PRINCIPLES OF ANTINEOPLASTIC THERAPY

INTRODUCTION

This section of the hematology-oncology handbook is an overview of antineoplastic drugs. It is intended for the physician, physician assistant, nurse, or pharmacist new to the area of oncology. It is meant to provide thumbnail sketches of anticancer drugs and does not serve as a comprehensive review of each agent. Not all anticancer drugs are included but those most pertinent to practice today and those for which immediate mastery is very important are included. The emphasis is on parenteral agents although some oral agents are included. The reader should recognize that information about anticancer drugs is ever changing and reference to various contemporary sources should always be considered.

PRINCIPLES OF CANCER CHEMOTHERAPY

1) Antineoplastic drugs are one of three potential modalities in the treatment of cancer. The other two are **surgery** and **radiation therapy**. Antineoplastics can be used as primary treatment in tumors not amenable to surgery or radiation such as leukemia or in widespread metastatic disease. Most commonly, chemotherapy is used in conjunction with surgery or radiation or both.

2) Many antineoplastics act at different phases of the **CELL CYCLE.** Agents that act at a particular part of the cell cycle are described as cell cycle specific. Many other antineoplastics are instead cell cycle nonspecific.

   G_0 Dormant phase. Cell is resting and is not committed to cell division. When cells are in G_0 they are not sensitive to chemotherapy.

   G_1 Postmitotic phase when synthesis of many enzymes necessary for DNA synthesis occurs. Glucocorticoids and asparaginase most active

   S Unwinding of DNA. Synthesis of DNA. Active drugs include methotrexate, fluorouracil, floxuridine, thioguanine, mercaptopurine, cytarabine, doxorubicin, hydroxyurea, glucocorticoids, and procarbazine. Percentage of cells in the S phase can be measured by flow cytometry ("S-phase fraction"), and is an indicator of cellular turnover. A large S phase fraction indicates a greater tumor turnover.

   G_2 Premitotic phase when RNA and specific proteins are synthesized ($t_{1/2}$ = 2 – 10 hours). Bleomycin and etoposide are active

   M Mitosis – cell division takes place; $t_{1/2}$ = 0.5 – 1 hour. Vincristine, vinblastine, paclitaxel active

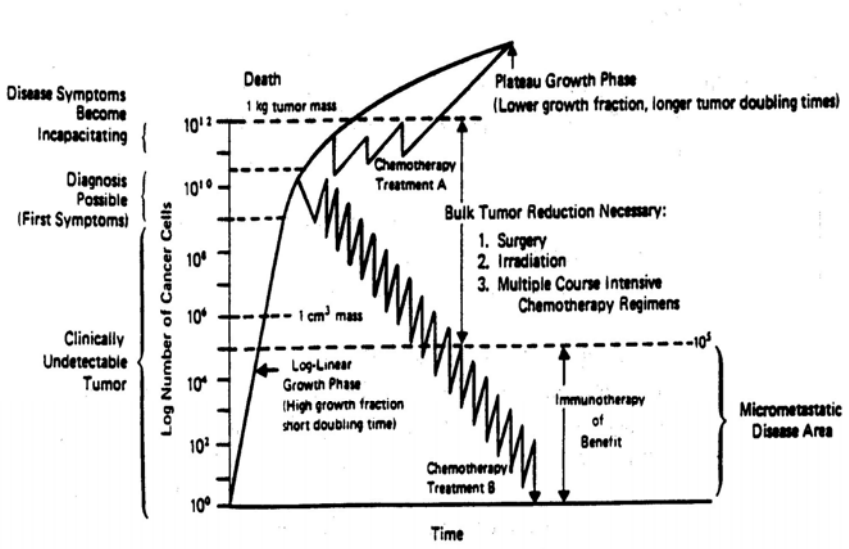
Cell Cycle Nonspecific Drugs

Busulfan	Cyclophosphamide	Idarubicin	Mitomycin C
Carmustine	Dactinomycin	Ifosfamide	Mitoxantrone
Carboplatin	Daunorubicin	Lomustine	Streptozocin
Chlorambucil	Doxorubicin	Mechlorethamine	Thiotepa
Cisplatin	DTIC	Melphalan	

3) Factors Affecting Chemotherapy Effectiveness

A) Correct diagnosis. The minimum detectable size of a tumor is 1 cc in volume, which weighs 1 g and contains 1 billion cells. Prior to administering antineoplastic agents, appropriate diagnosis from a tissue specimen must be performed.

B) Gompertzian growth versus fractional cell kill. The rate of tumor growth is initially rapid and then flattens off. Gompertzian growth means the tumor takes the same amount of time to double in size until it slows down because it out grows its blood supply. Chemotherapy kills the same fraction of tumor cells each time. The effectiveness of chemotherapy will depend on whether the fraction of cells killed each time is greater than the fraction of tumor cells that regrow in between cycles.



Reference: Buick RN. Cellular Basis of Chemotherapy. In: Cancer Chemotherapy Handbook, 2nd Edition. Editors: Dorr RT, Von Hoff DD. Appleton and Lange.

C) Sanctuary sites, metastatic disease, or poor tumor vascularity. The tumor may spread to sites chemotherapy can't reach such as the CSF or sites of poor blood flow and may prevent delivery of chemotherapy throughout the mass.

D) Failure to adequately debulk a tumor.

E) Primary and secondary resistance. The tumor is originally resistant or a resistant subset emerges after therapy begins.

F) Failure to maintain dose intensity by reducing the dose or lengthening the interval between treatments. Dose intensity is less of a problem due to neutropenia because of the colony stimulating factors.

4) Creating a Chemotherapy Regimen:
   A) Single agent therapy rarely is curative.
   B) Each drug in a regimen should be active alone against the particular tumor.

C) Choose drugs with different mechanisms of action, which will compliment each other.
D) Choose drugs with different types of toxicity and/or timing of toxicity.
E) Consider the patient's previous history of chemotherapy and radiation, especially bone marrow reserve.
F) Consider the patient's renal, hepatic, cardiac, pulmonary, neurologic, nutritional and overall performance status.
G) Consider the patient's vascular access status.
H) Optimize dose and schedule so that the maximal dose of each drug relative to the others is given as quickly as the most sensitive host tissue recovers.
I) What is the goal of therapy-**cure** versus **palliation**
J) Number of complete remissions-CR is a prerequisite for cure
K) Duration of disease control - disease free survival-a measure of the quality of a CR.
L) Chemotherapy is dosed on body surface area (BSA) because this allows interspecies comparison and because BSA correlates well with cardiac output, which reflects blood flow to the liver and kidney.
M) To calculate BSA use slide rules, a nomogram, or this handy formula

$$BSA = \sqrt{\frac{\text{Height (in cm)} \times \text{Weight (in kilograms)}}{3600}}$$

5) DEFINITIONS:

INDUCTION- Chemotherapy given to achieve a remission.

CONSOLIDATION - Chemotherapy given after induction to control microscopic disease. Drugs given in consolidation usually have a different mechanism of action from those given in induction or else are given in higher doses. Typically given as part of leukemia regimens.

MAINTENANCE - Chemotherapy given on a long-term basis to maintain a remission.

COMPLETE REMISSION - The elimination of all signs and symptoms of disease as measured by radiographic means, laboratory tests, and physical examination, lasting more than one month. See specific diseases for various definitions.

PARTIAL REMISSION - A 50% or greater reduction in sum of products of greater and lesser diameters of all measured lesions lasting at least 1 month, and an absence of any new lesions during treatment.

PROGRESSIVE DISEASE - A 25% or greater increase in sum of products of greater and lesser diameters of all measured lesions or development of new lesions.

ADJUVANT THERAPY - Chemotherapy given during or after surgery or radiation in order to eliminate microscopic disease and reduce the risk of relapse.

NEO-ADJUVANT THERAPY - Chemotherapy commonly given prior to surgery or radiation in order to shrink the tumor so it is amenable to surgery or radiation.