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CHAPTER 8

Principles of Chemotherapy for Genitourinary Cancer

Implications for Development of New Anticancer Drugs

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Cytotoxic chemotherapy has been in use for the management of advanced cancer for more than a century,[1] arising from concepts developed by Lissauer, Ehrlich, and many others. The initial attempts at such treatment were characterized by a lack of specificity, with a fine balance between the toxicity to the tumor and that experienced by the host. As reviewed in detail elsewhere,[1] during the past century, our application of chemotherapy to the treatment of cancer has been refined, predicated on an improved understanding of the biochemical basis of its action and a clearer insight into the cellular and molecular mechanisms underlying normal and malignant growth.

TUMOR CELL BIOLOGY IN RELATION TO CHEMOTHERAPY

The anticancer agents are a varied collection of drugs that act through a range of mechanisms, predominantly focused on interference with cell reproduction. Investigators generally agree that the differences between the growth characteristics of normal and malignant tissues form the major basis of the effective use of cytotoxic chemotherapy.[2] Differences among cellular transport characteristics, with differential uptake and efflux of cytotoxic agents, may also contribute to the difference in response to some cytotoxic agents. Moreover, important differences apparently exist among intracellular metabolic functions, such as the expression of glutathione, an intracellular scavenger, which interacts with some alkylating agents and the platinum complexes to inactivate them. More recent data suggest the possibility of subtle interactions between the expression of growth-controlling factors, such as the receptor for the epidermal growth factor, and the impact of cytotoxic agents, with resulting synergistic or antagonistic effects.

Normal tissues are composed predominantly of a static population of cells that rarely undergo cell division, an expanding population of cells that retain the ability to grow, under stringent physiologic control mechanisms, and a self-renewing population for tissues that turn over rapidly, such as bone marrow and gastrointestinal epithelium. In this situation, balance is maintained between natural attrition and replacement.

The static, or terminally differentiated, population usually includes cells that do not undergo cell division after fetal life, such as skeletal muscle and neuronal tissue. The cells of an expanding population do not normally undergo continuous growth and division, but they may respond to stress, such as injury, with a period of replacement growth. For example, hepatocytes can respond to surgical resection of liver tissue by reentering the cell cycle and replacing the lost tissue. Another example of the expanding population is the stem cells in the bone marrow; these cells normally rest in the G_0 phase, but they can reenter the cell cycle. That they are predominantly in G_0 may protect them, in part, from the effects of cytotoxic agents.

By contrast, the self-renewing cell populations, such as cells of the gastrointestinal tract, hair follicles, and bone marrow, are in a continuous proliferative state, with constant cell turnover, and are thus most commonly injured by cytotoxic chemotherapy; the static cell populations are the least vulnerable to the effects of chemotherapy.

Malignant growth is essentially uncontrolled, occurring as a result of a breakdown in the mechanisms that turn off growth. The patterns that contribute to tumor growth may include a reduction in the length of the cell cycle, a decrease in the rate of cell death, or an increase in recruitment of cells into the active cell cycle. In general, malignant growth appears to follow a Gompertzian pattern,[2] in which a period of exponential growth is followed by a slowing of the growth rate. This process may occur through the tumor's outgrowing its vascular supply, as a result of the development of toxic breakdown products associated with cellular turnover, or through other subtle cell–cell interactions.

Cellular Kinetics and Cell Cycle Control

The kinetics of tumor cell growth, both in vitro and in vivo, has been the subject of considerable study,[2] although our concepts on this topic remain fluid. Surprisingly little information is available regarding the kinetics of human tumor growth,[3] although a greater body of information is available on the growth of animal tumors.[2] Investigators generally agree that tumor cells grow through an orderly sequence of steps:

1. The initial growth phase (G_1) is characterized by synthesis of ribonucleic acid (RNA) and protein, as well as deoxyribonucleic acid (DNA) repair; this is a period of variable length, and its duration determines the length of the total cell cycle of the individual cell.
2. This phase is followed by the synthetic (S) phase, in which new DNA is synthesized.
3. The cells progress through the G_2 phase, in which the total DNA content is double that of the normal cell.
4. The mitotic (M) phase sees the division of the chromosomes and separation into two offspring cells.
5. After mitosis, the cells may spend a variable period in a resting state known as G_0: the cells are out of active cycle and appear not to be affected by chemotherapy to any major extent.

A detailed description of the molecular biology of cell cycle control is beyond the scope of this chapter, and the principles are reviewed elsewhere.[4] In brief, several candidate genes and growth factors appear to regulate the various steps of the cell cycle. For example, in different tissues, entry into G_1 appears to be regulated by a range of factors, including *MYC* and *FOS* (formerly known as c-*myc* and c-*fos*), platelet-derived growth factors, and insulin-like growth factor-1 and its receptor.

A major cell cycle controller, $p34^{cdc2}$, regulates entry into S phase; this protein appears to have been conserved during evolution from yeasts to humans, with regard to both structure and function.[5] In turn, this kinase appears to interact with its targets by association with the cyclins, a family of proteins found in different stages of the cell cycle. The G_1 cyclins are present before S phase, and they interact with p34 to cause the cells to enter S phase. Entry into S phase is the first major cell cycle control point. These cyclins appear to interact directly with oncogenes and suppressor genes, probably through a phosphorylation function of the cyclin-p34 complex.

Several oncogenes, such as *RAS* and *SRC* (formerly known as *ras* and *src*), have activity in the M phase of the cell cycle; in fact, they may actually interact in the process leading to activation of the M-phase promoting factor, which, in turn, controls entry into mitosis (the second major cell cycle control point). Tumor progression may be a function of a series of events involving progressive loss of control over entry into the S phase and loss of regulation of M phase; such progression is due to genetic instability and is central to the evolution of malignancy. These changes may be contingent on the loss of checkpoint function, a mechanism by which the cell cycle pauses transiently and allows checking of the accuracy of replication.[6]

The concept of the cell cycle is of great importance to our understanding of cytotoxic action. Most agents affect some aspect of the synthesis of DNA, RNA, or protein and act at different points within the cell cycle. This finding may be important when adding agents in a combination regimen; for example, the use of a spindle poison (such as a vinca alkaloid) may hold up cells from entry into the G_1 phase and thus may reduce the impact of an agent that acts predominantly at that point of the cell cycle. This effect is limited by the finding that many agents act at multiple points in the cell cycle. Inhibition of checkpoint function may explain the way in which tumor cells can be more vulnerable to the effects of cytotoxic agents than are normal cells; thus, the vulnerability of cancer cells to agents that target the S phase or the M phase may occur because the malignant cells proceed unchecked through the cell cycle despite a series of errors, whereas the normal cells stop at finite checkpoints while needed repairs occur.

Cell cycle characteristics can be measured in several ways, including the use of labeling of mitoses[2] and flow cytometry. When considering the biology of tumor growth as assessed by flow cytometry, the proportion of cells in the G_1 and S phases is thought to be most important, although the level of aneuploidy (proportion of cells that do not have a normal or diploid DNA content) appears to be an important prognostic determinant in some tumors. Another, more direct parameter of the cell cycle is measurement of tumor doubling time.[2]

Also of importance is the growth fraction (proportion of cells within a tumor that are in active proliferative phase), which can range from 25% to over 90% in human tumors. The rate of cell loss is also important; in most tumors, it is high, ranging from 70% to over 90%.[2] In general, the length of the G_1 phase is one of the primary determinants of proliferative behavior; thus, if G_1 is short, the duration of the cell cycle is usually rapid, whereas cells with a long G_1 or those that spend considerable time in G_0 have a much longer cell cycle and are less sensitive to the impact of chemotherapy.

Clonality of Tumor Cell Populations

In animal tumors, which tend to be clonal, first-order kinetics appears to apply in response to chemotherapy; that is, a dose of single-agent chemotherapy kills a fixed proportion of tumor cells. For example, if a tumor mass containing 10^7 cells is treated with an agent that kills 90% of the cells, 9×10^6 cells will be killed by a single dose, leaving behind 10^6 viable cells (or 10% of the original tumor mass). A second dose kills 9×10^5 cells and leaves 10^5 cells still alive. If treatment is not repeated, these cells will regrow, and the mass will rapidly return to its former size. This process is also influenced by the proportion of cells that undergo spontaneous cell death, as well as the proliferative rate of any remaining viable cells.

Clinically, the situation is much more complex, because many human tumors appear not to be purely uniclonal, but rather are composed of multiple subpopulations of cells with different characteristics.[7] Whether this phenomenon is due to the evolution from single clonal populations (stem cells) or is caused by initial evolution of multiple clones in response to an initial carcinogenic stimulus is not clear.

PHARMACOLOGY OF ANTICANCER AGENTS

The time course of the sojourn of drugs in the body is determined by the rates of drug absorption, distribution, metabolism, and excretion. The mathematic description of these rate pro-

cesses is referred to as pharmacokinetics. Often, the data can be fitted to mathematic models that are simplified descriptions of the complex physiologic realities. Many of these processes are so-called first order: that is, the rate at which the process occurs is proportional to the drug concentration, although some processes that depend on enzymes or carriers follow Michaelis-Menten kinetics, in which the process is first order at low concentrations and zero order (i.e., occurring at a fixed rate) at high concentrations of the drug.

Absorption

Cytotoxic agents may be administered directly into the circulation (intravenous or intraarterial administration) or by the extravascular approach, which includes oral, intramuscular, intrathecal, intravesical, and intraperitoneal routes. The route of extravascular delivery influences absorption. Factors that determine the uptake characteristics of a drug include the structure and size of the molecule and its negative log of dissociation constant (pKa) and, thus, its solubility characteristics.

The clinical activity of specific agents may vary with the nature of the route and schedule of administration and consequent absorption. For example, cyclophosphamide can be administered orally in a dose of 100 mg/m^2/d for 14 days to patients with advanced prostate cancer and is well tolerated, causing only modest myelosuppression and gastrointestinal toxicity.[8] When the drug is administered to similar populations of patients by intravenous bolus injection (e.g., 750 to 1000 mg/m^2 every 3 weeks), the side effects may be more substantial,[9] with no apparent improvement in therapeutic outcome.

Successful intravesical chemotherapy is predicated on the desire for cytotoxic agents to be active locally *without* systemic absorption, thus protecting the patient from systemic side effects while maximizing the concentration at the tumor surface. Thus, thiotepa, a small, readily absorbed molecule, is potentially less useful in this context than larger molecules, such as doxorubicin or mitomycin C.[10] Furthermore, the level of systemic absorption of thiotepa can be increased if the agent is administered soon after transurethral tumor resection in the presence of a residual denuded bladder epithelium.

Ultimately, the key to therapeutic effectiveness of any cytotoxic agent is a function of the product of its concentration and the time available at the tumor site (C $\times$ t). Most cytotoxic agents are administered by intravenous or intraarterial routes, and calculations of the actual plasma C $\times$ t equation are made accordingly.

Distribution and Transport

The amount of cytotoxic agent available at the tumor target and the length of time during which it is present determine its level of efficacy. Several factors are influential, including the lipid solubility of the drug, its binding to protein and other carriers, and the mechanisms available to allow entry into the tumor (such as passive diffusion or active transport). A major factor is the plasma level of the drug, major determinants of which are its distribution characteristics. After rapid intravenous injection, the plasma concentration of the drug initially falls rapidly. In time, the rate of decline decreases. A plot of the natural logarithm (ln) against time (semilog plot) generally shows two components of the plasma decay: an initial rapid component and a subsequent slower component, both of which have the characteristics of log-linear, that is, first-order, processes. Mathematically, such a plasma decay can be fitted to a two-compartment model in which the body is conceptualized as consisting of two compartments, a central compartment into which the drug is introduced and a peripheral or tissue compartment into which it diffuses, ultimately to equilibrium. The second component of the plasma decay consists of the elimination processes of metabolism or excretion. The rate of this second process gives the half-life of the drug in the body and is an important pharmacokinetic characteristic of all drugs ($t_{1/2}\beta$). For some drugs such as the anthracyclines, a third component of the plasma decay is seen indicating a so-called deep tissue compartment usually corresponding to the binding of the drug to some tissue component such as nucleic acid from which the drug is slowly released. An even simpler model in which the body is regarded as a single compartment can sometimes be used, but for many drugs it can lead to major errors in computing the important pharmacokinetic parameters. These ''compartments'' are mathematic constructs that usually have little or no correspondence with actual physiologic compartments. The total area under the plasma concentration $\times$ time curve (AUC or C $\times$ t) is an important measure of the total exposure of the tissues to the drug. Other important pharmacokinetic parameters that can be calculated from the indices of plasma decay are the total body clearance and the apparent volume of distribution, the theoretic volume required to dissolve the total body content of the drug if it were uniformly distributed in the concentration found in plasma.

In general, the drug is distributed in intravascular, extracellular, and intracellular water, but it must cross a membrane to pass from one of these locations to another. In addition, certain sites are protected from easy drug access. Such sanctuaries are usually characterized by lower drug concentration than other tissues.

The presence of sanctuary sites may be of real importance; for example, the blood-brain barrier appears to protect the brain against the local uptake of cytotoxic agents, and thus the brain may be the site of first relapse in tumors otherwise responsive to chemotherapy. Similarly, the testis apparently may functionally constitute a sanctuary site against the effect of chemotherapy; up to a third of patients treated for metastatic testis cancer before surgical removal of the affected testis have residual cancer within the testis at subsequent orchiectomy, despite an extratesticular complete response.

Metabolism

Two important types of metabolism of antitumor agents are known. Antitumor agents that resemble normal metabolites are often metabolized by the same mechanisms as the normal metabolites. Most purine and pyrimidine antimetabolites require activation to a nucleotide, usually the triphosphate, to be active, and these reactions are carried out by the mechanisms in the cell used to metabolize the corresponding normal preformed purines and pyrimidines (the so-called salvage pathways). Some of the antifolates undergo polyglutamation by the mechanisms used for folates. Degradative pathways are also active in the cell, such as those responsible for reducing 5-fluorouracil (5-FU) to dihydro-5-fluorouracil and converting cytosine arabino-

side to the corresponding uracil arabinoside by deamination. These reactions occur in the cells of the tumor and in the cells of normal tissues. In addition to these specific metabolic reactions, compounds that do not show resemblance to physiologic substrates are metabolized primarily in the liver by the pathways used for detoxification of xenobiotics. Most important is oxidation, often followed by conjugation. Oxidation is carried out by cytochrome P450, a family of enzymes located primarily in the microsomal or smooth endoplasmic reticulum fraction of the liver. This pathway is nonspecific in terms of structural requirements and oxidizes most lipid-soluble compounds. This pathway is responsible for the initial oxidation of the oxazaphosphorine ring of the oxazaphosphorines cyclophosphamide and ifosfamide, a reaction leading to the conversion of these compounds to their active metabolites.

Knowledge of the metabolism of cytotoxic agents is important in designing treatment strategies; for example, intravesical delivery of cyclophosphamide would make no sense, because the drug requires hepatic metabolism to its active form to be effective (see later). In the patient with hepatic dysfunction or hepatic failure, impaired hepatic conjugation alters the metabolism of doxorubicin and of the vinca alkaloids, whereas the microsomal activation of cyclophosphamide may be impaired in this clinical setting.

Excretion

Excretion of cytotoxic agents occurs predominantly in the kidneys and liver, and abnormalities in the function of either or both organs may influence the pattern of toxicity.[11] Renal dysfunction particularly affects the disposition of the platinum complexes, methotrexate, and bleomycin.

Factors Modifying Pharmacokinetics

Absorption of drugs may be affected by diseases of the gastrointestinal tract, by previous surgical procedures, by compounds that change the pH of the gut, by coadministration of other drugs, and by other factors.[12,13] Distribution can be influenced by disease states, such as cardiac failure, ascites, pleural effusion, and edema, and by the coadministration of substances that can displace compounds from binding to serum albumin.[14] Age and amount of adipose tissue may have an impact on the clearance and toxic effects of cytotoxic agents. For example, obesity appears to reduce the clearance of doxorubicin in adults,[15] although the impact on toxicity of the drug is unclear. Age may alter disposition of doxorobucin; for example, Robert and Hoerni[16] demonstrated reduced clearance in older patients, compared with younger cohorts (Chap. 29). Numerous factors affect the rate at which drugs are metabolized by cytochrome P450.[17] Many compounds can induce cytochrome P450, including phenobarbitol and hydantoin, chlorinated hydrocarbon insecticides, food additives, and carcinogens present in tobacco smoke. Some antineoplastic agents may inhibit drug metabolism,[18] as may the presence of hepatic disease.[19] Excretion of compounds by the kidneys depends heavily on renal function. Coincidental administration of compounds that can compete for tubular reabsorption may affect renal clearance of certain compounds,[20] as may urinary pH if the compound is able to become ionized.[21]

MECHANISMS OF DRUG RESISTANCE

Several mechanisms of resistance to cytotoxic chemotherapy are known (Table 8-1). In general, these mechanisms can be classified on the basis of cellular distribution. Intracellular factors include those that act at the cell surface, others within the cytoplasm, and those functioning at the level of the nucleus. In addition are extracellular factors, such as those that affect the distribution and metabolism of the drugs, including competitors for cellular transport mechanisms.

Some cytotoxic agents can be exported from tumor cells through a mechanism based on the cellular surface, the so-called multidrug efflux pump, which is characterized by the expression of a specific 170-kd protein complex, P glycoprotein.[22] Investigators initially demonstrated that response to the cellular effects of agents as diverse as the vinca alkaloids, actinomycin D, and doxorubicin is reduced in normal and malignant cells that express a protein complex on the cell surface, coded by a series of multidrug resistance genes (*PGY*, formerly known as *mdr*). This occurs as a result of reduced intracellular concentrations of the agents because of increased cellular efflux.[23] Expression of the *PGY* phenotype appears to be an example of induced resistance, because previous exposure to colchicine or to one of these agents can induce *PGY*-based resistance to the entire group.

Expression of *PGY* phenotype has been identified in renal carcinoma, although its significance has been difficult to define because most renal carcinomas are resistant to the available cytotoxic agents, and the presence or absence of this phenotype does not correlate with outcome. The study of the multidrug phenotype in bladder cancer cells has also proved difficult; the expression of P glyoprotein in bladder cancer has been variable and inconstant.[24,25] Expression of P glycoprotein may be upregulated in resistant populations of bladder cancer cells after treatment with the methotrexate, vinblastine, Adriamycin (doxorubicin), cisplatin (MVAC) regimen.[26] In other tumor types, multidrug resistance can occur in the absence of expression of the 170-kd P glycoprotein, whereas other proteins may be associated with similar patterns of resistance,[27] a finding that perhaps explains this phenomenon in the absence of expression of P glycoprotein.

Ultimately, apart from its predictive function, this work is unlikely to be of great importance unless the multidrug resistance phenotype can be overcome at a functional level. For example, the calcium channel blockers, such as verapamil, have been shown to reverse multidrug resistance,[28] although the toxic side effects of this approach have precluded routine use. Although clinical trials have not yet been published in bladder cancer, work initiated in our laboratories suggests that verapamil can overcome the impact of the *PGY* phenotype, at least in bladder cancer cell lines in vitro.[29]

The mechanisms of resistance to the platinum coordination complexes have been studied in detail, particularly in relation to ovarian cancer and malignant melanoma (Chap. 9). Although several mechanisms have been identified, including factors that influence cellular accumulation, signal transduction, ionic fluxes, and intracellular enzyme function,[30] the function of the intracellular scavenger, glutathione (GSH), has been the focus of particular attention in the context of the resistance of bladder cancer to the effects of cisplatin. GSH is found in most mamma-

Table 8-1. *Targets of modulation of resistance*

Mechanism	Effector	Agent
Accumulation	Hyperthermia	Cisplatin (cDDP)
	Dipyridamole	Cisplatin
Membrane activity	Tamoxifen	Cisplatin
	Epidermal growth factor	Cisplatin
	Cyclosporin A	Cisplatin
Detoxification		
Glutathione	Buthionine sulfoximine	Cisplatin, alkylating agents
Metallothioneins	?	Cisplatin
DNA repair	Polymerase inhibitors	
	Thymidine triphosphate inhibitors	Cisplatin
Access to DNA	DFMO	Cisplatin
	Hyperthermia	Cisplatin
Gene amplification	Dihydrofolate reductase	Methotrexate
Target alteration	Tubulin	Vinca alkaloids
	Thymidylate synthase	5-Fluorouracil
Poor activation	Low uridine kinase	5-Fluorouracil
	Low polyglutamylation	Methotrexate

in cells and has many functions, including regulation of protein and DNA synthesis and detoxification. It appears to react with cisplatin to reduce the drug's intracellular availability. Inhibitors of GSH synthesis, such as buthionine sulfoximine, have been shown to cause a decrease in intracellular levels of GSH, with a concomitant increase in the cytotoxicity of some anticancer agents, such as the alkylating agents, cisplatin,[31] and paclitaxel.[32] Although many of the experimental data regarding the significance of glutathione in cisplatin resistance have been derived from models of ovarian cancer, we have demonstrated that high levels of glutathione are present in cell lines derived from bladder cancer, and this finding may correlate with cisplatin resistance.[33]

Our understanding of these mechanisms is relatively crude, and other factors appear to influence the responsiveness of bladder cancer to cytotoxic chemotherapy. The expression of several oncogene products seems to influence resistance to cytotoxic agents. The exact nature of this interaction is not yet clear and is particularly difficult to define because several of these products code for specific aspects of cellular growth control, irrespective of exposure to cytotoxic agents. For example, the interaction of epidermal growth factor and its specific receptor (epidermal growth factor receptor [EGFR]) is involved in the regulation of growth of bladder cancer. In vitro treatment with epidermal growth factor can increase cellular sensitivity of epithelial tumors to cisplatin, however, presumably by an effect on a signal transduction pathway.[34] Investigators have also reported that specific monoclonal antibodies can block the function of the EGFR,[35] and further, treatment with these anti-EGFR monoclonal antibodies plus cisplatin can cause a synergistic antitumor effect.[36] These data are particularly difficult to interpret in view of the previously documented impact of expression of EGFR on the natural history of bladder cancer, as well as the demonstration that *ERB2* (formerly known as *erb*B-2) gene amplification and overexpression are adverse prognostic determinants in bladder cancer.

Another complex relationship has been demonstrated among the expression of P53 (a suppressor gene product), growth regulation, and cytotoxic response in bladder cancer. Alterations of the *P53* gene are among the most frequent genetic abnormalities found in human cancer and appear to have a broad range of postulated roles in cell growth control, including involvement in cellular repair and apoptosis. Apoptosis, or programmed cell death, is regarded as a form of physiologic cell death because it represents a genetically determined cellular sequence that is part of the normal tissue homeostatic mechanism. Investigators have shown that P53, which is normally present only transiently, can be induced to accumulate within the cell by exposure to cytotoxic agents, such as cisplatin and mitomycin C,[37] and conversely, P53-dependent apoptosis modulates the cytotoxicity of radiotherapy, 5-FU, and doxorubicin.[38] In our laboratory, however, we have demonstrated that cisplatin cytotoxicity appears not to be mediated by apoptosis in bladder cancer cell lines.[39] These issues may be of particular importance because investigators have already postulated that P53 expression may constitute an independent prognosticator of response to the MVAC regimen. Because P53 may be induced by cytotoxic exposure, the timing of tissue sampling may possibly be critical in determining the expression of this potential prognostic factor, especially if intravesical or systemic chemotherapy has been used previously.

Models for Overcoming Drug Resistance of Tumor Populations: Clinical Implications

Several models have been proposed to explain the varying levels of resistance to the impact of chemotherapy seen in human tumors. For example, Goldie and Coldman[40] proposed that tumors have a spontaneous mutation rate, and the larger the number of tumor cells, the greater the chance of spontaneous mutation. As a consequence, these investigators proposed that the most effective mechanism for cancer killing would be to initiate chemotherapy early (with a small cellular burden) and to introduce multiple agents in an attempt to overcome the various mechanisms of resistance. To date, this hypothesis has not been validated in clinical trials, although most of the studies reported have been flawed and have not truly evaluated the principles of this hypothesis.

Another model of resistance, proposed after a reanalysis of

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