Cancer Chemotherapy

Professor Clement A. Adebamowo
BM ChB Hons. (Jos), FWACS, FACS, D.Sc. (Harvard)

Division of Oncology, Department of Surgery,
College of Medicine, University of Ibadan,
University College Hospital, Ibadan, Oyo
State, Nigeria
Introduction

- Increased role of chemotherapy in the management of all types of tumor
- Due to:
  - Development of new drugs
  - Development of combination regimes
  - Integration into the overall management of patients
- Most were discovered by chance
  - Recently, targeted development of active molecules has become very important
Principles of new drug development

- It costs approximately $900 million to bring new drugs into the market
- Classically
  - Phase I – assess maximum tolerated dose within a schedule and route of administration
  - Phase II – establish spectrum of activity
  - Phase III – Compare drugs with established treatment methods
  - Phase IV – Post marketing studies, etc
Classification of chemotherapeutic agents

- There are several methods because –
  - Classification can be based on many issues such as structure, biochemical pathways or site of action on the cell cycle
  - They are all limited by the focus on one method of action of the drug, while the drug may have several
- Drugs are either classified on presumed mode of action or on the phase of the cell cycle during which they are active
Cells within tumors consist of 3 subpopulations
- Non-dividing terminally differentiated cells
- Continually proliferating cells
- Resting cells

Tumor growth depends on
- Growth fraction – actively growing fraction of the tumor
- Tumor doubling time
- Rate of cell loss due to immune system’s activity, tumor shedding, apoptosis and necrosis

In most instances, tumor becomes detectable when there is at least $10^9$ cells (1 gm)
Cancer chemotherapy

- Many of the current concepts in cancer chemotherapy arise from the Skipper-Schabel model for tumor growth. Simply stated,
  - if one dose of a drug (d) improved survival by a certain time interval (t), then additional doses (z) would improve survival by $z \times t$. Therefore chemotherapy always kill a constant fraction of cells – first order kinetics

- This model was based on the L1210 murine leukemia model whose attributes include exponential growth and spontaneous generation of drug resistant phenotypes
Cancer chemotherapy

- However the observation that cures are rare and patients with early disease treated on the basis of this model relapse suggest that the Skipper-Schabel model is inadequate.
- Gompertz provided an alternative model which applies to most growth phenomenon in biology.
The Gompertzian model suggests that unimpeded growth eventually leads to a plateau phase of slow growth and functionally stable cell population size.

This model led Norton and Simon to propose the theory that cell kill is proportional to growth activity and that some drugs are cell-cycle dependent – their efficacy is dependent on growth activity of the particular cancer. Simply put, the rate of response to them is higher when growth rate is higher.
Implications of the Gompertzian growth model

- initial tumor growth is first order, with later growth being much slower
- smaller tumor grows slowly but large % of cell dividing
- medium size tumor grows more quickly but with smaller growth fraction
- large tumor has small growth rate and growth fraction
Implication of Gompertzian model of clinical presentation

Number of cancer cells over time:
- Undetectable cancer
- Detectable cancer
- Limit of clinical detection
- Host death

Diagnostic threshold (1cm): $10^{12}$
Cancer chemotherapy

- New theory of tumor growth has been proposed because of:
  - Discrepancy between the exponential tumor growth theory and experimental \textit{in vivo} data
  - Lower than predicted activity of tumor cells
  - Greater than expected aneuploidy

- Based on fractal nature of the contours of tumors and cell colonies and their scale invariance (self-affine character) allowing use of scaling analysis
Cancer chemotherapy

- Brú et al., applied this theory to cell lines and in vivo tumors and found that their growth is compatible with molecular beam epitaxy (MBE) universality class characterized by:
  - Linear growth rate
  - Constraint of growth activity to the outer border of the cell colony or tumor
  - Diffusion at the colony surface
Cancer chemotherapy

- Implications
  - All tumors exhibit similar growth dynamics
  - It contradicts the Gompertzian model which is based on nutrient limitation ideas derived from studying bacterial colonies
  - Cell diffusion on the border is balanced with random duplication
  - Movement of cells away from the tumor does not influence growth
Cancer chemotherapy

- Tumor growth is linear to the extent that the rate changes with time in a completely linear way.
- There are less actively dividing cells which are constrained at the border of the tumor or colony.
- Cell movement occurs at the front invalidating the hypothesis that the main mechanism responsible for tumor growth is nutrient competition.
- Tumor cells invariably move to the position with the lower nutrient content because that is where they are surrounded by the most number of cells.
**Cancer chemotherapy**

- Consequences of these hypothesis
  - Effectiveness of chemotherapy depends on specific surface of tumors and decreases as the tumor size decreases
  - Efficacy of chemotherapy will be lower than expected if all the cells are proliferating
  - Primary and metastases show the same growth characteristics
  - Aneuploidy is more common in advanced than in early tumors. The somatic mutation in tumors is linked to number of mitosis. In exponential growth, each cell must undergo 32 divisions to reach a 2 cm$^3$ size tumor
Cancer chemotherapy

- However with this theory, cells near the surface would divide about 30 times more than cells in the center and therefore a higher number of somatic mutations occur in the cells at the border.
- Therefore if metastases are generated from the cells at the border, then the mets will have more aneuploidy.
- The most malignant cells are located at the tumor border and degree of malignancy should progress along the tumor radius.
- Inhibition of cell proliferation in tumors was often ascribed to necrosis but often not demonstrated. This hypothesis suggest that the inhibitory factor is cell density and pressure.
Cell cycle

- $G_1$ - RNA and protein synthesis – cells that are committed to dividing enter this phase. They undergo preliminary synthetic cellular processes that prepares them for the next (S) phase.
- $S$ - DNA synthesis and replication of the genome occurs. The genome becomes tetraploid.
- $G_2$ - RNA and protein synthesis. This is a second resting phase prior to mitosis.
- $M$ - mitosis.
THE CELL CYCLE

DEATH

DIFFERENTIATION

DNA content = 4n

M

G2

G1

S

DNA synthesis

DNA content = 2n

G0
Characteristics of Cancer and Normal Cells

**CANCER CELLS**
- Loss of contact inhibition
- Increase in growth factor secretion
- Increase in oncogene expression
- Loss of tumor suppressor genes
- Frequent mitoses
- Nucleus
- Blood vessel
- Abnormal heterogeneous cells

**NORMAL CELLS**
- Oncogene expression is rare
- Intermittent or coordinated growth factor secretion
- Presence of tumor suppressor genes
- Few mitoses
- Normal cell
- Blood vessel
GROWTH FACTORS AND ONCOGENES

- Paracrine (Adjacent cells)
- Autocrine stimulation
- Growth Factor and Receptor Synthesis
- Gene Activation
- Oncogenes
- Post receptor signal transduction pathways

Growth Factor
Growth Factor Receptor
ONCOGENESIS

NORMAL GROWTH AND DEVELOPMENT

NORMAL EXPRESSION

CELLULAR ONCOGENE

INCREASED OR ABNORMAL EXPRESSION

CANCER GROWTH

MUTAGENIC OR CARCINOGENIC AGENTS

VIRAL ONCOGENE
Chemotherapy

Basic Principles

● Growth rate
  ◆ Rate of increase in tumor size
  ◆ Plateaus with time
  ◆ Due to hypoxia, decreased nutrients, increased cell death

● Growth fraction
  ◆ Defined as the proportion of actively proliferating cells
  ◆ $G_0$ - rest phase
Chemotherapy

Basic Principles

- Greatest efficacy against cycling cells
- high growth fraction $\Rightarrow$ ↑ chemosensitivity
  - neoplastic cells
  - gastrointestinal mucosa
  - bone marrow
- Low growth fraction $\Rightarrow$ ↓ chemosensitivity
  - plateau phase of growth
  - cells in $G_0$
Chemotherapy

Basic Principles

- Pharmacologic principles
  - peak plasma concentration vs. concentration over time
    - varies with drug
    - affects optimal method of administration
  - therapeutic index
    - ratio of toxic dose to effective antitumor dose
    - optimal dose balances toxicity to tumor and host
    - body surface area vs. body weight dosing
Chemotherapy

Basic Principles

- Goals of treatment must be clearly defined
  - cure vs. palliation
  - acceptable toxicity
  - quality of life
- Cures are rare
  - aggressive therapy
  - short-term toxicity
Chemotherapy
Basic Principles

- detailed patient evaluation and staging
  - accurately define extent of disease
  - detect concurrent disease
  - identify paraneoplastic syndromes
    - CBC, chemistry panel, urinalysis
    - Imaging (radiographs +/- ultrasound)
    - Histologic diagnosis of malignancy
Chemotherapy Safety

- Safe storage
  - clear labels for all cytotoxic drugs
  - storage shelves or bins with front barriers
  - separate ziploc bags for refrigerated drugs
- no eating, drinking or cosmetic application in any area where drugs are handled
- minimize exposure for women of child-bearing age
Chemotherapy Safety

- Drug reconstitution
  - isolated, draft-free area
  - cover work area with plastic backed absorbent liner
  - protection from aerosol exposure
    - fume hood or biologic safety cabinet
    - high efficiency respirator mask
      - surgical masks inadequate
    - venting devices or alcohol dampened gauze pads
Chemotherapy Safety

Drug reconstitution (cont’d)

- talc-free latex gloves
  - wash hands before gloving, after degloving
- disposable low-permeability gown
  - isolation gowns inadequate
- protective eyewear or face shield
- transport drugs to administration area in well labeled ziploc container
Chemotherapy Safety

• Drug administration
  ◆ recheck drug selection and dose calculation
  ◆ latex gloves, low-permeability gown and eye protection
    • restraint and drug administration personnel
  ◆ aseptically placed indwelling catheter
  ◆ Luer lock syringes
Chemotherapy Safety

- Patient care after chemotherapy
- Disposal of contaminated items and waste
  - contaminated soft goods bagged separately and labeled (IV lines, gown, gloves, etc.)
  - contaminated sharps in separate container
  - follow appropriate regulations
Alkylating agents

- Examples are cyclophosphamide, chlorambucil, melphalan
- These are highly reactive drugs that restrict the action of biological molecules such as proteins and DNA by binding to them
- They add alkyl groups to the electronegative groups in cancer cells
Antimetabolites

- Methotrexate, 5-FU, cytosine arabinoside, pemetrexed
- These drugs masquerade as either purines or pyrimidines and prevent these substances becoming incorporated into DNA during the “S” phase of the cell cycle
- Act by inhibiting specific metabolic pathways, usually of DNA synthesis, thus preventing replication and inducing cell death
Plant alkaloids

- Vincristine, vinblastine, taxanes
- Cause mitotic arrest by poisoning the spindles
- Mitotic spindles are vital for cell division
Antibiotics

- Adriamycin, epirubicin, bleomycin
- Cause linkage of double strands of DNA and prevent replication
Podophyllotoxin

- This is a plant derived compound that is used to produce
  - Etoposide, Teniposide
- They prevent the cell from entering the G1 and the S phase of the cell cycle
Platinum compounds

- Cisplatinum, Carboplatin, Oxaliplatin
- They are alkylating agents and they form cross-linking adducts thus blocking DNA replication and transcription
- Oxaliplatin is part of the FOLFOX4 regime used to treat colorectal cancer with 51% response rate and time to progression of 9 months and median survival of 16.2 months
Topoisomerase inhibitors

- Topoisomerases are enzymes essential for maintaining the topology of DNA.
- Inhibition of type I or II topoisomerases interferes with both transcription and replication of DNA by upsetting proper DNA supercoiling.
- Camptothecins e.g. Irinotecan, topotecan – inhibits topoisomerase I
- Type II inhibitors include etoposide, teniposide
Hormonal treatment

- Anti-estrogen
  - Radiation, surgical or medical oophorectomy
    - Tamoxifen, Raloxifene

- Estrogen

- Aromatase inhibitors
  - Anastrozole, Letrozole
Hormonal therapy

- Steroids e.g. Dexamethasone – used to inhibit tumor growth, reduce inflammation and the edema associated with it, prevent vomiting and cause regression of lymph node malignancies
- Anti-testosterone e.g. finasteride blocks peripheral conversion of testosterone to dihydrotestosterone
Hormonal therapy

- Gonadotropin-releasing hormone agonists (GnRH) e.g. goserelin produced paradoxical negative feedback effect followed by inhibition of the release of FSH and LH when given continuously
Biological agents

- HER1/EGFR tyrosine kinase inhibitor.
  - This inhibition prevents intracellular phosphorylation of EGFR which is expressed on the cell surface of normal and cancer cells
  - Cetuximab, Gefinitib, Erlotinib

- VEGF inhibitor
  - Molecules that bind to VEGF to reduce microvascular growth and inhibit progression of metastatic disease
  - Bevacizumab
Biologics

- Cancer vaccines
  - G17DT, an immunoconjugate of amino-terminal sequence of gastrin-17 linked to diphteria toxoid
  - Vaccine against Hepatitis B
  - Anti-HPV vaccine
Miscellaneous

- COX-2 inhibitors
  - Celecoxib
- Heparin
- Heat shock protein inhibitors - Geldanamycin
Mechanism of action in relation to the cell cycle

- **Cell cycle specific**
  - Drugs that act on cells within the cell cycle
  - They can be subclassified into
    - Phase specific – when they are active in only certain phases of the cell cycle, e.g. 5FU
    - Phase non-specific where the phase does not matter, e.g. cyclophosphomide
  - Tend to have a linear dose response curve
  - There is a plateau to their cell kill ability

- **Cycle non-specific**
  - These drugs act on all phases of the cell cycle, for example, asparaginase, corticosteroids
**Cell-cycle, phase-specific agents**

- **S-phase dependent drugs**
  - Capecitabine, Cytarabine, Doxorubicin, 5-Fluorouracil, Methotrexate

- **M-phase dependent drugs**
  - Vinca alkaloids, taxanes

- **G2 phase-dependent drugs**
  - Irinotecan, bleomycin

- **G1 phase dependent**
  - Asparaginase, corticosteroids
SITES OF ACTION OF CYTOTOXIC AGENTS

Cell cycle level

Antibiotics

Antimetabolites

S
(2-6h)

G2
(2-32h)

M
(0.5-2h)

Alkylating agents

G1
(2-∞h)

G0

Vinca alkaloids

Mitotic inhibitors

Taxoids
SITES OF ACTION OF CYTOTOXIC AGENTS

Cellular level

DNA synthesis

DNA transcription

DNA duplication

Intercalating agents

Antimetabolites

Alkylating agents

Mitosis

Spindle poisons
SITES OF ACTION OF CYTOTOXIC AGENTS

- **PURINE SYNTHESIS**
  - 6-MERCAPTOPURINE
  - 6-THIOGUANINE

- **PYRIMIDINE SYNTHESIS**
  - METHOTREXATE
  - 5-FLUOROURACIL
  - HYDROXYUREA

- **RIBONUCLEOTIDES**
  - CYTARABINE

- **DEOXYRIBONUCLEOTIDES**
  - ETOPOSIDE

- **DNA**
  - ALKYLATING AGENTS
  - ANTIBIOTICS

- **RNA**
  - L-ASPARAGINASE
  - VINCA ALKALOIDS

- **PROTEINS**
  - MICROTUBULES

- **ENZYMES**
Principles of combination chemotherapy

- In general, combination chemotherapy is superior to single-agent therapy.
- While some were discovered by accident, others were designed based on the following considerations:
  - Drug should be active as a single agent
  - Avoid drugs with similar toxicity
  - Use drugs with different mechanisms of actions
  - Use maximum therapeutic doses
Clinical chemotherapy

- 3 factors affect how, where and when chemotherapy is to be used

  - Patient related factors
    - Diagnosis
    - Site and histology of tumor
    - Patients clinical condition, e.g. WHO or ECOG or Karnofsky performance indices
    - Other treatments that the patient may be getting

  - Environment related factors
    - Type and quality of equipment
    - State of support services
    - Availability of adjuvant treatment

  - Health care provider related factor
Criteria for monitoring response

- **RECIST (Response Evaluation Criteria in Solid Tumors)**
  - Objective response – change in longest diameter of target lesion(s)
  - Complete response (CR) – disappearance of all target lesions confirmed 4 or more weeks after treatment
  - Partial response - > 30% decrease from baseline at more than 4 weeks
  - Progressive disease - >20 increase in size or appearance of new lesions
  - Stable disease – neither PR nor PD
Criteria for monitoring response

● WHO
  ◆ Objective response – change in longest diameter of target lesions
  ◆ Complete response – disappearance of all known disease confirmed at more than 5 weeks
  ◆ Partial response - >50% decrease from baseline at 4 weeks
  ◆ Progressive disease - >25% increase in size of lesions
  ◆ Stable disease – Neither PR nor PD
Chemotherapy Drug Resistance

Drug may be actively pumped out of the cancer cell using a protein called p-glycoprotein.
Chemotherapy resistance

- Cancer cells may mutate and develop pathways that are independent of those blocked by the chemotherapy.
- Gene amplification can lead to an overproduction of proteins that are blocked by the anticancer agent.
- The cancer cell may no longer take the drugs from the interstitial fluids into themselves either because they stop making the relevant transport protein or the protein stops working.
Chemotherapy resistance

- Cancer cells may develop mechanisms that inactivate the chemotherapeutic agent
- The cancer cell may learn to repair the DNA and protein damages that are induced by the anti-cancer drugs
- Resistant clones of cancer cells may develop
- This is why it is important to use the best treatment protocol first in patient management
Chemotherapy resistance

- Primary resistance – when the cancer does not respond to standard chemotherapy from the very first exposure
- Acquired resistance – when the tumor initially responds then becomes resistance
- Drugs like verapamil, diltiazem and quinidine overcome chemotherapy resistance in cell culture and have been used clinically
Routes of administration of chemotherapy

- Intrathecal, intraventricular in meningeal metastases from leukemia, lymphoma, breast cancer etc
- Intrapericardial – in malignant pericardial effusions
- Intraperitoneal in ovarian cancer, colorectal cancer, mesothelioma
- Intra-arterial in liver cancer
- Isolated limb perfusion in melanoma
- Intravenous
- Oral
Routes of administration

Repeated intravenous administration may lead to peripheral thrombo-phlebitis and venous inaccessibility. In order to avoid repeated venipuncture, increased access and permit patient mobility particularly in continuous infusion regimes, Port-a-cath was developed for implantation under the skin and central venous access.
Definition of terms

- Combined modality chemotherapy is the use of several drugs in combination with other modalities for cancer treatment.
- Neoadjuvant chemotherapy – when the initial chemotherapy is given to shrink the tumor and make it amenable to other treatments or make those other treatments less destructive.
**Definition of terms**

- Adjuvant chemotherapy – when chemotherapy is used in situations where it is presumed that there is little cancer present.
- Palliative chemotherapy – when chemotherapy is used without curative intent, but to decrease tumor load and increase life expectancy.
Examples of cancers and result of chemotherapy

- **Cure**
  - Acute leukemia in children
  - Testicular carcinoma
  - Wilm’s tumor
  - Retinoblastoma
  - Choriocarcinoma

- **Improved survival**
  - Ovarian cancer
  - Breast cancer
  - Adult acute leukemia
  - Osteogenic carcinoma
Examples of cancers and result of chemotherapy

- Responsive tumors, but no improvement in outcome
  - Head and neck cancers
  - Endocrine gland cancers
  - Soft tissue sarcoma
- Marginally responsive/unresponsive
  - Bladder carcinoma
  - PLCC
  - Cancer of the esophagus
Performance status measurements and quality of life

- Before, during and after chemotherapy, it is important to monitor the response to the treatment and patient’s quality of life.
- Popular instruments in oncology include
  - Karnofsky performance index – ranges from 100% = normal to 0% = death
  - ECOG – from 0 = asymptomatic to 5 = death
Complications of chemotherapy

- Gastrointestinal
  - Nausea, vomiting, mucositis, gastrointestinal infections – almost all the drugs

- Hematological
  - Anemia, leucopenia, thrombocytopenia – almost all the drugs

- Skin
  - Alopecia, darkening of the skin, nail changes – particularly noticeable with 5FU
Complications of chemotherapy

- Endocrine
  - Infertility, Irregular periods, amenorrhea – almost all

- Neurological complications
  - Peripheral neuropathy, fatigue, loss of interest, confusion – common with the plant alkaloids
Complications of chemotherapy

- Ototoxicity – platinum compounds
- Second tumors – alkylating agents, procarbazine
- Cardiac toxicity – anthracyclines, cyclophosphomide
- Pulmonary toxicity – bleomycin, busulfan
- Bladder toxicity - cyclophosphomide
- Nephrotoxicity – Platinum compounds
Prevention and management of complications

- **Immunosuppression**
  - Fresh blood transfusion
  - Broad spectrum antibiotics
  - Colony-stimulating factors, e.g. filgrastim
  - Bone marrow stem cells derived from autologous bone marrow cell transplant

- **Anemia**
  - Erythropoietin
  - Blood transfusion
Prevention and management of complications

- Nausea and vomiting
  - 5-HT3 receptor inhibitors like ondasetron, granisetron
  - Cannabinoids

- Tumor lysis syndrome
  - Particularly during treatment of chemo-responsive lymphomas

- Secondary cancer
  - Requires careful follow-up
Chemotherapy regimes can also be planned to include supportive treatments:

- Addition of leucovorin (folinic acid) to increase the total amount of antimetabolites (5FU, Methotrexate) that can be given to patients.
- Colony stimulating factor and erythropoietin can be used to supplement high dose chemotherapy.