Esters of Chlorohydroxyacetone in Chemotherapy of Murine Tumors

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ABSTRACT

1-Deoxyhalo analogs of dihydroxyacetone and of D,L-glycerol were tested for cytostatic effects in vitro against dividing cell lines of murine L1210 leukemia and Ehrlich carcinoma, against primary stationary Ehrlich cells in vitro, and for in vivo chemotherapeutic effects against a number of murine tumors. Benzoate, p-nitrobenzoate, and 3,5-dinitrobenzoate esters of 1-chloro-3-hydroxyacetone inhibited proliferation in log-phase cultured cells by 50% at concentrations between 2 and 4 μM and inhibited thymidine incorporation by 50% into stationary cells at 60 to 150 μM. Comparable in vitro activities were obtained with the acetate ester and with chloroacetone. Corresponding glycerol analogs and the fluoro analogs in either the glycerol or dihydroxyacetone series were inactive. Chlorohydroxyacetone benzoate, chlorohydroxyacetone p-nitrobenzoate, and chlorohydroxyacetone 3,5-dinitrobenzoate produced 50 to 100% cure of 2.5 x 10^6 Ehrlich tumor cell challenges in C57Bl/6 x DBA/2F1 (hereafter called B6D2F1) hosts with only a single drug injection, but only if the hosts were immunocompetent. The 3,5-dinitrobenzoate ester was the most effective, while the acetate ester was only weakly active and neither the phosphate ester nor chloroacetone was active in vivo. Chlorohydroxyacetone 3,5-dinitrobenzoate produced significant increases in life span and a number of long-term cures of P815 mastocytoma in semisyngeneic B6D2F1 hosts, but had no effect in syngeneic DBA/2 hosts. The analog was inactive against L1210 leukemia, EL4 lymphoma, and C3H mammary adenocarcinoma in B6D2F1, semisyngeneic hosts. Tumor-bearing treated animals were able completely to resist an added normally lethal tumor challenge given as soon as 24 hr after single-drug injection chemotherapy. After initial tumor challenge and single-injection treatment, viable tumor cells were recovered from treated animals that were lethal to naive passive recipients, even though cagemates of the treated tumor cell donors were cured. These results show that chlorohydroxyacetone benzoate esters are chemotherapeutically active in vivo under conditions that suggest drug-induced alteration of host-tumor interaction after initial direct cytotoxicity. Such results are consistent with previously obtained altered host response to murine Friend erythroleukemia cells treated in vitro with the same agents. It is not yet known whether the mechanisms responsible for the in vitro alteration of erythroblast cells are related to in vivo chemotherapy obtained in this work with Ehrlich tumor cells.

INTRODUCTION

The plasma membrane of the cell governs biological functions important in neoplasia, including transport of ions and metabolites, immunogenicity of surface antigens, cell-cell interactions, tissue and organ morphology, and recognition of molecular control signals that regulate proliferation and differentiation. Modifications of cell surface groups by chemical and biological agents have produced effects on membrane-mediated phenomena in both normal and neoplastic cells (1, 7, 10, 12, 14, 15). This suggests that drug-induced alteration of membrane structures may provide new approaches to both chemotherapy and immunotherapy. Such therapeutic approaches based on drug-induced alteration of plasma membrane structures have the added potential advantage that drug resistance based on failure of drug transport or resistance arising from drug deactivation by intracellular enzyme systems may not be a significant limitation.

We have observed that murine DBA/2-derived Friend erythroleukemia cells treated in culture with CLHAB or with related analogs and implanted into syngeneic hosts generate altered host-tumor interaction of protective benefit to the host. Molecular features of the active analogs suggest that they function as lipophilic alkylating agents and thus may exert effects at least in part by reaction with electron donors in lipopilic cell compartments, including the plasma membrane.

Alteration of host-tumor interaction by prior treatment of the tumor cells in culture has a number of attractive features with respect to characterization of biochemical and immunological events. However, it is also important to determine whether direct treatment in vivo is capable of altering host-tumor interaction in a manner that is empirically beneficial to the host. We have therefore examined the in vivo chemotherapeutic effects of esters of chlorohydroxyacetone and related compounds in allogeneic and syngeneic tumor model systems. The work was designed to determine (a) whether there are significant in vivo chemotherapeutic effects with CLHAB and related benzoate esters and (b) whether any such observed effects reflect altered host-tumor interaction beyond direct cytotoxicity, possibly paralleling the in vitro alteration effects observed in the Friend erythroleukemia studies.

MATERIALS AND METHODS

Halo Analogs. The agents used in this work are shown in Chart 1. The D,L-1-deoxyhaloglycerols, their 3-phosphate esters, and the halohydroxyacetone phosphates were prepared and characterized as previously described (3, 5, 9). The other halohydroxyacetone analogs and hydroxyacetone benzoate were prepared and characterized as detailed elsewhere (13, 14).
Chemotherapy with Esters of Chlorohydroxyacetone

In Vitro Cytotoxicity against in Vivo-derived Ehrlich Tumor Cells. Chlorohydroxyacetone esters, chloroacetone, and chloroacetate were tested against Ehrlich tumor cells derived directly from passage animals. Cytotoxicity was measured by inhibition of tritiated thymidine incorporation and by in vivo bioassay for tumorigenicity of treated cells. Chart 2 shows that the benzene and acetate esters of chlorohydroxyacetone inhibited thymidine incorporation more strongly than did chloroacetone. CLHA-3,5-DNB was markedly less cytotoxic than

**In Vitro Cytostatic Activity against Proliferating Ehrlich Carcinoma and L1210 Leukemia Cell Lines.** IC₅₀'s were determined for each of the compounds shown in Chart 1. The results were essentially the same as those previously reported

**Table 1.** Structures of analogs. CIDG-3-P, chlorodeoxyglycerol 3-phosphate; CIDG-3-benzene, chlorodeoxyglycerol 3-benzene; CIDG-3-p-nitro-benzoate, chlorodeoxyglycerol 3-p-nitro-benzoate; CIDG-2,3-diacetate, chlorodeoxyglycerol 2,3-diacetate; CIHAP, chlorohydroxyacetone phosphate; CIHA-acetate, chlorohydroxyacetone acetate.

for dividing Friend erythroleukemia cells (6), with the exception of the benzene and p-nitrobenzene esters of DL-1-chloro-1-deoxyglycerol, which gave IC₅₀'s in the range of 20 to 30 μM in the Ehrlich and L1210 systems compared to 500 μM or greater for the benzene ester in the Friend erythroleukemia system. CLHAB, CLHA-pNB, CLHA-3,5-DNB, and the acetate esters of chlorohydroxyacetone, as well as chloroacetone and 1,3-di-

chloroacetone, all gave IC₅₀'s between 2 and 4 μM, whereas the corresponding glycerol analogs, the fluoro analogs in either the Friend erythroleukemia system, these results show that the chlorohydroxyacetone molecule is required for activity.

**Table 2.** Glycerol Analogs:

- CH₂Cl (F) R₂ - OH
- CH₂R₂ - CH₃
- CH₂CH₂OCH₂Cl

**Table 3.** Dihydroxyacetone Analogs:

- CH₂Cl (F) R₂ - OH
- CH₂R₂ - CH₃
- CH₂CH₂OCH₂Cl

**Table 4.** Control Compounds:

- CH₃ CH₂Cl
- CH₂Cl(CH₂)₂Cl
- CH₂CH₂OCH₂OCH₂Cl

**Chart 1.** Structures of analogs. CIDG-3-P, chlorodeoxyglycerol 3-phosphate; CIDG-3-benzene, chlorodeoxyglycerol 3-benzene; CIDG-3-p-nitro-benzoate, chlorodeoxyglycerol 3-p-nitro-benzoate; CIDG-2,3-diacetate, chlorodeoxyglycerol 2,3-diacetate; CIHAP, chlorohydroxyacetone phosphate; CIHA-acetate, chlorohydroxyacetone acetate.

For dividing Friend erythroleukemia cells (6), with the exception of the benzene and p-nitrobenzene esters of DL-1-chloro-1-deoxyglycerol, which gave IC₅₀'s in the range of 20 to 30 μM in the Ehrlich and L1210 systems compared to 500 μM or greater for the benzene ester in the Friend erythroleukemia system. CLHAB, CLHA-pNB, CLHA-3,5-DNB, and the acetate esters of chlorohydroxyacetone, as well as chloroacetone and 1,3-di-

chloroacetone, all gave IC₅₀'s between 2 and 4 μM, whereas the corresponding glycerol analogs, the fluoro analogs in either the glycerol or the halohydroxyacetone series, and the hydro-

philic phosphate ester of chlorohydroxyacetone were less cy-

tostatic by factors ranging from 5- to 250-fold or more. As with

the Friend erythroleukemia system, these results show that the presence of an α-chloroketone group and a relatively lipophilic molecule are required for activity.

**In Vitro Cytotoxicity against in Vivo-derived Ehrlich Tumor Cells.** Chlorohydroxyacetone esters, chloroacetone, and chloroacetate were tested against Ehrlich tumor cells derived directly from passage animals. Cytotoxicity was measured by inhibition of tritiated thymidine incorporation and by in vivo bioassay for tumorigenicity of treated cells. Chart 2 shows that the benzene and acetate esters of chlorohydroxyacetone inhibited thymidine incorporation more strongly than did chloroacetone. CLHA-3,5-DNB was markedly less cytotoxic than
and mean survival and a number of long-term cures in B6D2F1 doses. Assays when administered at the highest tolerated in vivo erol series (see Chart 1) produced significant effects in survival i.p. to animals bearing various i.p. challenge doses of P8i 5 neic and Semisyngeneic Hosts. CLHA-3,5-DNB administered drug treatment (data not shown). Neither dichloroacetone, of total packed cell volume 8 days after tumor challenge and 3276 CANCER RESEARCH VOL. 40 8th condition was very weakly active at best. Chloroacetone, despite acetate ester of chlorohydroxyacetone under comparable con-


estures of 1 x 10^6 cells or less or if the beginning of treatment of the 10^6 cell challenge was delayed until 12 or 24 hr after tumor implantation.

The role of Host Immunocompetence in Cure of Ehrlich Tumor with Chlorohydroxyacetone Esters. It was apparent that some features of host, tumor, and drug interaction other than direct cytotoxicity were in part responsible for the cures obtained in the Ehrlich tumor system, since the cytotoxic properties of the chlorohydroxyacetone esters were only weakly effective or completely ineffective in other tumor systems. Moreover, the most effective of the analogs in terms of chemotherapy in vivo, CLHA-3,5-DNB, was the least cytotoxic of the active analogs tested in vitro against Ehrlich cells. In order to test for the extent of host participation in the cures obtained with the chlorohydroxyacetone esters, the esters were used for chemotherapy either in single-dose or in multiple-dose regimens in animals that had been partially immunosuppressed by exposure to 500 rads whole-body X-irradiation prior to tumor challenge and drug treatment. The results of multiple-dose treatments in normal and immunosuppressed tumor-bearing hosts are shown in Chart 4A, and the single-dose results are shown in Chart 4B. Immunocompetent control animals responded with the proportion of survivors expected from earlier experiments shown in Table 1. For all of the treated immunosuppressed animals, there was an increase in median life span compared to untreated suppressed controls, as might be expected due to direct cytotoxicity of the agents, but chemotherapy benefit was transient, and none of the animals were long-term survivors. Only immunocompetent hosts could be cured of Ehrlich tumor challenge by either single- or multiple-dose treatment.
Chlorohydroxyacetone esters can be used as chemotherapy agents. Table 1 shows the results of survival assays using Ehrlich ascites tumor mice. The table lists the number of experiments, cumulative dose schedule, and 60-day survivors per number of mice treated. Table 2 details the chemotherapy against P815 mastocytoma with CLHA-3,5-DNB. Treated mice received graded doses of Ehrlich cells ranging from 1 x 10^6 to 2.5 x 10^5, and survival results were compared with those of matched immunocompetent controls. Animals that were partially immunosuppressed by whole-body X-irradiation under the conditions used in Chart 4 were given graded doses of Ehrlich cells ranging from 1 x 10^5 to 2.5 x 10^5 in 24 days. Median survival times were 20 (normal hosts) to 23 (suppressed hosts) days. Inocula of 2.5 x 10^5 cells were nontumorigenic in normal animals but fully tumorigenic in X-ray-treated hosts, with median survival times of 24 days in one experiment and 36 days in another. An inoculum of 1 x 10^6 was also fully tumorigenic in suppressed animals and gave a median survival of 39 days, while 1 x 10^6 cells were essentially nontumorigenic in X-ray-treated hosts. These results establish that somewhere between 2.5 x 10^5 and 1 x 10^6 viable Ehrlich cells have survived the cytotoxic action of the analogs.
Resistance to Additional Viable Tumor Cell Challenge in Drug-treated Animals. Since the number of viable Ehrlich cells surviving drug treatment is in the range of $1 \times 10^6$ and this number is above, but close to, the tumorigenic threshold in immunocompetent hosts, additional evidence is required to confirm that treated hosts are capable of rejecting a normally lethal surviving fraction of tumor cells. To determine whether drug-treated immunocompetent animals were capable of rejecting an otherwise lethal tumor cell challenge, animals treated with a curative dose of CLHA-3,5-DNB 1 day after challenge with $2.5 \times 10^7$ Ehrlich cells were given a second challenge with graded doses of Ehrlich cells 24 hr after drug treatment. We have separately determined (data not shown) that CLHAB loses its reactive chloride rapidly under physiological conditions and has essentially disappeared after 1 hr. Table 3 shows that animals subjected to an additional tumor burden of between $1 \times 10^6$ and $2.5 \times 10^6$ Ehrlich cells, doses that were lethal to 100% of control mice, were at least partially protected. These animals may have been completely protected, since the primary treatment used is capable of curing only about 50% of the challenged animals, even without an additional cell burden administered on Day 2 (see Table 1).

Survival of Viable Tumor Cells in Drug-treated Animals. It is apparent that drug-treated animals are capable of rejecting an additional otherwise lethal tumor challenge given shortly after initial challenge and curative drug treatment. It is not necessarily true that the initial cure itself depends on augmentation of host resistance to an otherwise lethal surviving tumor cell fraction. In order to determine whether the hosts were in fact resisting a lethal tumor challenge as part of the curative effects of the chlorohydroxyacetone esters, we transferred surviving Ehrlich tumor cells from treated hosts to matched naive control animals. Day 8 following challenge with $2.5 \times 10^7$ Ehrlich cells and cure with CLHA-3,5-DNB, peritoneal cells from each of 9 donor mice were separately collected, washed, and transferred to each of 9 recipient mice. Eleven other drug-treated tumor-bearing animals were retained as survival controls. Of the 9 recipients of the peritoneal contents remaining in the 9 donor mice after a single injection of CLHA-3,5-DNB, 7 mice died, demonstrating that at least $1 \times 10^6$ viable Ehrlich cells had remained in the original treated donors. In the survival assay conducted in parallel with the primary treated animals, 8 of the 11 mice were cured, a proportion consistent with that expected from the results previously shown in Table 1.

Effects of Drug Pretreatment and Antigenic Load on Tumorigenicity of Cells. Host participation in drug-induced cure could arise from indirect effects of the drug on the host or from indirect effects of tumor cell cytotoxicity on the host and might not involve simultaneous effects on drug-tumor-host interactions. In chemotherapy of Ehrlich tumor with N-haloacetylhexosamine tetra-O-acetates (17), we have observed that i.p. injection of the chemotherapeutic agents prior to i.p. tumor challenge enhanced host resistance. In order to determine whether the chlorohydroxyacetone esters exhibit a similar effect, we administered a normally curative dose of CLHA-3,5-DNB i.p. 24 hr before i.p. challenge with tumor cells. There was no distinction in proportion of survivors or in median day of death between animals receiving drug pretreatment and those receiving no drug treatment.

It is conceivable that primary treated hosts are able to reject an otherwise lethal surviving tumor cell fraction because of the presence of a large proportion of dead tumor cells. The dead tumor cell fraction could generate either a specific host antitumor response by virtue of the relatively high antigenic load, or it could generate a nonspecific influx of peritoneal cells augmenting host resistance to the surviving viable cells. To examine this alternative, Ehrlich ascites cells, rendered nontumorigenic by 4000 rads of X-irradiation, were mixed with viable Ehrlich cells. The proportion of killed cells ranged from 4 to 96% in a total inoculum of $25 \times 10^6$ cells. All the mice died from the viable cells present in the inoculum. As judged by the median day of death for all groups, 106 Ehrlich cells, it appeared that death was directly related only to the number of viable cells injected.

Effect on PMN Influx and Comparison with N-Bromoacetylhexosamine Tetra-O-acetates. In the chemotherapy of Ehrlich tumor with N-bromoacetylhexosamine tetra-O-acetates, we observed that drug-induced cure as associated with a significant increase in the percentage of PMN's in the total WBC population in the peritoneal cavity of treated animals compared to untreated tumor-bearing controls. There was also an increase in the absolute numbers of PMN's in the peritoneal cavities of treated mice (17). We suggested that the carbohydrate analogs were enhancing host inflammatory processes at the site of tumor injection, accounting for the ability of the drug-pretreated hosts to resist subsequent lethal tumor challenge as noted in the previous section and possibly contributing to the drug-induced cure of tumor-bearing hosts. Since pretreatment with CLHA-3,5-DNB prior to tumor challenge did not augment host resistance to challenge with $10^6$ Ehrlich cells, we compared the effects of i.p. treatment with CLHA-3,5-DNB to treatment with N-bromoacetylgalactosamine teta-O-acetate in animals in the absence of any tumor challenge. Mice were given injections of the normally curative doses of each agent and sacrificed 1, 2, 3, or 5 days after treatment. Peritoneal cells were quantitatively harvested, and differential staining was performed as detailed previously (17). Chart 5 shows the pattern of host cell infiltration obtained in response to each agent in the absence of Ehrlich cell challenge. N-Bromoacetylglutathione tetra-O-acetate caused a rapid influx of PMN's and lymphocytes into the peritoneal cavities, whereas CLHA-3,5-DNB had no such effect on PMN infiltration and only marginal effect on lymphocyte infiltration. These results indicate that these 2 classes of lipophilic thiol reagents are exerting host-mediated antitumor effects by significantly different mechanisms.

Effect of CLHAB on Primary Humoral Immunity. Effects on the primary IgG and IgM responses in B6D2F1, mice to sheep

<table>
<thead>
<tr>
<th>Additional cell burden</th>
<th>No. of survivors/no. of mice treated</th>
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<tbody>
<tr>
<td>$1.0 \times 10^6$</td>
<td>6/10</td>
</tr>
<tr>
<td>$1.5 \times 10^6$</td>
<td>3/5</td>
</tr>
<tr>
<td>$2.5 \times 10^6$</td>
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<td>$1.0 \times 10^6$</td>
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erythrocytes were examined as a function of the timing of drug administration. Mice treated with a single injection of drug at chemotherapeutic dose levels 24 hr after antigen (CLHA-3,5-DNB, 125 mg/kg; CLHA, 50 mg/kg; and CLHA-pNB, 100 mg/kg) showed no significant reduction in the number of splenic IgG PFC’s 6 days after antigen administration, as compared with vehicle controls. Multiple injections with CLHA-3,5-DNB (75 mg/kg/day, Days 1, 3, and 5) also failed to affect IgG PFC numbers. Complete suppression of spleen IgG PFC response (no PFC’s/spleen) versus vehicle control (8.4 ± 0.5 × 10^6 PFC’s/spleen) was obtained if treatment with CLHA-3,5-DNB (75 mg/kg/day) was begun 7 days before antigen administration and was continued every other day until 1 day after antigen administration.

Mice treated with single injections of CLHAB or CLHA-3,5-DNB (at dose levels active in chemotherapy) 1 day after antigen administration showed no reduction in Day +4 hemolytic titer (IgM response) compared to vehicle control mice. Suppressed IgM response (−log2 hemolysin titer = 7, compared to vehicle control titer = 10) was observed only when CLHA-3,5-DNB treatment (75 mg/kg/day) was begun 7 days before antigen administration and continued every other day until 1 day after administration.

**DISCUSSION**

**Chemotherapy with Chlorohydroxyacetone Esters.** The benzoate esters of chlorohydroxyacetone have potent anti-Ehrlich tumor activity in vivo even with only a single-drug injection. The most effective of these esters, CLHA-3,5-DNB, also produces less marked but still significant in vivo chemotherapeutic effect against the P815 mastocytoma in semisyngeneic hosts. Antiproliferative activity against log-phase cultured cell lines of Ehrlich tumor and of L1210 leukemia parallel results observed previously against log-phase Friend erythroleukemia cells (6). When used as a measure of cytotoxic activity, inhibition of incorporation of labeled thymidine into both L1210 and Ehrlich tumor cells derived directly from passage hosts parallels the dividing cell culture results and confirms that the active analogs require an α-chloroketone group and lipophilic characteristics. Further structure-activity studies are in progress, designed to determine whether these agents are monofunctional lipophilic alkylation agents or whether they require the benzoate or nitrobenzoate group as second leaving group for in vivo activity. At this point it is apparent that the CLHA benzoate esters are able to generate altered host-tumor interaction to DBA/2-derived Friend erythroleukemia cells when the cells are drug treated in vitro and reimplanted into syngeneic hosts (6). The agents are also able to produce chemotherapeutic responses in vivo in other tumor model systems, even though they are chemotherapeutically inactive against the highly drug-resistant cultured Friend erythroleukemia cells implanted and treated in vivo (6). There is no evidence at present that the mechanisms producing chemical alteration of Friend erythroleukemia cells in vitro are related to the mechanisms producing in vivo chemotherapeutic activity. However, some features of the in vivo curative responses in this work suggest that host-tumor interaction has been altered by in vivo drug treatment, producing a chemotherapeutic response that includes but extends beyond direct cytotoxicity.

**Host Participation in Cure of Ehrlich Tumor with CLHA Esters.** The inability of the CLHA esters to effect long-term cures in animals that have been immunosuppressed shows that a surviving viable cell fraction is being overcome in immunocompetent mice that are cured after parallel treatment schedules. The most potent cytotoxic analogs in vitro are not the most effective in vivo (Charts 2 and 3), and one of them chloroacetone, is not effective at all in vivo. Moreover, if direct tumor cell cytotoxicity accounted for all of the in vivo activity of these agents, one would expect a broader spectrum of at least delayed tumor growth in other tumor model systems, and some activity would be likely to persist in syngeneic hosts if activity was observed in semisyngeneic hosts. In fact, in 5 tumor model systems studied in this work and one in earlier work (6), antitumor activity is observed in 2 of the 6 systems.

Treatment in vivo with CLHA esters could produce cures by reducing the surviving tumor cell population to a level below the tumorigenic threshold in the Ehrlich system in immunocompetent hosts. However, transfer to naive animals of peritoneal cells from cagemates of animals destined to survive shows that the survivors harbor a leathal tumor burden after drug treatment that kills the recipients but fails to kill the donors. In addition, lethal tumor challenges can be administered shortly after initial tumor treatment (Table 3), and animals so treated can survive the otherwise lethal challenge. A full exploration of rechallenge immunity after cure with CLHA analogs is in progress. It is important at this juncture to point out that rechallenge survival in this allogeneic tumor model system is by no means as simple to achieve as is sometimes assumed. We have shown that animals cured of primary Ehrlich tumor by methotrexate or 1-β-D-arabinofuranosylcytosine are not immune to rechallenge survival in this allogeneic tumor model system is by no means as simple to achieve as is sometimes assumed. We have shown that animals cured of primary Ehrlich tumor by methotrexate or 1-β-D-arabinofuranosylcytosine are not immune to secondary tumor regrowth at other sites, whereas cure with agents such as nitrogen mustard or mitomycin C does produce rechallenge immunity (17). Arnold et al. (2) showed that animals cured of a 10^7 Ehrlich cell challenge using poly-L-lysine were fully susceptible to rechallenge with 4 × 10^6 cells.

**Basis for Host Participation in Cure with CLHA Esters.** Although features of altered host-tumor interaction appear to be involved in the cures obtained with the CLHA esters, it is not clear what those features are or whether they are potentially significant or relatively trivial. It is clear that direct effects of antigen load are not involved, since mixtures of live and dead
cells affected host animals only in proportion to the dose of live cells administered. It is also apparent that the CLHA esters produce anti-Ehrlich tumor effects by mechanisms that are at least in part distinct from those involved in cures with N-bromoacethylhexosamine tetra-O-acetates in this same system (17). With the carbohydrate analogs, drug treatment prior to tumor challenge has some measurable antitumor effect (17), and, as shown in this present work, the carbohydrate analogs themselves produce altered patterns of host cell infiltration into the site of drug administration in the absence of tumor challenge. Neither of these properties is exhibited by the active CLHA esters.

It is probable that the CLHA esters are lipophilic alkylling agents that are chemotherapeutically active under conditions that do not suppress a primary humoral immune response. Tumor-bearing animals treated with these agents in vivo exhibit increased host resistance to live tumor cells. These in vivo results are consistent with the increased host resistance to live Friend erythroleukemia cells obtained by treating Friend erythroleukemia cells in vitro with the analogs, reimplanting the treated cells into normal recipients, and challenging the recipients with live Friend erythroleukemia cells (6). However, in both cases, it is not yet clear whether treatment with the analogs delays primary tumor cell growth sufficiently to permit unsuppressed host response to limit the surviving cell fraction and concomitantly to produce increased host resistance to tumor rechallenge or whether increased tumor cell immunogenicity is involved. Additional experiments in the in vivo Ehrlich tumor system are in progress to test these 2 alternatives.

References

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