior response rate, and combination therapy demonstrated an improved toxicity profile, the authors felt that "the combination of cisplatin and paclitaxel remains the preferred initial treatment option. GOG has also studied during the infusion time for paclitaxel part of the combination regimen of cisplatin in patients with advanced ovarian cancer (29). Of the 324 patients that were accrued, 293 were analyzed. Patients were randomized to receive cisplatin 75 mg/m² and paclitaxel 135 mg/m² over 24 hours versus paclitaxel 120 mg/m² over 96 hours. This study was closed prematurely because of a scheduled interim futility analysis. There were differences in hematologic toxicities amongst the two arms. Grade 4 granulocytopenia was more common in the 24-hour cisplatin and paclitaxel infusion arm whereas grade 3 or worse anemia was more common in the experimental 96-hour paclitaxel and cisplatin arm. There were no differences in overall survival. Results of therapy were not improved by prolonging the paclitaxel infusion from 24 to 96 hours.

GOG 158 compared cisplatin and paclitaxel (24-hour infusion) to carboplatin and paclitaxel (3-hour infusion) in optimal stage III epithelial ovarian carcinoma (30). PFS and OS were similar. As a result, the combination of carboplatin and 3-hour paclitaxel infusion has become the standard of care for the treatment of advanced stage epithelial carcinoma of the ovary.

The fact remained that eventually the vast majority of patients with this disease relapse and die of their disease. A number of additional cytotoxic drugs (liposomal doxorubicin, topotecan, gemcitabine) had a favorable response rate for relapsed ovarian cancer. GOG protocol 182 evaluated a five-arm randomized clinical trial investigating the efficacy of various platinum-containing doublet and triplet combination regimens compared to a standard carboplatin and paclitaxel control (31). The regimens were defined as follows: Carboplatin AUC of 6 and paclitaxel 175 mg/m² on day 1 times eight cycles. Regimen two, carboplatin AUC of 5, paclitaxel 175 mg/m² on day 1, gemcitabine 800 mg/m² on day 1 and 8 times ten cycles, followed by carboplatin AUC of 6, paclitaxel 175 mg/m² on day 1 times cycles five through eight. Regimen three, carboplatin AUC of 5, paclitaxel 175 mg/m² on day 1, liposomal doxorubicin 30 mg/m² on day 1 times four cycles, followed by carboplatin AUC of 5, paclitaxel 175 mg/m² times cycles five through eight. Regimen four, topotecan 1.25 mg/m² per day times three days plus carboplatin AUC of 5 for cycles one through four followed by carboplatin AUC of 5, paclitaxel 175 mg/m² for cycles five through eight. Regimen five, carboplatin AUC of 6, gemcitabine 1000 mg/m² on day 1 and day 8 for cycles one through four followed by carboplatin AUC of 6, paclitaxel 175 mg/m² for cycles five through eight. The endpoint of the study was overall survival. The study was closed after 4312 women were enrolled. Seventy nine percent of patients completed eight cycles of therapy. There were no improvements in either progression-free survival or overall survival associated with any of the experimental regimens as compared to the standard paclitaxel and carboplatin arm. The authors concluded that "compared with standard paclitaxel and carboplatin, the addition of a third cytotoxic agent provided no benefit in progression-free survival or overall survival after suboptimal cytoreduction."
Intraperitoneal Therapy as Primary Treatment of Advanced Disease

As ovarian cancer is primarily an intraperitoneal disease, it has long been postulated that the administration of cytotoxic agents directly into the peritoneal cavity to provide both for increased exposure of intraperitoneal tumor implants, higher chemotherapy concentrations than can be achieved in the systemic circulation, but also thereby potentially lowering toxicities engendered by systemic chemotherapy administration. A number of earlier phase I and II trials clearly demonstrated that certain chemotherapy agents can be safely infused into the peritoneal cavity. As intraperitoneally administered chemotherapy is known to penetrate tumor nodules only to a depth of 2 mm; however, it was felt that any potential benefits of intraperitoneal chemotherapy would largely be confined to patients who tumors had been optimally or nearly optimally cyto-reduced.

Over a 10-year period, the Gynecologic Oncology Group reported on the results of three randomized clinical trials of intraperitoneal chemotherapy in advanced ovarian cancer. First, reported by Alberts, et al. in 1996, randomized patients to receive either intravenous cisplatin (100 mg/m²), and cyclophosphamide (600 mg/m²) or intraperitoneal cisplatin at (100 mg/m²) and intravenous cyclophosphamide (600 mg/m²) (32). Patients were eligible for this disease who had stage III ovarian cancer and underwent tumor debulking down to a residual tumor size of 2 cm or less. Five hundred and forty six patients were found eligible in this study. In this trial, there was an eight month improvement estimated in median survival in the patients receiving intraperitoneal cisplatin as opposed to intravenous cisplatin (49 months versus 41 months). Hazard ratio for the risk of death in the intraperitoneal group as compared to the intravenous group was 0.76 (95% confidence interval 0.61-0.96, P = 0.02). An unexpected finding was that the apparent advantage of intraperitoneal cisplatin extended even to those patients who had disease >0.5 cm. It should also be mentioned that this was the only GOG trial of intraperitoneal chemotherapy where doses were equivalent for both treatment arms, varying only the route of administration.

The second GOG trial of intraperitoneal chemotherapy in advanced ovarian cancer was published by Markman et al. in 2001 (33). This protocol randomized 523 patients (462 were assessable) to receive either IV paclitaxel 135 mg/m² over 24 hours followed by IV cisplatin 75 mg/m² q3 weeks for six courses, or an experimental arm consisting of high dose IV carboplatin (area under the curve of 9) every 28 days for two courses followed by IV paclitaxel 135 mg/m² over 24 hours followed by intraperitoneal cisplatin (100 mg/m² every three weeks for six courses). Neutropenia, thrombocytopenia and gastrointestinal metabolic toxicities were substantially greater in the experimental arm such that 20% of patients in the experimental arm received less than or equal to two courses of intraperitoneal chemotherapy. There was a six month improvement in progression free survival (28 versus 22 months, respectively, P = 0.01), and a borderline improvement in overall survival associated with this regimen (63 versus 52 months, P = 0.05). Nonetheless, because of the substantial toxicity associated with the experimental regimen, the authors concluded that “the experimental arm is not recommended for routine use”.

The third and by far most influential trial of intraperitoneal chemotherapy performed by the Gynecologic Oncology Group (GOG-172) was published by Armstrong et al. in 2006 (34). In this trial, 429 patients underwent randomization (415 were eligible) to optimally debulked stage III ovarian cancer (residual disease ≤1 cm) either intravenous paclitaxel 135 mg over 24 hours followed by cisplatin 75 mg/m² for six cycles, or paclitaxel 135 mg/m² on day 1 over 24 hours followed by cisplatin 100 mg/m² intraperitoneal on day 2, with the addition of Taxol 60 mg/m² intraperitoneal on day 8 cycled every three weeks for six cycles. In contrast to the Albert’s study, grade 3 and 4 pain, fatigue, hematologic, gastrointestinal, metabolic and neurologic side effects were substantially more common in the intraperitoneal therapy group than in the intravenous therapy group (P ≤0.001). Because of toxicities, nearly 60% of the patients who were randomized to the intraperitoneal therapy arm could not complete the prescribed six cycles of therapy. Median progression-free survival increased from 18.3 to 23.8 months in the intraperitoneal arm (P = 0.05), and median overall survival improved in the intraperitoneal therapy group from 47.9 to 65.6 months (P = 0.03). The intraperitoneal therapy group was associated with a decrease in quality of life during treatment, that had resolved by one year of followup. Based on these observations, the authors recommended that “these results should encourage the use of intraperitoneal chemotherapy in patients with advanced ovarian cancer”.

Results of the three randomized GOG trials showing improvement in prognosis for patients with small volume ovarian cancer treated with intraperitoneal chemotherapy (along with the results of other trials), resulted in the National Cancer Institute issuing a clinical alert on January 5, 2006. In this report, combined results of six randomized clinical trials involving intraperitoneal chemotherapy for ovarian cancer (including the three GOG trials mentioned above) were analyzed. This had an overall hazard ratio for progression-free survival of 0.79 (95% confidence interval 0.07-0.90), and the NCI clinical alert urges that “women with optimally debulked FIGO stage III ovarian cancer should be counseled about the clinical benefit associated with the combined IV and IP administration of chemotherapy”.

Numerous weaknesses and inconsistencies in GOG protocol 172 have been suggested, which in the minds of many clinicians have blurred the clarity of the study conclusions and its relevance for treating an average population of patients with ovarian cancer. Unlike GOG protocol 104, where only the route of chemotherapy administration was varied, GOG-172 varied not only the route of administration between the treatment arms, but also the cisplatin dose (100 mg/ m² in the IP arm versus 75 mg/m² in the IV arm), as well as both dose intensity and total dose over the protocol of both cisplatin and paclitaxel (the IP arm, for example, for an
additional 60 mg/m² of intraperitoneal paclitaxel per cycle as compared with the IV arm). Importantly, because almost 60% of the patients could not complete the prescribed course of IP therapy, were thereafter treated at the discretion of the attending physician, with many of those patients ultimately receiving intravenous carboplatin and taxol. While cross-trial comparisons can be problematic, it has been pointed out that GOG-158 demonstrated almost a nine month improvement in overall survival for patients receiving carboplatin and taxol as opposed to those receiving cisplatin and taxol (57.4 months versus 48.7 months) though this was not statistically significant. Nonetheless, since GOG-172 relied on an intent to treat analysis, whereby patient outcomes were counted in the IP arm, even though they may have only received one cycle of IP therapy and the rest of their therapy as IV carboplatin and taxol, many clinicians are troubled by the possibility that results achieved in the IP arm of GOG protocol 172 may be at least to some degree a reflection of the enhanced efficacy of carboplatin versus cisplatin.

Consolidation Treatment

Despite high initial response rates, improved progression-free and overall survival in the era of platinum and taxane chemotherapy, the fact remains that the vast majority of patients with advanced carcinoma of the ovary eventually relapse from their disease, presumably from the regrowth of subclinical microscopic residual disease. In theory, maintenance (or “consolidation”) chemotherapy administration following completion of primary chemotherapy might prevent or significantly delay regrowth of these cells. In that regard, in 2003, Markman et al. reported the results of 277 patients who achieved complete clinical remission with standard platinum and taxane based chemotherapy were then randomized to receive either three or twelve cycles of single-agent monthly paclitaxel consolidation (35). Of 277 patients (262 assessable) entered the clinical trial, which was terminated early by the Southwest Oncology Group Data Monitoring Committee with a significant difference in progression-free survival demonstrated between the three-cycle and the twelve-cycle paclitaxel arms (21 versus 28 months, respectively). Interestingly, while the initial prescribed dose of paclitaxel was 175 mg/m² every three weeks, the dose was subsequently reduced to 135 mg/m², because of the treatment discontinuation from symptomatic peripheral neuropathy. Ironically, at least in part due to the study being closed prematurely, no improvement in overall survival could be demonstrated. As a result of this study, it was felt by the study authors that “it is most reasonable to conclude that oncologists have discussed with appropriate patients the results of this trial and possible implications for their subsequent management: The absence of improvement in overall survival, however, led the study authors to include that consolidation therapy was not a new addition to the standard of care, but rather a concept that should be explored further in additional randomized trials.

Biologic Therapy for Relapsed Disease

As mentioned previously, the vast majority of patients with advanced ovarian cancer, even those who achieve complete clinical remission with platinum and taxane chemotherapy (either IV or IP), will unfortunately relapse. While life can be extended often for years, the judicious combination of re-operation, re-treatment with platinum-containing compounds, and the use of second and third-line salvage chemotherapy agents, the fact remains that ultimately, relapsed ovarian cancers cannot be cured, and essentially all patients will succumb from their disease. This ultimately incurability of relapsed disease, the limitation of side effects, costs, conventional second and third-line cytotoxic agents, and an increased understanding that the biologic and molecular pathways of tumor agenesis has led over the last several years, in an explosion in the development and understanding of novel biologic therapeutic agents in the treatment of adult solid tumors, including ovarian cancer. Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor, has proven to be one of the most exciting of these agents. In 2007, Berger et al. reported that results of a phase II trial by the Gynecologic Oncology Group investigating bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer (36). Sixty-two patients were enrolled, 41 (66.1%) of whom had received two prior chemotherapy regimens, 26 (41.9%) of whom were considered platinum resistant. Fifty-one percent of patients experienced clinical response, 40.3% survived progression free for at least six months. Median progression-free and overall survival were 4.7 and 17 months, respectively. Four patients (6.5%) experienced grade 3 or grade 4 gastrointestinal toxicity, though none experienced perforations or fistula. 9.7% of patients developed grade 3 hypertension. Two patients experienced deep venous thrombosis, one with pulmonary embolism. A variety of other non-life-threatening heterogenous toxicities were encountered. The authors concluded that bevacizumab seems to be well tolerated and active in second and third-line treatment of patients with epithelial ovarian cancer and primary peritoneal cancer, and merits a phase III investigation. Interestingly, bevacizumab has now been incorporated by the GOG into the ongoing primary treatment protocol for advanced ovarian cancer (GOG-218).

An abstract has reported the results of GOG 218 in which 1873 patients with Stage III, IV primary ovarian cancer, primary peritoneal cancer or fallopian tube cancers were randomized post surgery to CT (IV paclitaxel 175 mg/m² + carboplatin AUC 6, cycle 1-6) + placebo cycles 2-22 (R1), or CT + concurrent bevacizumab (BEV) 15 mg/kg cycle 2-6 + placebo cycle 7-22 (R2) or CT + concurrent BEV cycle 2-6 + maintenance BEV cycle 7-22 (R3). Relative to R1, the hazard of first progression or death for R2 was 0.908 (CI 0.796-1.04) and for R3 was 0.717 (CI 0.625-0.824, p <0.001). We await the final publication (58).
Carcinoma of The Endometrium

Surgical Pathologic Spread Patterns of Endometrial Cancer and the Importance of Surgical Staging

The Gynecologic Oncology Group investigated the metastatic potential of endometrial cancer in a series of prospective trials, first in a pilot study of 222 patients and by a larger subsequent trial (GOG-33) reported by Creasman et al. in 1987 (37, 38). GOG protocol 33 was a prospective multi-institutional trial of 621 patients with a clinical diagnosis of early stage uterine cancer, and who underwent in addition to hysterectomy and bilateral salpingo-oophorectomy, the procurement of cytologic washings and pelvic and paraaortic lymphadenectomy. Tumor grades and histologies were initially accrued (grade 1 tumors were excluded for the last two years of the trial). Overall, the incidence of extrauterine disease was 22%. Pelvic and paraaortic lymph node metastasis were detected in 9% and 5% of patients respectively. 34 of 621 or 5% of patients, 76 of 621 or 12% of patients had adnexal metastasis or malignant peritoneal cytology, respectively. The study confirmed in a prospective fashion significant incidence of occult extrauterine disease in clinical stage I uterine cancer. The authors suggested that “certain patients have significant risk of lymph node metastasis and histological evaluation of the regional lymph nodes as warranted.

It should be mentioned that 43 institutions entered 1,180 patients on GOG protocol 33 during the approximately six study years. Though 425 of these patients were felt ineligible for inclusion into the report on the surgical pathology spread patterns discussed above, 195 patients were thought valuable in subsequent report relating surgical pathologic parameters in postoperative treatment to recurrence-free interval and recurrent site. This data was reported by Boronow et al. in 1991 (39). Proportional hazard modeling of time to recurrence was performed. Patients with surgical pathologic staging revealed no evidence of metastatic disease, the greatest determinate of recurrence was grade 3 histology (relative risk = 15). 48 patients with documented aortic node metastasis, 47 patients had one or more of the following features: 1) Grossly positive pelvic nodes, 2) Grossly positive adnexal metastasis, 3) Outer one-third myometrial invasion. While postoperative adjuvant treatment was not specified, controlled, nor randomized in the study, 48% of patients received postoperative pelvic brachytherapy. Of the patients receiving no further treatment, a percentage of the recurrences were vaginal and/or pelvic, though the authors felt that no valid comparisons could be made, given the high degree of selection bias. Five-year recurrence-free interval for patients with negative surgical pathologic risk factors (other than grade and myoinvasion) was 92.7%, as compared to 69.8% for those with involvement of the cervix, 56% for those with involvement of the peritoneal cytology, 57% for those with involvement of the pelvic node or adnexal metastasis, and 41% for those with involvement of aortic nodes or gross intraperitoneal disease. 29% of the 97 patients in the study with malignant cytology had regional or distant site failure, as compared to 10% of the cytology-negative patients, confirming the prognostic significance of malignant cytology in endometrial cancer.

LAP 2 was a study to compare laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer. Patients with clinical Stage I and IIA uterine cancer (FIGO 1988) were randomly assigned to laparoscopy (n=1696) or open laparotomy (n=921) to include hysterectomy, BSO, peritoneal cytology, pelvic and paraaortic lymphadenectomy. The main end points were 6 week morbidity and mortality, hospital length of stay, conversion from laparoscopy to laparotomy, recurrence free survival, site of recurrence and QoL outcomes (55).

Conversion to open laparotomy was 25.8% of laparoscopy for a variety of reasons. Laparoscopy had fewer moderate to severe post op adverse events (14% v 21%; p<0.0001) but similar rates of intraoperative complications. Laparoscopy had a longer operative time (204 v 130 minutes; p<0.001). Hospitalization was shorter with laparoscopy. Pelvic and paraaortic nodes were not removed in 8% of laparoscopy patients vs 4% of laparotomy patients (p<0.0001). Other end points were to be reported later. The authors felt that laparoscopy was feasible and safe in terms of short term outcomes.

Postoperative Adjunctive Radiotherapy in Early Stage Uterine Cancer

In 2004, Keys et al. reported the results of GOG protocol 99 (40). 448 patients with intermediate risk endometrial cancer were randomized after surgery to receive either no additional treatment or 5040 cGy whole pelvic radiotherapy. To be eligible for the study, patients had to have undergone abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and aortic lymphadenectomy, and cytologic washings. Additionally, patients with any degree of myometrial invasion, of any grade with no evidence of lymph node involvement, including those with occult endocervical involvement, were included in the study, with the exception that clear cell and papillary serous adenocarcinomas were excluded. In the course of the study, it became apparent that the patient population targeted for the study was at lower risk of recurrence than originally anticipated, and the definition of intermediate risk was revised. A new category of “high intermediate risk” was defined as: 1) Greater than or equal to 70 years of age with other risk factor (grade 2 or 3 tumor, lymphovascular invasion, outer one-third myometrial invasion), 2) Greater than or equal to 50 years of age with two of the other risk factors mentioned above, or 3) Any age with all three of the other risk factors. Ultimately, 392 patients were found eligible for the study. Postoperative adjunctive whole pelvic radiation reduced pelvic and vaginal recurrence (18 and no further treatment versus 3 in the radiation arm), with the overall survival 86% and 92% in the no further treatment versus RT arm, respectively, which was not significantly different. The group treated with radiation therapy experienced more frequent and more severe toxicities than
those undergoing no further treatment. Two women on the radiation arm died from complications involving intestinal injury felt to be radiation related. Statistically significant (P < 0.001) differences in the frequency and severity of hematologic, gastrointestinal, genitourinary and cutaneous toxicities were seen in the group undergoing pelvic irradiation. The study authors concluded that there was “strong evidence for the use of adjuvant RT in the subgroup defined here and is high intermediate risk.” They also noted that “in view of the potential toxicity of such adjuvant treatment is not recommended for those patients at lower risk of recurrence.” Indeed, data from GOG-99 suggests reduction in vaginal recurrence remains the most profound impact of postoperative adjuvant radiation therapy for early stage uterine cancer, no difference in either distant site recurrence and overall survival. With the toxicity of postoperative radiation therapy, high salvageability of vaginal recurrence on irradiated patients, the existence of several other randomized trials of endometrial cancer that failed to show benefit for postoperative radiotherapy in early stage patients, the availability of vaginal vault brachytherapy as a ‘faster less toxic alternative to pelvic radiotherapy to lower vaginal cuff recurrence, and perhaps most importantly the existence now in several other randomized trials failing to show a survival advantage in patients undergoing postoperative pelvic radiotherapy for surgery for early stage uterine cancer urged the current authors to conclude pelvic radiation has a very limited role in the adjuvant setting.

**Chemotherapy for Advanced Disease**

Patients with documented metastatic uterine cancer have historically been treated with radiotherapy, though a high incidence of distant site visceral organ failure or intraperitoneal failure have led many investigators to explore further the possible role of cytotoxic chemotherapy in the adjuvant treatment of completely resected (or nearly completely resected disease). GOG protocol 122 was an important trial comparing whole abdominal radiation and doxorubicin and cisplatin chemotherapy in women with stage III or stage IV uterine cancer who postoperatively had a maximum of 2 cm of postoperative residual disease (41). 422 patients were entered into the trial, of whom 396 were assessable. 202 were randomly allocated to receive whole abdominal radiation, and 194 were allocated to receive Adriamycin and platinum chemotherapy. Those allocated to the radiation arm received 3000 cGy to the whole abdomen, with a 1500 cGy boost to the pelvis, and in some cases paraaortic region as well. Mean patient age was 63 years, 50% had endometrioid tumors and median followup was 74 months. The hazard ratio for progression adjusted for stage was 0.71. In 60 months, 50% of patients receiving chemotherapy were predicted to be alive and disease free compared to 38% of patients receiving whole abdominal irradiation. The study authors concluded that chemotherapy with Adriamycin and cisplatin significantly improves progression-free interval in overall survival compared with whole abdomen radiation therapy. Related toxicity contributed to the deaths of 8 patients (4%) on the chemotherapy arm, and 5 patients (2%) on the whole abdominal radiation arm.

In a phase III trial patients with advanced endometrial cancer after surgery and volume directed radiation were randomized to cisplatin 50 mg/m² and doxorubicin 45 mg/m² with (CDP) or without paclitaxel 160 mg/m² (CD) for 6 cycles. Filgrastim 5 mcg/kg/day on day 3-12 or pegfilgrastim 6 mg on day 3 was also given. RFS at 36 months was 62% for CD vs 64% for CDP. Hematologic adverse events, sensory neuropathy and myalgia were more frequent and severe in the CDP arm (p<0.01); however in those patients with gross residual disease there was a 50% reduction in the risk of recurrence or deaths in the CDP arm (56).

**Cytotoxic Chemotherapy, Measurable Disease**

Several important GOG trials have addressed the efficacy of various chemotherapy regimens in advanced uterine cancer. GOG-177, reported by Fleming et al. in 2004, of a phase III randomized trial, doxorubicin and cisplatin plus/minus paclitaxel plus filgrastim in advanced uterine cancer (42). In this trial, 273 women were registered, histologically documented measurable stage III, stage IV recurrent uterine cancer of any cell type. Patients were randomized to receive either Adriamycin (60 mg/m²) and cisplatin (50 mg/m²) or Adriamycin (45 mg/m²), cisplatin (50 mg/m²) followed by paclitaxel (160 mg/m²) day 2 with filgrastim support (TAP regimen). The regimens were cycled every three weeks to a maximum of seven cycles. Active response (57% versus 34%; P < 0.01), progression-free survival (median 8.3 versus 5.3 months; P < 0.01), and overall survival (median 15.3 months versus 12.3 months; P = 0.037), all favored the three-drug regimen. It was generally well tolerated, with only 2% and 3% experiencing neutropenic fever. Hematologic toxicity and peripheral neuropathy were higher in those undergoing three-drug therapy. Ongoing GOG trial is currently under way comparing the efficacy of TAP chemotherapy to carboplatin/Taxol, regimen commonly used by clinicians given its minimal toxicity profile.

In a phase III trial (GOG-163), reported by Fleming et al. in 2004, patients were randomized to receive doxorubicin and cisplatin at standard doses versus doxorubicin followed with 24 hour infusion paclitaxel (150 mg/m²) followed by growth factor support (43). 328 patients with primary stage III, stage IV recurrent endometrial cancer were enrolled, 11 of whom were ineligible. There were no significant differences in response rate, progression-free survival or overall survival. This concluded that doxorubicin and 24-hour paclitaxel plus filgrastim was not superior to doxorubicin and cisplatin for uterine cancer.

**Uterine Sarcomas**

Uterine sarcomas are a rare but highly aggressive form of corpus cancer which traditionally manifest a high relapse rate and a poor prognosis. A number of investigations have been performed by the GOG exploring whether adjuvant therapy would be useful in reducing recurrence risk after surgery for these rare but deadly malignancies. In GOG-150, 232 patients with stage I to stage IV uterine carcinosarcoma (MMT) were
randomized to receive whole abdominal radiation versus cisplatin/ifosfamide/mesna chemotherapy (44). 106 patients were eligible. Patients randomized received radiotherapy, the whole abdomen was treated to 3000 cGy, whole pelvis boosted to 5000 cGy. Chemotherapy regimen was specified as ifosfamide 1.5 gram/m²/day x 4 days with mesna 20 mg/m² IV bolus followed by 1.5 gram/m²/day x 4 days, plus cisplatin (20 mg/m²/day x 4 days). Patient demographics and characteristics were similar between arms. The estimated crude probability of recurring within 5 years was 58% and 52%, respectively, in the whole abdominal radiation and chemotherapy arms. Recurrence rate for the chemotherapy arm was 21% lower, which did not translate into a statistically significant advantage, recurrence rate or survival for chemotherapy versus whole abdominal radiation therapy in patients with uterine carcinosarcoma. However, the authors felt that the observed differences favor the use of combination chemotherapy in future trials.

Gestational Trophoblastic Disease (GTD)

During the 1960’s, 1970’s and early 1980’s, established trophoblastic centers in the United States, Europe and the Far East were primarily responsible for major contributions to this disease entity. In patients with poor prognostic GTD, two regimens have been used with moderate success. In the United States, MAC chemotherapy (methotrexate, dactinomycin and chlorambucil) had been championed, and in England, the so-called modified CHAMOMA regimen (hydroxyurea, dactinomycin, vincristine, methotrexate, folinic acid, melphalan and doxorubicin) was given over nine days, which was reported to be effective with relatively low toxicity. The GOG in 1981 began a prospective randomized study of these high-risk patients (duration of disease greater than four months, brain or liver metastasis, beta hCG titers greater than 42,000 mIU/mL, failed previous chemotherapy or postterm pregnancy - at least one of these qualified). Based on a projected 20% decreased toxicity with CHAMOMA, though with equal effectiveness, it was projected that 40 patients per arm were needed. In May 1986, 42 patients had been randomized. Of the 22 patients treated with MAC, 16 (73%) obtained remission with primary therapy, 5 (23%) attained remission with secondary treatment, and 1 (4%) died after achieving normal titers. In contrast, 6 (30%) of 20 patients receiving CHAMOMA died of disease. In addition, 90% of the CHAMOMA patients had grade 3 or 4 toxicity compared with 50% from MAC. As a result of this story, it was felt at that time that MAC was the treatment of choice in poor risk patients with gestational trophoblastic disease (45).

Another important contributory to GTD by the GOG was establishing hormone contraceptive as an effective method of contraception without a trophoblastic detrimental sequela. In a prospective randomized study, patients post-mole were randomly assigned to hormone or barrier contraception. Between 1981 and 1988, 266 patients were entered into the study after evacuation of a mole. In those receiving the hormone contraception, 23% had post-mole GTD, whereas those using barrier methods had a rate of 33%. Time to remission was equal in the two groups. Twice as many women in the barrier group became pregnant in the immediate followup period compared to those on oral contraception. This study suggested that oral contraception are the preferred methods of contraception after evacuation of a mole (46).

Historically, patients with non-metastatic GTD were treated with methotrexate over five days with or without folic acid or dactinomycin, again over five days. The response rates were excellent. The toxicity could be significant, and the five-day course certainly was inconvenient. A weekly methotrexate study (GOG-79) using 30 mg/m² escalating the dose by 5 mg/m² every three doses until a maximum dose of 50 mg/m² was given. There were 65 patients entered into this study. Weekly methotrexate induced a complete response in 81% between three and nine weeks of therapy (median seven weeks). There was a 92% complete response with dactinomycin salvage. Toxicity was minimal (47).

GOG-176 was a phase II study, evaluating dactinomycin 1.25 mg/m² every two weeks in patients with low-risk GTD who failed methotrexate therapy. Of the evaluable patients, 28/38 (74%) obtained complete response. All treatment failures were successfully treated with subsequent chemotherapy (three also had a hysterectomy). Severe toxicity was minimal, causing no patients to discontinue therapy (48).

A randomized phase III trial (GOG 174) in low risk GTD compared 216 eligible patients between biweekly IV dactinomycin 1.25 mg/m² and weekly IM methotrexate 30 mg/m². Response was 73% vs 58% respectively (p=0.03). Most patients who did not respond to their allocated therapy subsequently received the other study drug with either a 1 day or 5 day regime. Patients were followed longitudinally and all who completed follow-up were cured. Both regimes were well tolerated (57).

Vulva

In the middle part of the twentieth century, radical vulvectomy and bilateral groin node dissection had become the standard management of all patients with operative stages of vulvar cancer. Pelvic node dissection was usually performed if groin nodes were positive for metastasis. In the United States, radiation therapy had not been widely used as a primary or adjunctive therapy because of the poor tolerance of the vulva to this therapy, although there was some evidence in controlling groin node metastasis. In 1977, the GOG initiated a phase III randomized study of radiation therapy versus pelvic node resection for carcinoma of the vulva in patients with positive pelvic nodes (GOG-37) (49). Patients had standard radical vulvectomy and bilateral inguinal lymphadenectomy. If positive nodes were present, intraoperative randomization was carried out between pelvic node dissection versus pelvic and groin radiation. Those patients irradiated, 59 of 144 eligible patients, had a two-year survival of 68% and 54% in those individual who randomized to pelvic node dissection. Radiation therapy had the most dramatic survival advantage of those, if those were clinically suspicious or fixed ulcerative
grovin nodes or if two or more positive nodes were present (59% versus 31%, respectively). There was no benefit of radiation therapy in other patients. In this high-risk group of patients, adjunctive groin and pelvic irradiation after primary surgery proved superior to pelvic node dissections. A six-year followup of these patients noted that cancer-related survival continued to favor radiation (P = 0.03). Overall survival and recurrence-free survival no longer significantly favored radiation. For clinically advanced or two or more positive groin nodes, radiation therapy significantly improved cancer-related survival.

From 1977 to 1984, the GOG (36) evaluated 558 patients with vulvar cancer to determine risk factors for nodal metastasis. In 272 women, depth of invasion was ≤ 5 mm. Nodal metastasis was 1/32 if less than 1 mm invasion was present and progressively increased to 19/57 if 5 mm invasion was present. No lymph node metastasis occurred in about one-fourth of the patients with a combination of low-risk factors: No clinical suspicious node, negative capillary-like space involvement, and non-midline cancers that were either grade 1 and had 1-5 mm invasion or grade 2 and 1-2 mm invasion (50).

When all patients (637) were evaluated, almost one-half had minimal invasion (≤5 mm) and one-third had small lesions (≤2 cm). Predictor of nodal metastasis was less tumor differentiation, suspicious or fixed/ulcerated nodes, presence of capillary lymphatic involvement, older age and greater depth of invasion (logistic model). Lesion size and locations were not predictive of lymph node metastasis (51).

GOG-101 was a study of N2/N3 vulvar cancers treated with preoperative chemoradiation (52). After chemoradiation, 38/40 patients became resectable. Lymph node metastasis were negative in 15/37 patients. There were 19 patients who developed a recurrence; 20 are without evidence of disease at the time of the last evaluation. This treatment resulted in a high resectability and local control of lymph node metastasis. In GOG-73, 71 evaluable patients with melanoma of the vulva were studied (53). All patients were required to have a minimum of a modified radical hemivulvectomy. Multiple histopathological factors were evaluated. Independent risk factors for nodal metastasis were capillary lymphatic space involvement and central location. Using multiple regression, age, ACC stage was the only independent prognostic factor. In its absence, Breslow's depth of invasion was most prognostic. Vulvar melanoma is similar to other non-genital cutaneous malignant melanoma.

References


