Cytotoxic and Biochemical Effects of Thymidine and 3-Deazauridine on Human Tumor Cells

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ABSTRACT

Cytotoxicity and perturbations of the deoxyribonucleoside triphosphate pools caused by thymidine were studied in thymidine-sensitive and -resistant human tumor cells. Incubation with 1 mM thymidine reduced cell viability by more than 90% in the three sensitive cell lines (two melanomas and one adrenal carcinoma) and reduced the growth rate without decreasing the viability of resistant LO melanoma cells. Thymidine (1 mM) greatly increased the ratio of the deoxythymidine 5'-triphosphate to deoxyctydine 5'-triphosphate pools in the sensitive cells compared to LO cells and also caused larger relative increases in the pool sizes of deoxyguanosine 5'-triphosphate and deoxyadenosine 5'-triphosphate in the sensitive compared to the resistant cells.

3-Deazauridine, known to inhibit synthesis of deoxyctydine 5'-triphosphate and cytidine 5'-triphosphate in other cell lines, potentiated the cytotoxicity of thymidine for thymidine-sensitive BE melanoma and LO cells. In LO cells, 3-deazauridine (50 µM) decreased the intracellular pool of deoxyctydine 5'-triphosphate to the level obtained with 1 mM thymidine. Lower concentrations of deoxyctydine as compared to cytidine were required to protect BE and LO cells against the cytotoxicity of thymidine plus 3-deazauridine. Deoxyctydine also was more effective than was cytidine in preventing loss of cell viability after exposure to thymidine or to 3-deazauridine individually. In these human melanoma cells, ribonucleotide reductase may be a major site of action of thymidine, of 3-deazauridine, and of both drugs in combination.

These results indicate that in human tumor cells the cytotoxic effect of thymidine correlates with greater perturbations of the pyrimidine deoxyribonucleoside 5'-triphosphate pools and that thymidine and 3-deazauridine, which independently reduce the intracellular levels of deoxyctydine 5'-triphosphate, act synergistically against human tumor cells.

INTRODUCTION

High concentrations of thymidine selectively kill certain human tumor cells in vitro (21), and continual infusions of thymidine cause regression of human tumor heterotransplants in nude (athymic) mice (22). Clinical evidence of antitumor effect has been observed with T-cell leukemias, lymphomas, and metastatic melanomas when plasma levels of about 1 mM thymidine have been maintained (3, 7, 19, 20). Thymidine must be converted to dTTP in order to cause cytotoxicity or cytostasis. The sensitivity of human malignant T-cells to thymidine has been attributed to depletion of the intracellular dCTP pool brought about by allosteric effects of dTTP on ribonucleotide reductase (2, 33, 36). Other investigators have concluded that the decrease in the dCTP pool is too small to account for growth inhibition of L1210 murine leukemia cells (14) and that high levels of dTTP (and/or other dNTPs) interact with a regulatory protein for DNA polymerase (37). Yet another interpretation is that imbalance of the pyrimidine dNTP pools brought about by supranormal levels of exogenous thymidine causes misincorporation of bases into DNA, which leads to mutagenicity and cytotoxicity (4).

3-Deazauridine inhibits the growth of microbial and murine tumor cells in culture and of transplantable mouse tumors in vivo (5, 39). In patients with acute leukemia, infusions of 3-deazauridine resulted in hematological improvement but no significant responses (41). 3-Deazauridine 5'-triphosphate, an intracellular metabolite of 3-deazauridine, inhibits CTP synthetase from murine tumor cells and from calf liver, thereby lowering intracellular levels of CTP and indirectly those of dCTP (5, 26, 27). A secondary effect of 3-deazauridine in these cells is inhibition by 3-deazauridine 5'-diphosphate of the reduction of CDP to dCDP mediated by ribonucleoside reductase (5). Cytidine and less effectively deoxyctydine or uridine counteract growth inhibition caused by 3-deazauridine in murine adenocarcinoma Ca755 and in L1210 cells, whereas thymidine or deoxyuridine do not have this effect (5, 26). 3-Deazauridine is not incorporated into nucleic acids (39).

The major known effects of thymidine and 3-deazauridine metabolites on pyrimidine nucleotide biosynthesis are presented in Chart 1. Other biochemical effects include feedback inhibition by dTTP of thymidine kinase (15) and dCMP deaminase (25) and inhibition by 3-deazauridine and its 5'-monophosphate nucleotide of cytidine deaminase and dCMP deaminase, respectively (10).

We are exploring the potential therapeutic value of combining thymidine with agents that deplete the dCTP pool. Using human tumor cell lines, we are interested in determining (a) if differences in the intracellular dNTP pools are consistent with sensitivity and resistance to thymidine, and (b) if drugs which deplete dCTP pools enhance the cytotoxicity of thymidine. We report here our studies with 4 human cell lines, 3 derived from melanomas and one from an adrenal carcinoma. A preliminary report of some of these findings has been published (24).

MATERIALS AND METHODS

Cells. The human melanoma cell lines CA, BE, and LO were obtained from this laboratory (13), and the SW-13 human adrenal tumor cells were...
from Dr. A. Leibovitz (23). Cells were maintained as monolayer cultures in Eagle's minimal essential medium containing penicillin (50 units/ml), streptomycin (50 µg/ml), and supplemental 2 µM glutamine, all from Grand Island Biological Co. (Grand Island, NY), and 10% heat-inactivated fetal calf serum from Reheis Chemical Co. (Phoenix, AZ). Cultures were incubated at 37°C in a humidified 5% CO2 atmosphere. Periodic tests for Mycoplasma contamination were negative.

**Chemicals.** [methyl-3H]dTTP (60 Ci/mmol), [5-3H]dCTP (30 Ci/mmol), [8-3H]dGTP, (18 Ci/mmol), and [8-3H]dATP (17 Ci/mmol) were purchased from ICN Clinical Radioisotopes Div. (Irvine, CA). Lyophilized noncovalent deoxypolycytidylate, deoxyinosinate-deoxypolyguanylate-deoxypolyguanylate-deoxypolyolcytidylate, and deoxyinosinate-deoxypolyolcytidylate were obtained from P-L Biochemicals, Inc. (Milwaukee, WI), and Micrococcus luteus DNA polymerase (EC 2.7.7.7) (specific activity, 469 units/mg protein) was purchased from Miles Laboratories (Elkhart, IN). Thymidine, 3-deazauridine, and other nonlabeled chemicals were from Sigma Chemical Co. (St. Louis, MO).

**Growth and Cytotoxicity Assays.** Cells were seeded in 75-cm² culture flasks and allowed to plate for 24 hr, at which time the medium was removed and replaced with fresh medium with or without drugs. At indicated times, cells from one-half of the flasks were harvested with trypsin to determine cell number with a Model ZBI Coulter Counter. Aliquots from these flasks were incubated at 37°C in a humidified 5% CO2 atmosphere. Periodic tests for Mycoplasma contamination were negative.

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**dNTP Assays.** Flasks (75 cm²) which had been seeded and incubated in parallel with those used for cell growth and viability assays were washed with phosphate-buffered saline (Na2HPO4 (2.0 g/liter)-KH2PO4 (0.4 g/liter)-NaCl (8.0 g/liter)-KCl (0.2 g/liter)) and then quickly treated with 60% methanol for 20 min at 20°C followed by cold 80% methanol to extract the intracellular dNTPs (29, 38). Recovery of added dNTPs was 85 to 114%. In agreement with recent studies with human cells (12), we found no significant conversion of deoxynucleosides, or deoxynucleoside mono- or diphosphates to dNTPs, as has been observed when HeLa cells were extracted with cold methanol (31).

The dNTPs were quantitated by a modification of the DNA polymerase assay described by Kinahan et al. (17). The deoxypolyguanylate-deoxypolyolcytidylate copolymer was used for the dCTP assays. The polymerization reactions were conducted in 96-well culture plates, and aliquots (90 µl) of each reaction mixture were spotted on discs of Whatman GFA glass fiber filters (pretreated with cold 5% trichloroacetic acid containing 1% inorganic sodium pyrophosphate) placed on a manifold. After 10 min, each dish was washed 12 times with the cold trichloroacetic acid-inorganic sodium pyrophosphate solution followed by 4 washes with 100% methanol and 3 with diethyl ether. For each cell line, dNTP determinations were performed on extracts from 3 separate experiments with at least 2 flasks/treatment.

**RESULTS**

**Effect of Thymidine on Growth Rate and Cell Viability.** At plating densities of 500,000 cells/75-cm² flask, the logarithmic phase growth rates of all 4 cell lines were approximately the same (doubling times ranging from 29 to 33 hr). Under these conditions, 48-hr incubation of CA, BE, or SW-13 cells with 1 µM thymidine prevented cell division and decreased cell viability by more than 90%. LO cells divided more slowly in the presence of thymidine (see below), but their viability was enhanced after 24-hr incubation and was not impaired for up to 72 hr (Table 1).

**Effect of Thymidine on Intracellular dNTP Levels.** Chart 2 shows the changes in the dNTP pools caused by incubating these cell lines with 1 µM thymidine. After 24 hr, the dNTP pools of the sensitive lines increased 60-fold or more, whereas the relative increase in the LO cells was less than half these values.

**Table 1**

<table>
<thead>
<tr>
<th>Thymidine treatment (hr)</th>
<th>Cell viability (fraction of control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>BE</td>
</tr>
<tr>
<td>24</td>
<td>0.38 ± 0.06</td>
</tr>
<tr>
<td>48</td>
<td>0.08 ± 0.04</td>
</tr>
<tr>
<td>72</td>
<td>0.006 ± 0.003</td>
</tr>
</tbody>
</table>

* a. Incubation without thymidine.

b. Mean ± S.E.

**Chart 2.** Effect of 1 µM thymidine on dNTP pools in human tumor cells. Logarithmically growing cells (500,000/75-cm² flask) were incubated with or without 1 µM thymidine. The cells were harvested at the indicated times and were replated for colony formation.
The dCTP pools in untreated CA, BE, and SW-13 cells were lower than those of untreated LO cells. After incubation with thymidine, the dCTP pools of the sensitive cells decreased by 80% or more, whereas the decrease in LO cells was only 42%. The pyrimidine dNTP pools did not change further after 48-hr incubation. Thymidine caused the purine dNTP pools to increase.

Cytotoxicity of Thymidine plus 3-Deazauridine. Thymidine plus 3-deazauridine caused greater than additive cytotoxicity to the thymidine-sensitive BE melanoma cells (Chart 3). Thymidine (1 mM) reduced the growth rate of LO cells but not their viability. In combination with 3-deazauridine, the cytotoxicity was greater than additive (Chart 4). Similar results were obtained when the cells were plated in low number for colony formation assays only. Short-term (4-hr) incubation of 3-deazauridine prior to or simultaneously with thymidine also resulted in greater than additive toxicity (Chart 5). The sequence of thymidine followed by 3-deazauridine resulted in additive cytotoxicity only (data not shown).

Reversal of Cytotoxicity. Very low (0.04 to 1 μM) concentrations of deoxycytidine counteracted the cytotoxicity of thymidine plus 3-deazauridine to BE cells; cytidine at these concentrations was less effective (Chart 6). Much higher concentrations of cytidine as compared to deoxycytidine were required to prevent cytotoxicity caused by thymidine plus 3-deazauridine to LO cells (Chart 7). Cytosine at concentrations of up to 1 mM had no effect on the cytotoxicity of this drug combination. As shown in Table 2, lower concentrations of deoxycytidine as compared to cytidine also prevented cytotoxicity caused by thymidine or by 3-deazauridine alone to these cells. With one exception (thymidine at a concentration of 16 mM), deoxycytidine at a concentration of no greater than 5 μM counteracted 95 to 100% of the cytotoxicity of thymidine and/or 3-deazauridine at the concentrations shown in Charts 6 and 7 and Table 2. At the concentrations used in these experiments, neither deoxycytidine nor cytidine alone had any effect on the viability of BE or LO cells.

Effects of 3-Deazauridine and Thymidine plus 3-Deazauridine on dNTP Pools in LO Cells. 3-Deazauridine (50 μM) decreased the intracellular dCTP pool by 63%, which was similar in all 4 cell lines. These changes were also relatively greater in the thymidine-sensitive cells as compared to the resistant LO cells.
to the decrease caused by 1 mM thymidine. The combination of thymidine plus 3-deazauridine did not lower further the dCTP pool or increase the ratio of dTTP to dCTP (Table 3). 3-Deaza-
zauridine had no effect on the dNTP assay as determined by incorporation of known amounts of dNTPs added to assay mixtures.

**DISCUSSION**

Thymidine (1 mM) markedly altered the dNTP pools, especially the levels of the pyrimidine dNTPs, in the 3 thymidine-sensitive cell lines. After incubation with thymidine for 24 hr, the ratio of dTTP to dCTP changed from about 4 in untreated cells to 1900 in BE cells, to 3100 in CA 1 cells, and to an even higher value in SW-13 cells. In the thymidine-resistant LO melanoma cells, the increase in the dTTP pool was smaller; the dCTP pool decreased only to about the dCTP levels in untreated CA, BE, or SW-13 cells; and the ratio of dTTP to dCTP rose from 2.2 to only 130. These data suggest a correlation between cytotoxicity and the magnitude of the changes in the dTTP pools and/or the dCTP pools. The purine dNTP pools, especially dGTP, also increased to a greater extent in the thymidine-sensitive cells, and it cannot be excluded that these changes contributed to the observed cytotoxicity. Longer incubations of sensitive cells with thymidine increased the cytotoxicity without further altering the dNTP pools indicating that events subsequent to DNA precursor pool imbalance were the proximate cause of cell death.

The question arose as to whether an agent which depletes the dCTP pool might potentiate the effect of thymidine on human tumor cells. For these experiments, we selected 3-deazauridine, which lowers the intracellular pool of dCTP (and CTP) and is not

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**Table 3**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>dTTP (pmol/10⁶ cells)</th>
<th>dCTP (pmol/10⁶ cells)</th>
<th>dGTP (pmol/10⁶ cells)</th>
<th>dATP (pmol/10⁶ cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>105 ± 0.04*</td>
<td>43 ± 4.0</td>
<td>10 ± 0.8</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>Thymidine (1 mM)</td>
<td>1870 ± 220</td>
<td>18 ± 0.2</td>
<td>122 ± 3.0</td>
<td>130 ± 8.0</td>
</tr>
<tr>
<td>3-Deazauridine (50 μM)</td>
<td>211 ± 21</td>
<td>16 ± 0.8</td>
<td>11 ± 1.7</td>
<td>82 ± 0.3</td>
</tr>
<tr>
<td>Thymidine (1 mM) + 3-deazauridine (50 μM)</td>
<td>2260 ± 30</td>
<td>22 ± 1.5</td>
<td>88 ± 4.0</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± S.E.

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**Table 2**

<table>
<thead>
<tr>
<th>Cells</th>
<th>Concentration of added nucleoside required to decrease cytotoxicity by 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thymidine (mM)</td>
</tr>
<tr>
<td>BE</td>
<td>4.0</td>
</tr>
<tr>
<td>BE</td>
<td>1.0</td>
</tr>
<tr>
<td>BE</td>
<td>200</td>
</tr>
<tr>
<td>LO</td>
<td>16.0</td>
</tr>
<tr>
<td>LO</td>
<td>4.0</td>
</tr>
<tr>
<td>LO</td>
<td>200</td>
</tr>
</tbody>
</table>

* Relative to controls, 362 ± 6 colonies for BE cells and 565 ± 15 colonies for LO cells.

* Mean ± S.E.
incorporated into nucleic acids (5, 39). The combination of thymidine plus 3-deazauridine was synergistic against thymidine-sensitive BE cells and resistant LO cells. With LO cells, it was found that this drug combination was synergistic when 3-deazauridine was incubated prior to or simultaneously with thymidine. The lack of synergism when thymidine preceded 3-deazauridine may have been due to the rapid normalization of dNTP pools and resumption of DNA synthesis when exogenous thymidine is removed from mammalian cells (2, 8). Removal of thymidine but not of 3-deazauridine from LO cells was accompanied by rapid reversal of growth inhibition.4

The cytotoxicity caused by thymidine plus 3-deazauridine was prevented by lower concentrations of deoxycytidine as compared to cytidine, suggesting that this drug combination depletes a critical dCTP pool which can be repleted with exogenous deoxycytidine. Deoxycytidine also was more effective than was cytidine in protecting BE and LO cells against the toxicity of thymidine or 3-deazauridine alone. Because of the known allosteric inhibition of ribonucleotide reductase by dTTP (33), it would be expected that lower concentrations of deoxycytidine as compared to cytidine would prevent thymidine toxicity (40). The results with 3-deazauridine contrast, however, with earlier work with murine Ca755 adenocarcinoma and L1210 leukemia cells which showed that cytidine was much more effective than was deoxycytidine in protecting against 3-deazauridine (5, 26). These results led to the suggestion that CTP synthetase is the major site of inhibition by metabolites of 3-deazauridine. Further support for this conclusion was obtained from inhibition studies of dCTP pool in these cells. Further work, including enzyme studies, will be required to elucidate more fully the mechanisms of action of thymidine plus 3-deazauridine and of each drug separately on human melanoma cells.

Of potential practical importance is the effectiveness of very low concentrations of deoxycytidine in protecting cells from the toxicity of thymidine (42) as well as of 3-deazauridine and of both drugs in combination. These results suggest that plasma levels of deoxycytidine may affect critically the responsiveness to these drugs of tumors in animals or in patients.

In these studies, we did not examine whether the combination of thymidine and 3-deazauridine selectively kills tumor cells relative to sensitive normal tissues or whether this drug combination acts synergistically against normal cells. Certain human and murine tumor cells compared to nonmalignant cells of the same type are considerably more sensitive to thymidine (21, 32). To our knowledge, similar comparisons using 3-deazauridine are not available. According to one study, however, 10 to 20 times higher concentrations of 3-deazauridine 5'-diphosphate were produced in implanted L1210 cells as compared to the normal mouse tissues (9). Increased anabolism of 3-deazauridine in tumor tissues would be expected to enhance tumor cell kill relative to normal cells. If 3-deazauridine would potentiate the cytotoxicity of thymidine without negating the greater sensitivity of some tumor cells to this nucleoside, then this combination could have potential therapeutic benefit.

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