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Models of Anti-Cancer Therapy

Classical Chemotherapy

Mechanisms, Toxicities and the Therapeutic Window

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ABSTRACT

Chemotherapy can be best used by understanding the principles of pharmacology, tumor biology, cellular kinetics and drug resistance. Here we try to focus on the major classes of chemotherapeutic drugs, their mechanisms of action, toxicities, and the therapeutic window.

THE THERAPEUTIC WINDOW

The therapeutic window is the range of plasma drug concentrations with a high probability of therapeutic success, defined as tumor shrinkage. The therapeutic window for a typical population is sometimes inappropriate for an individual patient. This is related to the differing metabolism of chemotherapeutic agents in different individuals. The coexistence of genetic polymorphisms in drug metabolizing enzymes, targets, receptors, and transporters, in the context of drug and non-drug influences, may result in high frequencies of unusual drug toxicities. This has given rise to the new field of pharmacogenetics. The importance of the therapeutic window is related to the fact that to be effective the drug concentrations have to be in the appropriate range. Levels too high will increase toxicity without adding to clinical benefit and levels too low may not produce optimum benefit.

Normal Cell Kinetics. The cell cycle is composed of four phases. Cells that are committed to divide enter the G_1 phase. Preliminary synthetic cellular processes occur that prepare the cell to enter the DNA synthetic (S) phase. Specific protein signals regulate the cell cycle and allow replication of the genome where the DNA content becomes tetraploid (4N). After completion of the S phase, the cell enters a second resting phase, G_2, prior to undergoing mitosis. The cell progresses to the mitotic (M) phase, in which the chromosomes condense and separate and the cell divides, producing two daughter cells.

Chemotherapeutic agents may be cell cycle specific or cell cycle-nonspecific. Cell cycle non-specific drugs, like the alkylating agents have a linear dose-response curve; that is, the fraction of cell kill increases linearly with the dose of drug. However, cell cycle-phase-specific drugs have a plateau with respect to cell killing ability. For example cytarabine is active only in the S phase

Tumor Cell Kinetics. The growth of a tumor depends on several closely related factors:

1. Cell cycle time, or the average time for a cell that has just completed mitosis to grow, re-divide and again pass through mitosis, determines the maximum growth rate of a tumor.
2. Growth fraction is the fraction of cells undergoing cell division. This fraction is usually vulnerable to chemotherapy.
3. The total number of cancer cells in the population is an indicator of total cancer burden. As the number of cells increases, so does the number of resistant cells, which leads to decreased curability. Large tumors also have greater compromise of blood supply and therefore impaired drug delivery to the tumor.

Variations in these three factors are responsible for the variable rates of tumor growth observed among tumors of differing histologies, as well as among metastatic and primary tumors of the same histology. Tumors characteristically exhibit a sigmoid-shaped Gompertzian growth curve, in which tumor doubling time varies with tumor size. Tumors grow most rapidly at small tumor volumes. As tumors become larger, growth slows based on a complex process dependent on cell loss and tumor blood and oxygen supply. In order to have the best chance for cure, chemotherapy must be given that can achieve a fractional cell kill in a logarithmic fashion (i.e., 1-log-kill is 90% of cells, 2-log-kill 99% of cells). From these concepts, chemotherapy models have been developed utilizing alternating non-cross-resistant therapies, induction-intensification approaches, and adjuvant chemotherapy regimens.

Principles of Combination Chemotherapy. Combination chemotherapy provides maximum cell kill within the range of toxicity tolerated by the host for each drug. It also offers a broader range of coverage of resistant cell lines in a heterogeneous tumor population and prevents or slows the development of new drug-resistant cell lines. Drugs with different mechanisms of action and differing dose-limiting toxicities should be combined in order to allow for additive or synergistic effects on the tumor with minimum toxicity.

Dose Intensity. Kinetic principles predict that, for drug-sensitive cancers, the factor limiting the capacity to cure is proper dosing. A dose reduction of approximately 20% can lead to a loss of up to 50% of the cure rate. Conversely, a 2-fold increase in dose can be associated with a 10-fold (1-log) increase in tumor cell kill in animal models.

Drug Resistance. The most common mechanism of drug resistance is related to altered gene expression. Cells in the G_0 phase are generally resistant to all drugs active in the S phase. Chemotherapeutic agents may be unable to kill tumor cells if there is insufficient drug concentration due to their presence in body locations where it is difficult to achieve effective drug concentrations or if there is some alteration in the metabolism of the drug after it is administered.

MDR-1-Mediated Multidrug Resistance. Repeated exposure of a tumor to a single anti-neoplastic agent will generally result in cross-resistance to the drug and agents of the same drug class as the original drug. This can be due to the over expression of the MDR-1 gene, which encodes a 170-kd transmembrane P-glycoprotein.

P-glycoprotein is an energy-dependent pump that serves to remove exogenous toxins or endogenous metabolites from the cell. It is found in a wide range of normal tissues, including adrenal tissue, cells lining the renal tubule, cells lining the jejunum and colon, cells lining the bile canaliculi, and endothelial cells of capillaries in the brain and testes. A high level of MDR expression is reliably correlated with resistance to cytotoxic agents. Tumors that intrinsically express the MDR1 gene prior to chemotherapy characteristically display poor durable responses. MDR1 expression represents one of the most important mechanisms of acquired drug resistance. Rates of P-glycoprotein are commonly increased at relapse when compared to rates at diagnosis. Chemotherapeutic agents subject to MDR-1-mediated resistance include the anthracyclines, vinca alkaloids, paclitaxel , etoposide and mitomycin.

CHEMOTHERAPEUTIC AGENTS CLASSIFIED BY MECHANISM OF ACTION

Alkylating Agents. The alkylating agents impair cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules. The important sites of alkylation are on DNA, RNA, and proteins. The chemotherapeutic and cytotoxic effects are directly related to the alkylation of nitrogen at the 7 position of guanine in DNA. Alkylating agents depend on cell proliferation for activity but are not cell cycle phase-specific. A fixed percentage of cells are killed at a given dose. Tumor resistance probably occurs through efficient glutathione conjugation or by enhanced DNA repair mechanisms. Alkylating agents are classified according to their chemical structures and mechanisms of covalent bonding; this drug class includes the nitrogen mustards, nitrosoureas, and platinum complexes, among other agents.

Nitrogen Mustards. The nitrogen mustards, which include such drugs as mechlorethamine, mitomycin-C, vinca alkaloids, platinum and the anthracyclines are powerful local vesicants; as such, they can cause problems ranging from local tissue necrosis, to pulmonary fibrosis, to hemorrhagic cystitis. The metabolites of these compounds are highly reactive in aqueous solution, in which an active alkylating moiety, the ethylene immonium ion, binds to DNA. The hematopoietic system is especially susceptible to these compounds. Dose limiting toxicity (DLT) includes myelosuppression and severe nausea and vomiting are common side effects. Occasionally alopecia, sterility, diarrhea and thrombophlebitis may be seen.

Nitrosoureas. The nitrosoureas are distinguished by their high lipid solubility and chemical instability. These agents rapidly and spontaneously decompose into two highly reactive intermediates: chloroethyl diazohydroxide and isocyanate. They are thought to act through alkylation as well. The lipophilic nature of the nitrosoureas enables free passage across membranes; therefore, they rapidly penetrate the blood-brain barrier, achieving effective CNS concentrations. As a consequence, these agents are used for a variety of brain tumors. Their dose limiting toxicity is myelosuppression.

Platinum Agents. Cisplatin is an inorganic heavy metal complex that has activity typical of a cell cycle-phase-nonspecific alkylating agent. The compound produces intra-strand and inter-strand DNA cross-links and forms DNA adducts, thereby inhibiting the synthesis of DNA, RNA, and proteins. Carboplatin has the same active diamine platinum moiety as cisplatin, but this is bonded to an organic carboxylate group that allows increased water solubility and slower hydrolysis to the alkylating aqueous platinum complex, thus altering toxicity profiles. Dose limiting toxicities for cisplatin are renal insufficiency, peripheral sensory neuropathy and ototoxicity. For carboplatin the DLT is myelosuppression, especially thrombocytopenia.

Antimetabolites. Antimetabolites are structural analogs of the naturally occurring metabolites involved in DNA and RNA synthesis. Their major effect is interfering with the building blocks of DNA synthesis and they are therefore most active in the S phase of the cell cycle and have little effect on the cells in G_0. Consequently, these drugs are most effective in tumors that have a high growth fraction. Antimetabolites have a nonlinear dose-response curve, such that, after a certain dose, no more cells are killed despite increasing doses (fluorouracil [5-FU] is an exception). The antimetabolites can be divided into folate analogs, purine analogs, pyrimidine analogs, adenosine analogs, and substituted ureas. These include methotrexate, fluorouracil, cytarabine, gemcitabine, pentostatin, fludarabine and cladiribine.

Natural Products. A wide variety of compounds possessing antitumor activity have been isolated from natural substances, such as plants, fungi, and bacteria. Likewise, selected compounds have semisynthetic and synthetic designs based on the active chemical structure of the parent compounds, and these, too, have cytotoxic effects.

Antitumor Antibiotics. Bleomycin preferentially intercalates DNA at guanine-cytosine and guanine-thymine sequences, resulting in spontaneous oxidation and formation of free oxygen radicals that cause strand breakage. Major DLT is pulmonary toxicity occurring in 10–40% of the treated patients usually 4 to 10 weeks after starting therapy. Fevers, chills, anorexia and dermatologic toxicity are also frequently seen.

Anthracyclines. The anthracycline antibiotics are products of the fungus Streptomyces percetus var caesius. They are chemically very similar, with a basic anthracycline structure containing a glycoside bound to an amino sugar, daunosamine. The anthracyclines have several modes of action. Most notable is intercalation between DNA base pairs and inhibition of DNA topoisomerases I and II. Oxygen

free radical formation from reduced doxorubicin intermediates is thought to be a mechanism associated with cardiotoxicity.

Epipodophyllotoxins. Etoposide is a semisynthetic epipodophyllotoxin extracted from the root of Podophyllum peltatum (mandrake). It inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex; this ultimately results in the inability to synthesize DNA, and the cell cycle is stopped in G_1 phase. Myelosuppression is the DLT for this class of agents.

Vinca Alkaloids. The vinca alkaloids are derived from the periwinkle plant, *Vinca rosea*. This category includes vincristine, vinblastine and vinorelbine.Upon entering the cell, vinca alkaloids bind rapidly to the tubulin and inhibits its assembly.This binding occurs in S phase at a site different from that associated with paclitaxel and colchicine. Thus, polymerization of microtubules is blocked, resulting in impaired mitotic spindle formation in the M phase. Peripheral neurotoxicity is the DLT for this class of agents.

Taxanes. Paclitaxel and docetaxel are semisynthetic derivatives of extracted precursors from the needles of yew plants. These drugs have a novel 14-member ring, the taxane. Unlike the vinca alkaloids, which cause microtubule disassembly, the taxanes promote microtubule assembly and stability, therefore blocking the cell cycle in mitosis. Docetaxel is more potent in enhancing microtubule assembly and also induces apoptosis. The major side effects of paclitaxel include myelosuppression, peripheral neurotoxicity, myalgias and acute hypersensitivity reactions. In addition, docetaxel can cause a syndrome of cumulative fluid retention characterized by peripheral edema and occasionally pericardial and pleural effusions.

Camptothecin analogs. include irinotecan and topotecan. These semi-synthetic analogs of the alkaloid camptothecin, derived from the Chinese ornamental tree, *Camptotheca acuminata*, inihibit topoisomerase I and interrupt the elongation phase of DNA replication. Topotecan's DLT is myelosuppression, and in addition, irinotecan can cause acute and delayed onset diarrhea.

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