Chemotherapy of Subcutaneous and Intracranial Human Medulloblastoma Xenografts in Athymic Nude Mice

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ABSTRACT

The continuous human medulloblastoma cell line TE-671 was grown as s.c. and intracranial xenografts in athymic nude mice. Tumor-bearing animals were treated with chemotherapeutic agents at the 10% lethal dose; s.c. xenografts were sensitive to melphalan, 1-(2-chloroethyl)-3-(2,6-dioxo-1-piperidyl)-1-nitrosourea, and 5-azacytidine. No consistent response could be demonstrated to 9-β-o-arabinoferanosyl-2-fluoroadenosine 5'-monophosphate, and no response to methyglyoxal bisguanylhydrazone, N-trifluoroacetyl adriamycin-14-valerate, or to 1-β-o-arabinofuranoslyctosine was observed. Melphalan produced a significant (P = <0.007) increase in the median survival of mice bearing intracranial xenografts, whereas no response was seen to 1-(2-chloroethyl)-3-(2,6-dioxo-1-piperidyl)-1-nitrosourea or 5-azacytidine. This model will allow analysis of the chemotherapeutic profile of human medulloblastoma, and provides a means to differentiate cellular sensitivity and resistance from drug access to the intracranial site.

INTRODUCTION

Conventional therapy for children with medulloblastoma consists of surgical resection followed by whole neuraxis irradiation (1). These modalities will only result in a 40–60% 5-year survival (1), with salvage following relapse an unlikely event. Chemotherapeutic intervention, while transiently effective in treating recurrent disease (2–6) produces an unclear benefit when used in an adjuvant setting (7, 8).

The difficulty in designing effective chemotherapy for medulloblastoma is in part a consequence of the inability to differentiate cellular sensitivity and resistance from drug delivery to the tumor site. The notion of an impenetrable blood-brain barrier has been used to explain the failure of chemotherapy in the treatment of medulloblastoma (and glioma). The unique anatomy of the brain demonstrating tight junctions which circumscribe blood capillaries and are devoid of fenestrae is considered responsible for the limitation of exchange of most water-soluble agents between blood and brain (9, 10). The treatment of intracranial L1210 cells illustrated this by demonstrating minimal efficacy of several water soluble agents (11, 12), whereas the lipophilic nitrosoureas demonstrated marked efficacy (13). Agents in vogue for the treatment of human medulloblastoma cell line TE-671 growing s.c. and intracranially in athymic mice to 7 chemotherapeutic agents, allowing differentiation of cellular sensitivity from drug access to the tumor site.

We have previously described the establishment, characterization, and utilization of our model to study human medulloblastoma (16–18). We now report the therapeutic sensitivity of the human medulloblastoma cell line TE-671 growing s.c. and intracranially in athymic mice to 7 chemotherapeutic agents, allowing differentiation of cellular sensitivity from drug access to the tumor site. Agents studied included melphalan (NSC 8806), PCNU, 5-azacytidine (NSC 102816), fludarabine (9-β-o-arabinoferanosyl-2-fluoroadenosine 5'-monophosphate; NSC 312887), 1-β-o-arabinofuranoslyctosine (NSC 63878), MGBG, and AD-32. Melphalan, PCNU, and 5-azacytidine were the most effective agents in the therapy of mice bearing s.c. xenografts, with only melphalan producing a significant increase in the median survival of animals bearing intracranial xenografts.

MATERIALS AND METHODS

Animals. Male or female athymic BALB/c mice (nu/nu genotype, 6 weeks or older) were used for all experiments. The original stock was supplied by Grand Island Biological Co. (Grand Island, NY), but independent breeding at Duke (heterozygote nu/+ females paired with homozygote nu/nu males) yields 75 to 100 newborn mice per week. Animals were maintained as described previously (19).

Tumor Line. The human medulloblastoma cell line TE-671 established from a cerebellar tumor (20) was grown s.c. and intracranially in athymic nude mice as described previously (17).

Tumor (s.c.) Transplantation. Tumor-bearing animals were killed by cervical dislocation and tumors were removed in a laminar flow hood. Tumor fragments were passed through a bilafered 20 mesh screen in a tissue press. The tissue was passed through consecutively smaller gauge needles (16-, 19-, and 20-gauge) and the tumor homogenate was placed into a 500-μl Hamilton syringe (Hamilton Co., Reno, NV). Thirty μl of tumor homogenate were inoculated with a 19-gauge needle into the right flank of recipient mice.

Tumor (s.c.) Measurement. Tumors s.c. were measured every 3 to 4 days with vernier calipers (Scientific Products, McGaw Park, IL) until the volume exceeded 2000 mm3. Width and length in mm were measured, and volume was calculated by the formula (21):

\[
\text{volume} = \frac{\text{width} \times \text{length}}{2}
\]
Intracranial Tumor Transplantation. Tumor fragments, after removal from a donor animal, were forced through a 60 mesh tissue cytosieve, allowing passage through a 27-gauge needle. Tumor was washed through the cytosieve with minimal essential medium, which was subsequently removed by centrifugation. The resulting homogeneous tumor suspension was mixed with an equal volume of 7% methyl cellulose, and the mixture was loaded into a 250-μl Hamilton syringe. Animals were given injections of 5 μl of tumor suspension into the right cerebral hemisphere with a 27-gauge needle equipped with a sleeve allowing 4.5-mm penetration. Animals were checked daily for neurological symptoms and death. At the time of death, the head was removed and decalcified, and sections for morphological analysis were prepared.

Drug Toxicity. The lethal toxicity of individual drugs was assessed by probit analysis (22). A minimum of 4 doses with 10 animals/dose was used to calculate the 10% lethal dose of each drug. The dose used in the experiments was 100% of the calculated 10% lethal dose. These doses were: melphalan, 71 mg/m² for one dose; PCNU, 81 mg/m² for one dose; 5-azacytidine, 39 mg/m² daily for 5 doses; fludarabine, 821 mg/m² daily for 5 doses; 1-β-D-arabinofuranosylcytosine, 830 mg/m² daily for 5 doses; AD-32 (a lipophilic anthracycline) 297 mg/m² daily for 4 doses; and MGBG, 264 mg/m² daily for 5 doses. The m² of the animals was calculated from a conversion table (23). All drugs were administered i.p. in a volume of 90 ml/m² except fludarabine, which was delivered in a volume of 180 ml/m². Melphalan was administered in 17% dimethyl sulfoxide, PCNU in 5.7% dimethyl sulfoxide, 5-azacytidine, fludarabine, 1-β-D-arabinofuranosylcytosine, and MGBG in 0.9% NaCl solution, and AD-32 in 3.6% absolute ethanol:polyethoxylated castor oil. All drugs were generously provided by the Developmental Therapeutics Program, National Cancer Institute.

Tumor (s.c.) Therapy. Groups of 8 to 10 randomly assigned mice were treated i.p. with chemotherapeutic compounds according to the previously described dosages and schedule when the median tumor volume exceeded 200 mm³. One group of matching animals served as a control and received the drug vehicle.

Response was assessed by 3 methods. Mean treated versus control tumor volume (T/C) was measured 7 to 11 days after completion of therapy. The difference in days between the median of tumors of individually treated animals and the median of tumors of control animals to reach a volume of 5 times the initial treatment volume (T − C) was determined. Tumors smaller than 2000 mm³ did not have necrotic centers and did not require changes in measurement technique. Statistical significance for these 2 measurements was determined by the Wilcoxon rank sum test. Percentage of tumor regressions of treated animals was compared to the tumor regressions of control animals. Tumor regression was defined by a smaller volume on 2 consecutive measurements to the mixture was loaded into a 250-μl Hamilton syringe. Animals were given injections of 5 μl of tumor suspension into the right cerebral hemisphere with a 27-gauge needle equipped with a sleeve allowing 4.5-mm penetration. Animals were checked daily for neurological symptoms and death. At the time of death, the head was removed and decalcified, and sections for morphological analysis were prepared.

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Intracranial Tumor Therapy. Groups of 10 randomly assigned mice were treated i.p. with chemotherapeutic compounds according to the previously described dosages and schedule on Day 12 after tumor implantation. One group of 10 animals served as a control and received the drug vehicle. Assessment of response was the comparison of median survival time and long-term survivors (>60 days) between treated and control groups. Statistical significance was assessed by the Wilcoxon rank sum test for median survival and by the Fisher exact test for long-term survivors.

RESULTS

Drug Toxicity. Seven deaths in 189 tumor-bearing treated animals were attributed to drug toxicity with the following distribution: melphalan, 1 of 40; PCNU, 1 of 40; 5-azacytidine, 2 of 40; fludarabine, 2 of 19; 1-β-D-arabinofuranosylcytosine, 0 of 20; AD-32, 1 of 20; and MGBG, 0 of 10. Mean nadir weight loss was: melphalan, 17.7%; PCNU, 18.8%; 5-azacytidine, 12.0%; fludarabine, 8.1%; 1-β-D-arabinofuranosylcytosine, 8.1%; AD-32, 2.4%; and MGBG, 7.8%.

Tumors s.c. The response to chemotherapy is illustrated in Charts 1 and 2 and summarized in Table 1. There was a statistically significant response to PCNU and 5-azacytidine, but no response noted to 1-β-D-arabinofuranosylcytosine, AD-32, or MGBG. Fludarabine produced a statistically significant response in only 1 of 2 trials. Melphalan produced a marked effect with growth delays of 20.9 days (Trial 1) and 19.5 days (Trial 2) in duplicate trials, as well as a 100% incidence of tumor regressions. No cures or tumor regressions below the initial tumor treatment volume resulted from the administration of any of the drugs. No control animals demonstrated any tumor regressions.

Intracranial Tumors. The agents active against s.c. tumors were subsequently tested against intracranial tumor-bearing animals. The median survival of the control animals was 28 (range, 19–34), 35 (range, 24–40), 36 (range, 25–59) and 38 days (range,
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Table 1

Chemotherapeutic response of TE-671 growing s.c. in athymic mice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treated/control (days)</th>
<th>Treated/control (%)</th>
<th>Regressions</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan</td>
<td>20.9 0.0007 22.9</td>
<td>&lt;0.001</td>
<td>10/10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCNU</td>
<td>19.5 0.001 39.5</td>
<td>0.002</td>
<td>10/10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5-Azacytidine</td>
<td>6.2 0.007 47.9</td>
<td>0.001</td>
<td>0/10</td>
<td>NS</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>5.5 0.001 41.5</td>
<td>&lt;0.001</td>
<td>0/10</td>
<td>NS</td>
</tr>
<tr>
<td>1-β-D-Arabinofuranosylcytosine</td>
<td>6.3 0.006 39.5</td>
<td>NS</td>
<td>0/10</td>
<td>NS</td>
</tr>
<tr>
<td>AD-32</td>
<td>2.2 NS 65.7</td>
<td>NS</td>
<td>0/10</td>
<td>NS</td>
</tr>
<tr>
<td>MGBG</td>
<td>2.2 NS 60.1</td>
<td>NS</td>
<td>0/10</td>
<td>NS</td>
</tr>
<tr>
<td>1/3-D-Arabinofuranosylcytosine</td>
<td>2.1 NS 89.8</td>
<td>NS</td>
<td>0/10</td>
<td>NS</td>
</tr>
<tr>
<td>AD-32</td>
<td>0.7 NS 96.7</td>
<td>NS</td>
<td>0/10</td>
<td>NS</td>
</tr>
<tr>
<td>1/3-D-Arabinofuranosylcytosine</td>
<td>2.1 NS 49.0</td>
<td>NS</td>
<td>0/10</td>
<td>NS</td>
</tr>
<tr>
<td>AD-32</td>
<td>1.0 NS 89.4</td>
<td>NS</td>
<td>0/10</td>
<td>NS</td>
</tr>
<tr>
<td>MGBG</td>
<td>0.2 NS 91.6</td>
<td>NS</td>
<td>0/10</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Treated - control, difference in days between the median of tumors of individually treated animals and the median of tumors of control animals to reach a volume of 5 times the initial treatment volume.

† Treated/control, mean treated versus control tumor measured 7 to 11 days after completion of therapy.

NS, not significant (P > 0.01).

29–52) in the 4 intracranial experiments (Chart 3; Table 2). There was no significant increase in survival in response to 5-azacytidine with a median survival of 32.5 days (range, 27–63) and 37 days (range, 36–46 days), or to PCNU with a median survival of 39 days (range, 34–41) and 45 days (range, 36–54). Melphalan produced a marked (P = 0.007 and 0.001) increase in survival with a median survival of 59 days (range, 24–75+) and 54 days (38–75+). Three long-term survivors were seen in response to melphalan and represent apparent cures. All other animals, control and treated, with the exception of 2 early toxic deaths (Chart 3), died with extensive intracranial tumors.

DISCUSSION

Primary brain tumors, the most frequent solid tumors in children, are second only to leukemia as a cause of childhood cancer (24). Advances in chemotherapy and combined modality regimens have dramatically increased both survival and cures in children with many forms of cancer during the last two decades. These successes have not been translated, however, into effective therapy for children with brain tumors, particularly those with medulloblastoma. The resistance of this tumor to current therapy is multifactorial, and there is a great need to study the cellular sensitivity and resistance of this tumor, as well as the ability of active agents to reach the tumor site.

We have previously demonstrated the ability of our model of human medulloblastoma (16–18) to quantitate the therapeutic response to several chemotherapeutic agents and radiation. The present studies extend this work, utilizing athymic mice bearing...
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Table 2
Chemotherapeutic response of TE-671 growing intracranially in athymic mice

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Drug</th>
<th>Median survival (days)</th>
<th>P</th>
<th>Long-term survivors (&gt;60 days)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>28 (19-34)</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>5-Azacytidine</td>
<td>32.5 (27-63)</td>
<td>NS</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>Control</td>
<td>35 (24-40)</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>5-Azacytidine</td>
<td>37 (36-46)</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>Control</td>
<td>36 (25-59)</td>
<td>0.001</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Melphalan</td>
<td>59 (24-75+)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>PCNU</td>
<td>39 (34-41)</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>4</td>
<td>Control</td>
<td>38 (29-52)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Melphalan</td>
<td>54 (38-72+)</td>
<td>0.001</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>PCNU</td>
<td>45 (38-54)</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, range.

** NS, not significant (P > 0.01).

s.c. or intracranial xenografts. This methodology allows assessment of the cellular sensitivity of the highly permeable s.c. xenografts (25), without concern that limitation of drug accessibility is influencing the therapeutic outcome. Agents found active against s.c. xenografts can be studied in the intracranial model, allowing assessment of drug access to this more restricted site (15). Three agents produced significant reproducible growth delays when tested in the s.c. model: melphalan, PCNU, and 5-azacytidine. No significant reproducible growth delays were noted for fludarabine, AD-32, MGBG, or 1-β-D-arabinofuranosylcytosine.

Melphalan is a cell cycle nonspecific water soluble (log P = -1.70) (26) classical alkylator with cytotoxic effects similar to those of the parent compound nitrogen mustard. Its spectrum of clinical activity includes breast cancer and multiple myeloma (27, 28), and more recently neuroblastoma (29, 30) and rhabdomyosarcoma (31). Our studies demonstrated the marked efficacy of melphalan in the therapy of the human medulloblastoma cell line TE-671 growing s.c. and intracranially, indicating both cellular sensitivity and at least partial access to the intracranial tumors for this agent. No clinical trials, to our knowledge, have explored the use of melphalan in patients with medulloblastoma or other brain tumors, and these xenograft studies suggest a potential role for this alkylator. Previous studies in our laboratory (17) and in clinical trials (5, 32) have shown a role for another classical alkylator, cyclophosphamide, in the therapy of medulloblastoma. Although a lipophilic agent achieves greater access to the intracranial site than does a nonlipophilic agent of equal molecular weight (33), the use of a minimally active lipophilic compound may be less effective than a markedly active compound with relatively less penetration. A rational approach to the therapy of central nervous system tumors should include identification of active compounds, with subsequent efforts designed to maximize access of these agents to the intracranial tumor site. These efforts could include techniques designed to reversibly increase blood-brain (tumor) permeability or chemical modification to increase the lipophilicity of the agent (9, 34–36).

5-Azacytidine and PCNU were active in the s.c. system, but with shorter growth delays than those produced by melphalan. They did not produce significant prolongations of survival in the intracranial experiments, although the wide range of survival in the control animals may mask the detection of small differences. Direct comparisons between s.c. and intracranial tumor models are difficult, in part due to the profound effects that small increases in intracranial tumor size may produce (37). Furthermore s.c. tumors demonstrate higher permeability and lower blood flow than do intracranial tumors (15, 25, 38). Nevertheless we anticipated a larger effect on survival from PCNU in the intracranial studies due to its relatively high degree of lipophilicity (log P = 0.37) and consequent increased delivery to the intracranial site.

The much greater cellular sensitivity to melphalan compared to PCNU demonstrated in the s.c. studies may explain the superior efficacy of melphalan in the intracranial studies. Furthermore the facilitated transport of melphalan seen in L5178Y cells, L1210 cells, and normal brain (39–41) (as compared to the passive diffusion of nitrosoureas) may be particularly important in achieving cytotoxic levels against intracranial TE-671. Clinical trials to date with PCNU in patients with recurrent medulloblastoma have been disappointing (42).

5-Azacytidine was active against avian sarcoma virus-induced primary brain tumors in rats (43) but produced negligible activity against intracranial TE-671. Further studies with other experimental models will need to be performed before 5-azacytidine is chosen for clinical trial in patients with brain tumors.

The major limitation of our studies is the reliance on a single cell line, TE-671, to generate the therapeutic profile. Until the recent establishment and characterization of our new human medulloblastoma cell line and transplantable xenograft D283 Med (44), TE-671 was the only continuous human medulloblastoma cell line available for study. It is unlikely that a single cell line or xenograft can represent the therapeutic profile of medulloblastoma in general (45–48), and further efforts to define the sensitivity of D283 Med are in progress. Ultimately a series of cell lines and xenografts may provide more complete and representative data, as illustrated by the work of Houghton et al. with human rhabdomyosarcoma (31, 49, 50). Nevertheless our present studies with TE-671 offer the best available approach to differentiate the cellular sensitivity of human medulloblastoma from drug access to the intracranial site and offer a precise experimental means to study specific chemotherapeutic intervention. Ultimately validation of this model will require the successful clinical use of agents selected in these studies.

REFERENCES


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