Classification of Antineoplastic Agents by their Selective Toxicities toward Oxygenated and Hypoxic Tumor Cells

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ABSTRACT

The cytotoxicities of a number of antineoplastic agents to oxygenated and hypoxic EMT6 mouse mammary tumor cells in culture were examined. Based on the relative sensitivities of cells under aerobic and hypoxic conditions, drugs were placed into three categories. Drugs that were preferentially toxic to cells under oxygenated conditions were classified as type 1 agents; this group includes bleomycin, procarbazine, streptozotocin, actinomycin D, and vincristine. Type 2 agents were those preferentially toxic to cells under hypoxic conditions. These include mitomycin C and Adriamycin. On the basis of other published reports, the glucose analogs, 2-deoxy-D-glucose, and the radiosensitizers, misonidazole and metronidazole, can also be placed in this category. Several antineoplastic agents showed no major preferential toxicity to cells under the conditions of oxygenation or hypoxia used in these experiments and were placed in a third class. This group (type 3) includes 1,3-bis(2-chloroethyl)-1-nitrosourea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, cis-diaminedichloroplatinum(II), 5-fluorouracil, and methotrexate. The success of many combination chemotherapy and combined modality treatments may be due to their ability to kill both the hypoxic and aerobic cell populations of solid tumors. Future chemotherapeutic regimens for the treatment of solid tumors should include agents and modalities directed toward the hypoxic cell population of the tumor, as well as toward the proliferating and nonproliferating tumor cell compartments; a therapeutic approach to the selection of antineoplastic agents for use in combination based upon physiological considerations of the architecture of solid tumors is presented.

INTRODUCTION

Solid tumors are refractory to cytotoxic agents for several reasons including: (a) many antineoplastic agents do not reach the poorly vascularized regions of the tumor; and (b) the cellular populations in solid tumors are physiologically more heterogeneous with respect to oxygenation and proliferation than are the cellular components of hematological or particularly well-vascularized tumors.

Most of the currently used chemotherapeutic agents are more active against cells in exponential growth than against cells in the plateau phase, in which a relatively great proportion of the cells are not actively traversing the cell cycle (16, 68). However, little is known about the toxicity of most antineoplastici

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MATERIALS AND METHODS

Drugs. Mitomycin C and bleomycin (BleoXane) (1.6 units/mg) were the gifts of Dr. Maxwell Gordon and Dr. William T. Bradner, respectively, of the Bristol-Myers Company (New York, N. Y.). Vincristine sulfate (Oncovin) was obtained from Eli Lilly and Company (Indianapolis, Ind.). Streptozotocin and Adriamycin were the gifts of Dr. John D. Dourou of the Division of Cancer Treatment of the National Cancer Institute (Bethesda, Md.); cis-diaminedichloroplatinum(II), BCNU,3 and CCNU were also obtained from the Division of Cancer Treatment. Procarbazine-HCl was obtained from Hoffman-LaRoche Inc. (Nutley, N. J.) and actinomycin D from Calbiochem-Behring Corp. (La Jolla, Calif.). 5-Fluorouracil and methotrexate were purchased from Sigma Chemical Company (St. Louis, Mo.). All other reagents were obtained from standard chemical sources. Drugs were dissolved in acetone, ethanol, sterile distilled water, or sterile phosphate-buffered saline (8.0 g/l NaCl, 0.2 g/l KCl, 1.15 g/l Na2HPO4, 0.2 g/l KH2PO4) for addition to the tissue culture system.

Tumor Cells and Cytotoxicity Studies. Experiments were performed using EMT6 mouse mammary tumor cells in vitro. The techniques used for propagating the cells and measuring their survival by colony formation have been described in detail previously (50, 82, 83). Cells were grown as monolayers in 25
sq cm Corning plastic culture flasks in Waymouth’s medium supplemented with 15% fetal bovine serum and used for these experiments when in exponential growth. To produce hypoxia, flasks were fitted with sterile rubber sleeve serum stoppers and exposed to a continuously flowing 95% nitrogen/5% CO₂ humidified atmosphere for 4 hr at 37°C prior to drug treatment. These conditions produce a degree of hypoxia sufficient to result in radiobiological resistance (oxygen concentration 10 ppm or less). Parallel flasks were maintained in humidified 95% air/5% CO₂. At this time, each of the drugs or vehicle was added to the flasks by injection through the rubber stoppers without breaking the hypoxia. After exposure to each agent for 1 hr at 37°C under hypoxia or normal aeration, the cells were washed with 3 ml of sterile phosphate-buffered saline, suspended by treatment with 0.05% trypsin in phosphate-buffered saline for 15 min, plated in replicate dishes at 3 dilutions in Waymouth’s medium plus 15% fetal calf serum, and the surviving fraction of cells was measured by colony formation. No difference existed between the survival of untreated or vehicle-treated cells maintained under the aerobic and hypoxic conditions used; the plating efficiency for these control cultures was 65 to 80%. Cells exposed to hypoxic conditions appeared to continue traversing the cell cycle during the course of these experiments, since no decrease in the rate of [3H]thymidine incorporation into acid-insoluble material (data not shown) or in the mitotic index was observed after 4 hr of incubation in the hypoxic atmosphere. Each drug was tested in at least 3 separate experiments.

RESULTS AND DISCUSSION

Classification of Antineoplastic Agents. Based upon physiological considerations, solid tumors may be envisioned to consist of at least 3 classes of neoplastic cells. These include: (a) cells which are well oxygenated, are relatively rapidly traversing the cell cycle, and may correspond in drug sensitivities to logarithmically growing cells in culture; (b) non- or slowly proliferating oxygenated cells which may correspond in their susceptibilities to anticancer agents to plateau-phase cells in culture; and (c) cells in various degrees of hypoxia (108, 109). This last population may be composed of neoplastic cells with relatively normal or prolonged cell cycle times or with cells blocked in their progression through the cell cycle. Antineoplastic agents can be grouped into classes based upon their cytotoxicities toward the neoplastic cell populations present in each of these compartments (Table 1). Type 1 agents and treatment modalities were those which were more toxic to oxygenated cells than to chronically hypoxic cells. The compounds grouped as type 2 were agents which were more toxic to hypoxic cells than to cells under conditions of normal aeration. Type 3 agents and treatment modalities were essentially equitoxic to oxygenated and hypoxic cells.

Type 1 Agents. Bleomycin produces fragmentation of DNA in a reaction which is dependent upon the presence of ferrous ions and molecular oxygen (89, 90). Reactive free radicals of oxygen may be responsible for the cleavage of DNA by bleomycin (61, 73, 99). Sausville et al. (90) showed that the reaction of bleomycin and iron(II) with adenovirus [3H]DNA in phosphate buffer was virtually completely inhibited when the reaction mixture was equilibrated with argon. The survival of EMT6 cells exposed to bleomycin for 1 hr under either oxygenated or hypoxic conditions is shown in Chart 1. As reported by others (7, 85), the survival-dose response curve to short time exposure to bleomycin is bi- or multiphasic. At all concentrations examined, bleomycin was more toxic to oxygenated cells than to cells maintained in a hypoxic atmosphere for 4 hr prior to exposure to the drug. At 150 milliunits of the antibiotic

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Table 1

Classification of antineoplastic agents and treatment modalities based on cellular oxygenation

<table>
<thead>
<tr>
<th>Preferential toxicity to aerobic cells (type 1)</th>
<th>Preferential toxicity to hypoxic cells (type 2)</th>
<th>Minimal or no selectivity based on cellular oxygenation (type 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Mitomycin C</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Adriamycin</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Streptonigrin</td>
<td>Misonidazole, methotridazole</td>
<td>cis-Diaminedichloroplatinum (II)</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>5-Thio-o-glucose, 2-deoxy-o-glucose</td>
<td>BCNU, CCNU</td>
</tr>
<tr>
<td>Vincristine</td>
<td></td>
<td>High linear energy transfer radiation</td>
</tr>
</tbody>
</table>

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* Under the test conditions used in these experiments, hypoxic cells are still capable of DNA synthesis and of cellular replication. These agents have cytotoxic effects primarily on cells in the S phase of the cell cycle. Thus, in hypoxic cells that are blocked in their progression through the cell cycle or are cycling slowly, agents such as these that act on the S phase of the cell cycle would be expected to be relatively nonselective.

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Graph:

**Chart 1.** Survival of aerobic (●) and hypoxic (O) EMT6 cells treated for 1 hr with various concentrations of bleomycin in cell culture.
per ml, a 9-fold difference in drug sensitivity was observed. That bleomycin showed some toxicity toward chronically hypoxic cells may be the result of (a) residual antibiotic which exerted its cytotoxic effect after the hypoxic state was disrupted, (b) residual oxygen in hypoxic cells, or (c) a non-oxygen-dependent mechanism of drug cytotoxicity.

Procarbazine is rapidly oxidized in aqueous solution in the presence of oxygen to an azo derivative which is further oxidized in vivo and in vitro to alkylating species (112). Procarbazine is considerably more toxic to bacteria under aerobic conditions than under anaerobiosis (81). As shown in Chart 2, this differential cytotoxicity is also expressed with mammalian tumor cells, the drug being approximately 7 times more toxic to normally aerated EMT6 cells than to these cells maintained under conditions of chronic hypoxia during drug exposure. At a drug concentration of 1 µM, there was no kill of hypoxic cells, yet greater than 70% of the aerobic cells were killed. It is unclear whether the cytotoxicity of procarbazine to hypoxic cells is due to residual drug or to a non-oxygen-dependent mechanism.

Streptonigrin appears to damage DNA through the obligatory intermediacy of superoxide radical (22). As shown in Chart 3, only 20% survival of normally aerated EMT6 cells was obtained at a concentration of only 1 µM streptonigrin; under these conditions, the survival of hypoxic EMT6 tumor cells was unaffected. At all drug concentrations examined, streptonigrin was about 10 times more toxic to normally aerated cells than to hypoxic cells.

Actinomycin D binds to double-stranded DNA, permitting initiation of RNA synthesis but blocking the elongation process. The cytotoxicity of actinomycin D appears to be primarily a consequence of this interaction with DNA (36, 110). Chart 4 shows that, at concentrations less than 0.01 µM, no major difference was observed in the cytotoxicity of this antibiotic toward normally aerated and hypoxic cells; however, at drug concentrations approaching 1 µM, oxygenated cells are almost 100-fold more sensitive to the lethal actions of actinomycin D than are hypoxic cells. Thus, there may be a secondary oxygen-dependent cytotoxic mechanism of action for actinomycin D at relatively high drug concentrations.
Although the cytotoxicity of vincristine is attributed to its ability to interrupt cell division in metaphase (113), other effects may also contribute to cell death (23). In the range of vincristine concentrations tested (i.e., 0.01 to 50 \( \mu M \)), the drug showed minimal cytotoxicity to hypoxic cells, while toxicity to oxygenated cells was very clearly a dose-related process (Chart 5). This finding cannot be attributed to a decrease in mitoses in the hypoxic cells, since the mitotic index was 5.79 ± 0.89% for aerobic cells and 6.59 ± 1.69% for cells after 4 hr of hypoxia.

Agents classified as type 1 are primarily drugs that require molecular oxygen or oxidative biotransformation to exert a cytotoxic effect and includes the treatment modality ionizing radiation (52). Additionally, some drugs may be accumulated or retained intracellularly by energy-requiring processes that depend upon oxidative metabolism; therefore, intracellular concentrations of these drugs may be different in oxygenated and hypoxic cells. In this test system, streptonigrin showed the largest differential kill of aerobic cells, being greater than 1000 times more toxic to oxygenated cells at 50% survival and approximately 10,000 times more toxic to aerobic cells at 20% survival. Procarbazine required greater than 5000 times more drug to achieve a 50% kill of hypoxic cells than to kill 50% of aerobic cells. The degree of differential kill achieved by bleomycin, actinomycin D, and vincristine was similar, ranging between 50 to 100 times more toxic to oxygenated EMT6 cells than to their hypoxic counterparts at 50% survival levels.

**Type 2 Agents.** Early studies established that DNA is the principal target for the expression of the antineoplastic activity of mitomycin C (46, 47). The term bioreductive alkylating agent has been used by this laboratory to describe the class of drugs which require reductive transformation to exhibit alkylating activity (57, 58), and mitomycin C can be considered to be a naturally occurring bioreductive alkylating agent. Enzymatic reduction of this agent to the hydroquinone results in the loss of methanol to give an aziridinomitosene derivative (24). Spontaneous rearrangement of the reduced molecule can then theoretically lead to the production of a highly reactive quinone methide intermediate capable of alkylating cellular molecules (46, 47, 60, 92). Schwartz (91) demonstrated that liver contains an enzymatic system capable of metabolizing mitomycin C under anaerobic conditions; this enzyme system is found in both the microsomal and nuclear fractions (51). The bioactivation of mitomycin C to an alkylating species can occur in neoplastic cells in a reaction requiring anaerobiosis and an NADPH-generating system (50, 52). In agreement with these findings, mitomycin C was considerably more toxic to hypoxic cells than to oxygenated cells over a wide range of concentrations (Chart 6). This difference in sensitivity reached a maximum of about 10-fold at relatively high concentrations of drug; in addition, however, at a concentration range of 0.001 to 0.1 \( \mu M \) mitomycin C, little or no measurable cytotoxic activity occurred in oxygenated cells, while 50 to 90% of the hypoxic cells were unable to replicate.

The action of Adriamycin may involve activation via metabolic reduction, either by one- or 2-electron transfer (29, 30, 62). Anaerobic incubation of Adriamycin with liver microsomes in the presence of NADPH results in the appearance of an electron spin resonance signal attributed to the semiquinone free radical (1–3, 40, 88). Although the direct reaction of the anthracycline radical with tissue constituents has not been reported, Bachur et al. (3) have observed widespread apparent covalent binding of Adriamycin to tissue proteins. An explanation for this alkylating ability which involves 2-electron reduction of the quinone nucleus of Adriamycin followed by the elimination of the daunosamine sugar moiety with subsequent formation of a quinone methide alkylating species has been proposed by Moore (71). As shown in Chart 7, Adriamycin was more toxic to hypoxic cells at all of the concentrations of the...
antibiotic tested. At high drug levels, the differential kill of hypoxic cells was 10 times greater than the kill of oxygenated cells. It appears that, under hypoxic conditions, Adriamycin may act as a bioreductive alkylating agent, while under conditions of normal aeration, an oxygen-dependent mechanism of cytotoxicity may be operative. In contrast to these findings, Smith et al. (94) reported that hypoxic Chinese hamster ovary cells were more resistant to Adriamycin than their oxygenated counterparts, and Harris and Schrieve (41), using an EMT6 cell line, found no difference in the toxicity of Adriamycin to oxygenated and hypoxic cells. The latter authors indicate that the sensitivity of their line of EMT6 to antineoplastic agents differed from that of others. The results of these studies, however, indicate that all tumor cells may not be capable of carrying out the reductive reactions necessary to activate Adriamycin under hypoxic conditions.

Except for glucose analogs, all agents classified as type 2 seem to use mechanisms that involve enzymatic reduction of a functional group on the drug molecule to express their cytotoxic activity. The nitroheterocyclic radiosensitizers, exemplified by metronidazole and misonidazole, are selectively toxic to hypoxic cells in the absence of irradiation (27, 33-35, 67, 102, 107). This selective toxicity corresponds to the preferential formation of relatively large amounts of N-hydroxy and amine metabolites formed by nitro group reduction by hypoxic cells (8, 74, 103, 107). To attain cytotoxicity by the nitroimidazoles requires prolonged contact times of several hr and relatively high drug concentrations (e.g., 1 to 5 mM misonidazole) (32, 70, 115, 116); consequently, the selective action of these agents on hypoxic cells may not be exploitable in the treatment of human cancer (15, 26).

A prominent metabolic difference between aerobic and hypoxic cells is their degree of dependence upon the metabolism of glucose for survival; aerobic cells are more resistant to depletion of the glucose supply or to inhibition of glycolysis (96). Since hypoxic cells derive their energy primarily by anaerobic glycolysis, they are particularly vulnerable to either a diminished availability of glucose or an inhibition of glycolysis. 5-Thio-d-glucose and 2-deoxy-d-glucose, potent inhibitors of glycolysis, are preferentially cytotoxic to hypoxic cells (95-98). Glucose analogs may be of limited clinical utility, however, because of the relatively large quantities required to produce lethality by creating a shortage of glucose in hypoxic tumor cells.

**Type 3 Agents.** The mechanism by which 5-fluorouracil kills neoplastic cells is believed to require conversion to 5-fluoro-2'-deoxyuridylic acid, which forms a stable ternary complex with the cofactor, 5,10-methylenetetrahydrofolate and the enzyme thymidylate synthetase (42, 56, 64), leading to a state of "thymineless death" (21, 44, 87). As shown in Chart 8, no major difference was observed in the cytotoxicity of 5-fluorouracil to oxygenated and hypoxic cells. The aerobic and hypoxic cells used in this study incorporate [3H]thymidine into acid-insoluble material at equal rates, suggesting that cells under both of these conditions are actively traversing the cell cycle during the course of the experiment. This presumably explains the sensitivity of oxygenated and hypoxic cells to this antimetabolite.

Methotrexate is a potent inhibitor of dihydrofolate reductase (12); interference with this enzyme activity leads to a decrease in the rate of synthesis of cellular DNA, RNA, and protein (10, 11). As shown in Chart 9, methotrexate was similar to 5-fluorouracil, in that little difference was observed in the degree of cytotoxicity exhibited toward EMT6 cells which was dependent upon their state of oxygenation.

The neutral platinum complexes interact with DNA to impair its function as a template for further DNA replication (80). cis-Diamminedichloroplatinum(II) has been shown to cross-link
Antineoplastic agents considered to be type 3 were those in which the ratio of drug concentrations required to achieve either a 50% or 20% survival of oxygenated and hypoxic cells ranged between 0.5 and 5. Drugs in this category include alkylating agents, such as the 2-haloethylnitrosoureas and the neutral platinum compounds, and since in the methodology used in this study both oxygenated and hypoxic cells appear to be actively traversing the cell cycle, the S-phase inhibitors 5-fluorouracil and methotrexate fall into this group (45). It is essential to recognize, however, that long-term chronically hypoxic cells which are either noncycling or are slowly moving through the cycle would not be expected to be sensitive to these agents. High linear energy transfer radiation also has no oxygen requirement for cytotoxic activity and may be placed in this class.

Penetration. A property of major importance for hypoxic cell directed chemotherapeutic agents is the ability of the drugs to penetrate to poorly vascularized regions of the tumor to reach target hypoxic cells in therapeutically useful concentrations. Furthermore, the intracellular concentrations of the cytotoxic agents which can be achieved may differ for oxygenated and hypoxic cells. Although molecular oxygen penetrates only a short distance through tumor tissue, largely because of its rapid metabolic utilization, some dyes and some drugs can diffuse into the tumor mass over much greater distances (108, 109). Although the nitroimidazole radiosensitizers and the glucose analogs are both type 2 agents, since they are not exceedingly potent cytotoxic agents for hypoxic cells, large doses would appear to be required to achieve effective drug concentrations in the tumor. Adriamycin is exceedingly effective against hypoxic cells, but this agent has been reported to have poor tumor penetrating properties (101). In contrast, mitomycin C, also a potent type 2 agent, has been shown to have the ability to penetrate to hypoxic regions of a rodent solid tumor (84). Therefore, we believe that at present mitomycin C is the most promising agent with which to attack the hypoxic cell compartment of solid tumors currently available for clinical use.

Evidence for the Clinical Utility of the Concept. A variety of

DNA in mammalian cells (79). As might be expected for an agent which can covalently bind to critical molecules in cells regardless of their physiological state, no difference in the cytotoxicity of cis-diaminedichloroplatinum(II) toward oxygenated and hypoxic cells was observed (Chart 10).

The 2-haloethylnitrosoureas, BCNU and CCNU, are chemically reactive compounds that decompose nonenzymatically at relatively rapid rates under physiological conditions (28, 43, 69, 78). Furthermore, BCNU and related 2-haloethylnitrosoureas covalently cross-link DNA (48, 49, 93). As shown in Chart 11, BCNU has little selective cytotoxicity that is based upon the cellular state of oxygenation. A similar result was obtained with CCNU.
clinical trials have used mitomycin C or Adriamycin, the 2 agents which appear to be the most efficacious against the hypoxic cell component of solid tumors, in admixture with drugs capable of attacking cells in the oxygenated compartments of solid tumors. These studies encourage the utilization of combinations of drugs specifically designed to attack cellular compartments based upon the physiological status of the neoplastic cells. They include combination chemotherapy with mitomycin C, particularly mitomycin C in admixture with 5-fluorouracil, an agent capable of attacking well-oxygenated tumor cells in cycle, in the treatment of advanced carcinoma of the stomach, pancreas, and colon. This combination (often including additional agents) has produced significant increases in both the percentage and duration of responses as compared to either drug alone (17–19, 25, 39, 55, 63, 77). Mitomycin C in combination with bleomycin, an agent whose cytotoxicity is directed primarily against oxygenated cells, or in admixture with bleomycin and vincristine, also a type 1 agent, appears to represent a very significant advance in the chemotherapy of advanced squamous cell cervical cancer (4, 5, 66). Radiation therapy, a type 1 modality, plus chemotherapy consisting of 5-fluorouracil and mitomycin C has been reported to result in no evidence of disease in 3 patients presenting with surgically inoperable epidermoid carcinoma of the anus (72). Mitomycin C in combination chemotherapy or alone has also been reported to produce objective response in the treatment of liver (53, 65), breast (114), and lung cancer (86).

Adriamycin, a type 2 agent, is synergistic with several alkylating agents; thus, in clinical trials in advanced breast cancer, Adriamycin in combination with alkylating agents has resulted in a high percentage of responses to treatment (59, 76, 104, 111). Adriamycin in combination chemotherapy has also been effective in the treatment of advanced lung (20), bronchogenic carcinoma (105), and testicular carcinoma (31). The treatment of advanced epidermoid carcinoma of the cervix with this agent in combination with bleomycin gave poor results at the primary lesion; however, a satisfactory response rate was observed in metastatic growths (37). Response rates achieved with Adriamycin therapy appear to be of relatively short duration, perhaps due to inadequate penetration of the drug to the hypoxic tumor cells most distal from the tumor blood supply.

**Attack of Nonproliferating Cells.** The nonproliferating cellular compartment of solid tumors includes, in addition to a portion of the hypoxic cell subpopulation, a cellular component consisting of oxygenated cells comparable to the plateau phase in culture. Since plateau-phase cells differ markedly from exponentially growing cells in their sensitivities to antineoplastic agents, it would be expected that such a cellular component of a solid tumor would limit response and would require special consideration in the fashioning of a combination chemotherapeutic regimen. Agents which might be useful in attacking this cellular compartment include bleomycin and CCNU and BCNU (6, 7, 13, 38, 100, 106). Among other treatment modalities, hyperthermia has been reported to be more toxic to plateau-phase cells (75).

**An Approach to the Design of Chemotherapeutic Regimens.** Chemotherapeutic regimens for the treatment of solid tumors can be designed based upon a consideration of the physiological status of the cellular components of the tumor mass. Such a therapeutic approach would appear to require the combination of agents and/or modalities directed toward each of the cell types present in the tumor, including cycling and noncycling populations of oxygenated and hypoxic compartments. Selection of combinations of drugs (or other treatment modalities) based upon these concepts should include: (a) a bioreductive alkylating agent designed to attack the hypoxic cell compartment by exploitation of the capacity of these cells to accomplish reductive reactions; mitomycin C would appear to be the most efficacious agent of this class presently available for clinical use. To maximize the differential toxicity of this agent to hypoxic cells, it should be given in relatively low doses over a relatively long period. In addition, it should be administered prior to the component(s) of the drug combination used to kill oxygenated cells, to minimize the loss of effectiveness of this agent through reoxygenation of the hypoxic cell compartment after kill of aerobic cells, a process that is capable of occurring relatively rapidly (52); (b) an agent such as bleomycin or a nitrosourea would seem to be a reasonable addition to such therapy to specifically attack any nonproliferating oxygenated cells present in the tumor (i.e., plateau phase-like cells); and (c) X-irradiation and/or an agent or mixture of agents with specificity for actively proliferating aerated cells. The drug(s) selected to attack these cellular components of the malignant tumor obviously must be capable of achieving biochemical lesions which lead to cell death.

REFERENCES

Drug Cytotoxicity and Cellular Oxygenation

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