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Potentiation of DNA-reactive Antineoplastic Agents and Protection against S-Phase-specific Agents by Anguidine in Chinese Hamster Ovary Cells[1]

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ABSTRACT

Anguidine, a protein synthesis inhibitor, has been shown to induce a reversible cell cycle arrest in exponentially growing Chinese hamster ovary cells. The effect of pretreatment with anguidine on the cytotoxicity of subsequently administered various chemotherapeutic agents, hyperthermia, and radiation was investigated. We found that anguidine greatly potentiated the cytotoxic activity of *cis*-dichlorodiammineplatinum(II) and melphalan by abolishing the initial shoulder and steepening the subsequent exponential portion of the survival curves. Bleomycin-induced cell kill was also potentiated by anguidine pretreatment but to a lesser extent. However, anguidine pretreatment did not substantially alter radiation cytotoxicity. In contrast, anguidine markedly reduced the lethal effect of hydroxyurea, 5-fluorouracil, and hyperthermia, three modalities with S-phase activity. To investigate whether both anguidine-induced potentiation and protection of cells by different antitumor agents were due to its induction of complete suspension of cycle traverse, experiments were also conducted with plateau-phase cultures. Whereas anguidine potentiated *cis*-dichlorodiammineplatinum(II) cytotoxicity in an identical fashion as noted in exponentially growing cells, its protective effect against lethal damage from Adriamycin was absent. Thus, it appears that the two opposite effects of anguidine modification of cell kill by cytotoxic agents (protection and potentiation) come about by two different mechanisms, with cell cycle arrest underlying cytoprotection and the mechanism of synergistic toxicity remaining obscure.

INTRODUCTION

Differential protection of normal tissue against systemically administered antitumor therapy and selective potentiation of antitumor effect are 2 greatly desired goals of the cancer therapist. There is evidence that many human tumor cells progress through the cell cycle at a slower rate than do their normal tissue counterparts (3, 4, 13, 26). This creates a cytokinetic disadvantage for normal *versus* malignant cell damage by agents that exert their greatest cytotoxic effect on cycling cells. Thus, differential cell cycle arrest appears to be a promising strategy to reduce the normal tissue toxicity of anticancer agents (13). This has been attempted with varying success with polyamine synthesis inhibitors (21), substances that interfere with cyclic adenosine 3′:5′-monophosphate metabolism (19), interferon (11), and several protein synthesis inhibitors. Among the protein synthesis inhibitors, there is evidence that L-asparaginase (6), cycloheximide (5), and anguidine (24) can reduce the cytotoxicity of S-phase agents by reversibly arresting cellular proliferation. Phase I and II clinical trials have been concluded at this institution, demonstrating that anguidine can be administered safely to patients with cancer but that it has little antitumor effect at minimally tolerated dosages (18, 28). Studying the lethal and cytokinetic effects of anguidine, Dosik *et al.* (8) noted that anguidine completely suspends cell cycle progression at virtually no cytotoxic expense. On the basis of these considerations, Teodori *et al.* (24) investigated more precisely the cell cycle inhibition produced by anguidine. They showed that it induced a concentration- and time-dependent non-phase-specific cell cycle arrest and that this arrest led to protection against ara-C[3] and Adriamycin.

To investigate whether the protection by anguidine against ara-C- and Adriamycin-induced cytotoxicity was a general phenomenon applicable to all anticancer modalities, we studied the effect of anguidine pretreatment on *cis*-platinum, melphalan, bleomycin, hydroxyurea, 5-fluorouracil, radiation, and hyperthermia-induced cytotoxicity. We found that anguidine protected against hydroxyurea, 5-fluorouracil, and hyperthermia while potentiating the lethal effects of *cis*-platinum, melphalan, and bleomycin. There was no alteration of radiation cytotoxicity. In plateau-phase cells, anguidine did not protect against Adriamycin-induced cell kill but still potentiated *cis*-platinum cytotoxicity, implying that this synergism was due to another mechanism besides the cell cycle arrest anguidine produces. The long-range goal of these studies is to elucidate whether anguidine can be used as a protective agent for normal tissue in cancer chemotherapy and/or as a synergistic agent with drugs that induce DNA damage.

MATERIALS AND METHODS

Cell Line

CHO cells were routinely grown as monolayer cultures in a 5% CO_2, humidified atmosphere at 37° in McCoy's Medium 5A, Hsu's modification (Grand Island Biological Co., Grand Island, N. Y.), supplemented with 10% heat-inactivated fetal calf serum (Irvine Scientific, Santa Ana, Calif.). The cells were harvested by treatment with 0.125% trypsin (Irvine Scientific) for 5 min at 37°.

Drugs

Anguidine (manufactured by Ben Venue Laboratories) and hydroxyurea were obtained from the Division of Cancer Treatment, National

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[3] The abbreviations used are: ara-C, 1-β-D-arabinofuranosylcytosine; *cis*-platinum, *cis*-dichlorodiammineplatinum(II); CHO, Chinese hamster ovary cells; D_0, mean lethal dose equal to the concentration required to reduce survival by 63% on exponential part of survival curve.

Cancer Institute, Bethesda, Md. Adriamycin and 5-fluorouracil were purchased from Adria Laboratories, Columbus, Ohio. Bleomycin and *cis*-platinum were purchased from Bristol Laboratories, Syracuse, N. Y. Melphalan was obtained from Burroughs-Wellcome, Research Triangle Park, N. C. All drug solutions were prepared fresh on the day of each experiment. Drugs were initially dissolved in 0.9% sodium chloride solution and further diluted with medium.

Survival Studies

Cells in Exponential Growth. Cell survival was assessed by the colony formation technique (9, 20). In 3 ml of medium, 300,000 cells were seeded into 60-mm Petri dishes and incubated for 24 hr to ensure exponential growth. At the end of that time, all dishes were washed in medium, and fresh medium was added. To selected dishes, anguidine (5 μg/ml) was added for 4 hr to induce cell cycle arrest (8, 24).

Following this, all dishes were washed in medium, and the various drug concentrations to be tested were added. The dishes were then incubated for the time periods specified under "Results." After drug treatment, the cells were washed once in medium and once in 0.9% sodium chloride solution and were harvested with trypsin. Cell concentrations were determined with a Coulter Counter (Coulter Electronics, Hialeah, Fla.), and known aliquots of cells were dispensed into 5 ml of medium in 60-mm Petri dishes, so that 50 to 150 colonies would appear after 7 days of incubation. Colonies were washed once in 0.9% sodium chloride solution and stained with 2% crystal violet in 95% ethanol. Colonies containing more than 50 cells were counted as positive. All experiments were repeated at least twice with triplicate samples for each drug concentration. Cell survival after drug treatment was normalized with respect to untreated controls, which had a plating efficiency ranging from 75 to 90%.

Cells in Plateau Phase. Into 60-mm Petri dishes 1.5 million CHO cells were plated in 5 ml of medium, and they were incubated for 72 hr. Confluency was reached by 24 to 48 hr. By 72 hr, the proportion of cells in S phase according to DNA cytometric examination averaged 9.3%, down from an average of 55.2% for CHO cells in logarithmic growth (2).

Hyperthermia. Heat treatment was conducted by exposing the bottom surfaces of Petri dishes on a tray to heated water (1). The bath was maintained within ±0.1° (S.E.) of 43° by a Lauda circulator and regulator (Messgeräte-Werk, Lauda, Germany). Thermocouple probes (Bailey Instruments Co., Inc., Saddlebrook, N. J.) measured the water bath temperature. In the colony formation assay, the supernatant medium from the heat-treated cells was preserved and later added to the trypsinized cells before counting to take into account cells that may have detached from the plate during thermal treatment.

Radiation. The radiation source used was ^{127}Cs at a dose rate of 500 rads/min. A known aliquot of cells was suspended in medium in a sterile 5-ml culture tube and placed on ice for transport to the radiation source. After treatment, cells were transported back to the tissue culture facility on ice for the colony formation assay. Total elapsed time from trypsinization to return to culture for colony formation never exceeded 1 hr.

RESULTS

Protective Effects of Anguidine. The most pronounced protective effect of anguidine pretreatment occurred with 5-fluorouracil (Chart 1). The chosen preincubation with anguidine (5 μg/ml for 4 hr) provided more than 2 log decades of protection against treatment with 5-fluorouracil (25 μg/ml for 18 hr). At that concentration of 5-fluorouracil, anguidine-pretreated cells had a mean survival of 40.4%, while control cells had a mean survival of 0.17%. Protection against hydroxyurea cytotoxicity was not as pronounced as was that for 5-fluorouracil. At the highest dosage of hydroxyurea used, 100 μg/ml for 18 hr, anguidine-protected cells had a mean survival of 53.9%, while control cells had a mean survival of 13.2%.

Anguidine also reduced the toxicity of 43° hyperthermia (Chart 1). While not significantly changing the shoulder part of the survival curve (quasithreshold dose equal to the intercept with the abscissa of the exponential part of survival curve of 26 min as compared to that of 20 min for the control survival curve), anguidine reduced the slope of the hyperthermia survival curve from a D_0 of 18 min to 60 min. In contrast to 5-fluorouracil and hydroxyurea, anguidine did not produce a plateau of protection against hyperthermic toxicity. Rather, the survival curve of anguidine-pretreated cells resembled the shape of cellular survival following exposure to heat alone, except that survival declined at a lesser rate.

Potentiative Effects of Anguidine. Anguidine pretreatment greatly potentiated the cytotoxicity of *cis*-platinum, melphalan, and bleomycin (Chart 2). For the former 2 drugs, anguidine abolished the initial shoulder and, in addition, steepened the subsequent exponential portion of the survival curve. For a 1-hr treatment with melphalan, anguidine lowered the D_0 from 3.0 to 1.1 μg/ml. With melphalan at 5 μg/ml, survival of anguidine-treated cells averaged 0.53%, while survival of cells treated with melphalan alone averaged 17.0%. For a 1-hr incubation with *cis*-platinum, anguidine lowered the D_0 from 3.8 to 1.1 μg/ml. With *cis*-platinum at 5 μg/ml, anguidine-pretreated cells had a survival averaging 0.84%, while control cells showed a survival of 30.1%. In the case of bleomycin, anguidine lowered the first exponential survival function, D_{0_1}, by almost 4-fold, from 11 to 3 μg/ml for a

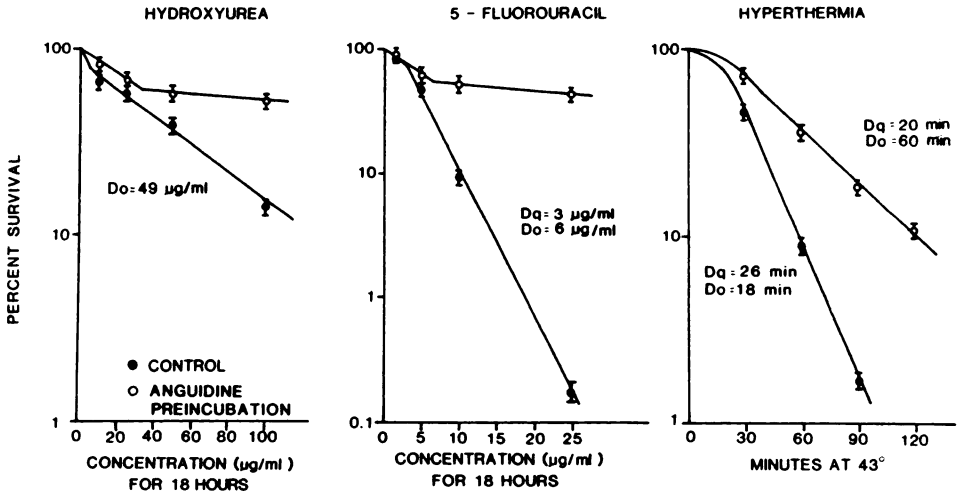

Chart 1. Protection of logarithmically growing CHO cells against the lethal effects of hydroxyurea, 5-fluorouracil, and hyperthermia by pretreatment with anguidine (5 μg/ml, 4 hr), a condition reported previously to induce complete suspension of cell cycle progression (8, 24). Protection is most pronounced for 5-fluorouracil, where anguidine increases cell survival by >100-fold after treatment with 5-fluorouracil (25 μg/ml) for 18 hr. Note the plateau of protection after anguidine treatment for hydroxyurea and 5-fluorouracil. In the case of hyperthermia, the ability of cells to absorb sublethal damage (D_q) is unaffected by anguidine, but the exponential cell kill function is more shallow (>3-fold increase in D_0). *Bars*, S.E. *Ordinate for 5-fluorouracil*, 3 log decades.

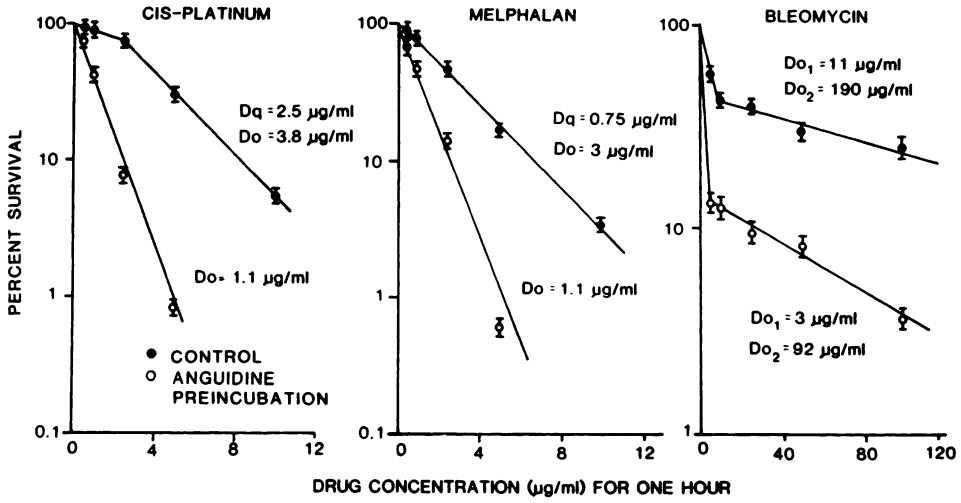

Chart 2. Enhancement of lethal effects of *cis*-platinum, melphalan, and bleomycin after pretreatment of exponentially growing CHO cells with anguidine (see Chart 1 legend). In the cases of *cis*-platinum and melphalan, the initial shoulder portions are eliminated, and subsequent exponential cell kill is associated with a 3-fold reduction in D_0 values. This also is true for the first exponential portion of the bleomycin dose-response survival function. The second exponential portion, representing a more resistant subpopulation, shows a 2-fold decrease in the D_0 value. Note: *ordinate for bleomycin*, only 2 log decades.

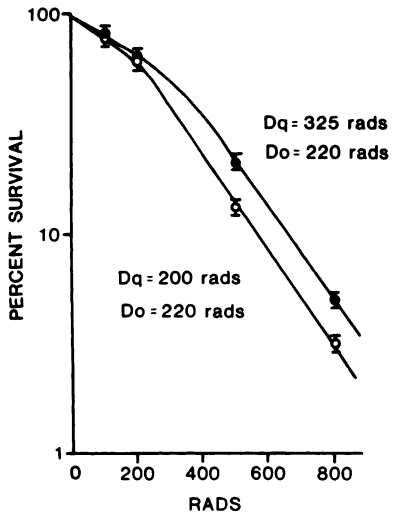

Chart 3. Effect of anguidine pretreatment on radiation dose-dependent survival of exponentially growing CHO cells. Pretreatment with anguidine (see Chart 1 legend) reduces the shoulder portion (D_q) by 125 rads but has no effect on the subsequent rate of exponential cell kill.

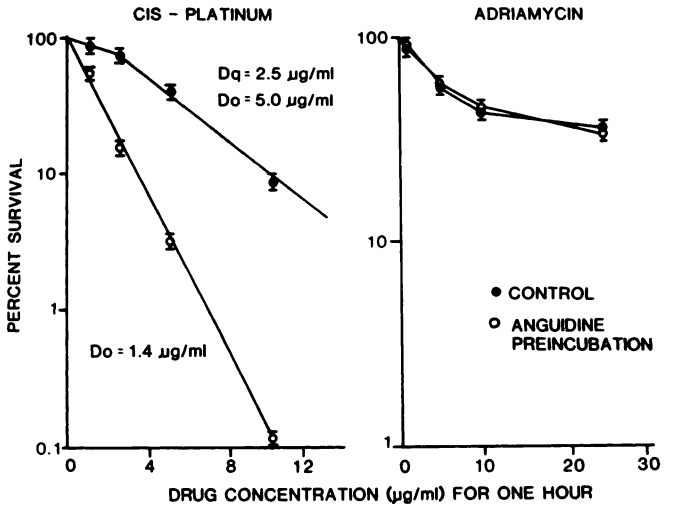

Chart 4. Modification of *cis*-platinum- and Adriamycin-induced cell kill by pretreatment with anguidine (see Chart 1 legend) in stationary CHO cell cultures. Anguidine potentiates the cytotoxic effect of *cis*-platinum on plateau-phase cells in an almost identical fashion as in cycling cells (abrogation of the shoulder portion, about 3-fold reduction in D_0 value). However, anguidine does not protect against Adriamycin toxicity as shown previously for cells in exponential growth (24). Thus, the protective effect of anguidine seems to be related to its ability to freeze the cell cycle, while the potentiative effect of anguidine is not cycle related. *Ordinate for Adriamycin*, 2 log decades; *ordinate for cis-platinum*, 3 decades.

1-hr treatment, while the second exponential portion of the survival curve was steepened by about 2-fold. With bleomycin at 100 μg/ml, anguidine-treated cells showed a survival of 3.6%, while control cell survival averaged 25.9%. As to ionizing radiation, anguidine pretreatment reduced the shoulder portion of cellular survival by 125 rads, while the exponential cell kill function was unaltered (Chart 3).

Plateau-Phase Studies. Since previous investigations had shown that the protective effect of anguidine on ara-C and Adriamycin was due to the cytostatic effect of anguidine (24), we investigated the type of modification of *cis*-platinum- and Adriamycin-induced cell kill by anguidine in plateau-phase cultures as an *in vitro* model for low-growth-fraction tumors. We postulated that, if anguidine potentiated *cis*-platinum-induced cell kill by arresting cell cycle traverse, then it would show little or no potentiation on cells arrested from cycling by other means. In the experiment presented here, anguidine still potentiated the cytotoxic effect of *cis*-platinum on CHO cells even when they were treated during plateau phase of growth (Chart 4). Anguidine again abolished the initial shoulder and steepened the exponential portion of the survival curve, lowering the D_0 from 5.0 to 1.4 μg/ml. With *cis*-platinum at 5 μg/ml, survival of anguidine-pretreated cells averaged 3.4%, while control cell survival averaged 42.6%. In the case of Adriamycin, we had demonstrated previously a protective effect by anguidine in exponentially growing cells (24). Pretreatment of plateau-phase cultures with anguidine, however, failed to exert such cellular protection (Chart 4).

DISCUSSION

Anguidine pretreatment, by itself virtually nontoxic (8, 24), substantially reduced the cytotoxicity of 5-fluorouracil, hydroxyurea, and hyperthermia for CHO cells in the logarithmic phase of growth. All of these agents are characterized by their greater efficacy towards cells in S phase (12, 15, 17, 25, 27). In a previous study conducted by Teodori *et al.* (24), anguidine protected CHO cells against ara-C and Adriamycin cell kill. ara-C is considered to be S-phase specific (23), and Adriamycin has been shown to have S-phase activity by inhibiting DNA polymerase α (10, 22). The exact lethal mechanism of hyperthermia is not

known. It probably involves denaturation of critical chromosomal proteins, which may include polymerases (16, 25). Thus, anguidine may protect against antitumor agents that require, for their lethal activity, the expression of DNA-synthetic enzymes.

The clinical relevance of these studies is easily appreciable as it becomes more clearly established that human tumors do not necessarily proliferate faster than their presumed normal tissue counterparts and thus do not exhibit a cytokinetic advantage for cell kill by most antitumor agents (3, 4, 26). If an agent could be identified that produced a preferential cell cycle suspension in normal cells and not, or to a lesser degree, in tumor cells, the therapeutic index could be favorably manipulated. Data obtained in our laboratory indicate that anguidine indeed promotes preferential suspension of cycle progression in normal *versus* transformed cells (14); anguidine arrests the cell cycle of WI38 fibroblasts at one-tenth the dosage required to inhibit the cycling of WI38 VA13 cells (the SV40 transformant). If this is a general phenomenon applicable to the rapidly proliferating normal human tissue, such as gut epithelium and bone marrow, anguidine may have an important future in clinical treatment strategies designed to protect normal tissue from drug-induced injury.

Our finding of the protection by anguidine of 5-fluorouracil cytotoxicity is at variance with data by Corbett *et al.* (7), who reported marked synergism in a murine colon tumor. However, the clinical observation of lack of objective response in a clinical trial of 5-fluorouracil and anguidine as a front line treatment for human metastatic colorectal cancer is consistent with our present findings.[4] It is conceivable that, for synergism to occur, a lower dose of anguidine that does not induce a frozen cell cycle state in tumor cells should be used.

On the other hand, anguidine substantially increased the cytotoxicity of *cis*-platinum, melphalan, and bleomycin, while not appreciably modifying radiation cytotoxicity. It is possible that such an increase in cell kill after pretreatment with anguidine was also due to the cell cycle-blocking properties of anguidine. However, at least in the case of *cis*-platinum, another mechanism seems to be operating, since anguidine potentiated *cis*-platinum even in cultures in the plateau phase of growth. Anguidine may enhance the cytoxocity of *cis*-platinum by preventing expression of DNA repair enzymes or by enhancing the critical concentration of the drug in proximity to the DNA suprastructure.

If anguidine preferentially freezes normal tissue from cycling (14), then *cis*-platinum toxicity would be potentiated in normal tissue if its mechanism of action were predicted on cell cycle arrest. However, the evidence favors another mechanism, and it might be possible that anguidine could be used clinically for both normal tissue protection against exquisitely cell cycle-active drugs and potentiation of DNA-reactive agents such as alkylating, cross-linking, and DNA strand scission-producing drugs. The fact that anguidine did not protect against Adriamycin in stationary CHO cells indicates that its protective effects are related to cell cycle arrest, and this further substantiates the possibility that the potentiative and protective effects of anguidine are not mutually exclusive.

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[4] M. Valdivieso, unpublished observation.

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