Review Article

Chemotherapy for malignant gliomas

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There continues to be an extensive effort to develop chemotherapeutic approaches to the treatment of malignant gliomas of the brain. In the past 5 years there have been literally hundreds of trials of new agents, combinations of old and new agents, and even new routes and approaches to the delivery of chemotherapy.

In this review, the literature has been studied and the individual reports analyzed to evaluate the impact of the new findings on clinical management of the patient with malignant glioma of the brain. The major areas of progress include the addition of new drugs with varying modes of action, the use of combinations of drugs in a synergistic fashion, and the development of new routes of drug delivery. None of the advances has brought about the revolution in clinical care that is so eagerly sought, but clearly the amount of new knowledge gained by these studies helps in understanding how to use chemotherapy more effectively. Furthermore, the remarkable degree of interest and involvement in the use of chemotherapy promises that an even greater number of patients with malignant gliomas will be considered for vigorous and enthusiastic clinical management programs even if chemotherapy itself is not the key modality in the treatment of a specific patient.

KEY WORDS - brain neoplasm - chemotherapy - BCNU - glioma

In the past decade, there has been increased interest in the role of chemotherapy in the treatment of malignant tumors of the brain and spinal cord. The major focus of the effort to develop chemotherapy programs has been on the malignant gliomas. Although some series of cases have been reported involving other types of central nervous system neoplasia, the series are too small and the data not subjected to careful controls. Thus, the emphasis in this review will be on the role of chemotherapy as an adjunct in the treatment of malignant gliomas of the brain.

Chemotherapy was extensively summarized in 1980, in the review article of Edwards, et al. This present paper reviews information that has become available since that review on the utilization of chemotherapy for the treatment of malignant gliomas, and indicates a considerable increase in interest in the treatment of this disease. A large number of chemotherapeutic agents are currently being evaluated. In the tables and text that follow abbreviations are used for these drugs, but a Definitions of Abbreviations table is provided. While each of the drugs will be discussed, the primary data concerning each of the studies cited will be found in the tables. In the vast majority of series, all patients have undergone a surgical procedure which has reduced the tumor burden and also provided tissue for more precise diagnosis. Radiotherapy was given in the range of 5500 to 6000 rads delivered in 30 to 35 fractions, with five treatments being given per week. In the standardized Phase III study of the Brain Tumor Study Group, the radiation dose used was 6000 rads. Radiation doses above 6000 rads present an increased risk of radionecrosis; lower doses are less likely to be effective.

Two major settings are commonly employed for the delivery of chemotherapy. The first involves administration of drugs immediately after surgery as an adjuvant along with radiotherapy or immediately after irradiation. Reports of series such as these are frequently presented as controlled clinical trials on the treatment of malignant gliomas after surgery (Table 1). The second setting includes trials in cases of recurrent tumor;
TABLE 1
Controlled clinical trials in malignant gliomas after surgery involving use of nitrosoureas*

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Authors &amp; Yr</th>
<th>Tumor Type, % Incidence</th>
<th>No. of Cases†</th>
<th>Treatment</th>
<th>Results‡</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Garrett, et al., 1978</td>
<td>glioma 50% astro 29% GBM 18% other 3%</td>
<td>69/74</td>
<td>RT: 4500 rads 4 wks RT + CCNU</td>
<td>MST 35</td>
<td>marked age bias; no significant difference between treatments dose of RT comparatively low</td>
</tr>
<tr>
<td>2</td>
<td>Eagan, et al., 1979</td>
<td>GBM 71% MG 29%</td>
<td>42/43</td>
<td>RT: 5000 rads DAG RT + CCNU</td>
<td>MST 35</td>
<td>after failure, patients given Benu</td>
</tr>
<tr>
<td>3</td>
<td>Levin, et al., 1979</td>
<td>GBM 62% other 38%</td>
<td>99</td>
<td>RT: 6000 rads + BCNU RT + HU + BCNU</td>
<td>MTP 31 (GBM), MTP 73 (non-GBM) MTP 42 (GBM), MTP 50 (non-GBM)</td>
<td>HU-enhanced RT in GBM group only (p = 0.04); MST low by comparison</td>
</tr>
<tr>
<td>4</td>
<td>Solero, et al., 1979</td>
<td>GBM</td>
<td>102</td>
<td>RT: 5000 rads RT + BCNU RT + CCNU</td>
<td>MTP 38, MTP 45</td>
<td>CCNU better than RT alone (p = 0.05); Benu: p = not significant</td>
</tr>
<tr>
<td>5</td>
<td>Walker, et al., 1978</td>
<td>GBM 84% MG 11% other 5%</td>
<td>358/467</td>
<td>MeCCNU alone RT: 6000 rads RT + MeCCNU RT + BCNU</td>
<td>MTP 24, 10% 18-mo Sv MTP 32, 17% 18-mo Sv MTP 51, 27% 18-mo Sv</td>
<td>RT, RT + MeCCNU, &amp; RT + Benu all significantly better than MeCCNU alone (p = 0.01, 0.006, 0.001); reconfirms prior study</td>
</tr>
<tr>
<td>6</td>
<td>Seiler, et al., 1980</td>
<td>GBM</td>
<td>32/39</td>
<td>RT: 6000–7000 rads RT + VM-26 + CCNU</td>
<td>MTP 40</td>
<td>not significant (p = 0.3); small sample size</td>
</tr>
<tr>
<td>7</td>
<td>Cianfriglia, et al., 1980</td>
<td>GBM</td>
<td>103</td>
<td>RT: 5000 rads CCNU RT + CCNU</td>
<td>MTP 34 MTP 36</td>
<td>difference not significant</td>
</tr>
<tr>
<td>8</td>
<td>Levin, et al., 1980</td>
<td>GBM</td>
<td>74/82</td>
<td>RT: 6000 rads &amp; HU then randomized to BCNU CCNU + PCZ + VCR</td>
<td>MTP 29, MTP 45</td>
<td>combination therapy not advantageous (p = 0.82)</td>
</tr>
<tr>
<td>9</td>
<td>Kristiansen, et al., 1981</td>
<td>astro III astro IV</td>
<td>118</td>
<td>surgery only RT: 4500 rads RT + bleomycin</td>
<td>MTP 22</td>
<td>contains surgery group only</td>
</tr>
<tr>
<td>11</td>
<td>Nelson, et al., 1983</td>
<td>GBM AnaA</td>
<td>202/245</td>
<td>RT + BCNU RT + miso then BCNU</td>
<td>MTP 32, MTP 54 MTP 31, MTP 46</td>
<td>weighted RT for days of mison 11% peripheral neuropathy</td>
</tr>
<tr>
<td>12</td>
<td>Chang, et al., 1984</td>
<td>MG</td>
<td>535/626</td>
<td>RT + booster 6000 + 1000 rads RT + booster 1000 rads RT + BCNU RT + MeCCNU &amp; DTIC</td>
<td>MTP 40, 9% 18-mo Sv MTP 38, 18% 18-mo Sv MTP 49, 28% 18-mo Sv MTP 43, 23% 18-mo Sv</td>
<td>booster RT toned down</td>
</tr>
<tr>
<td>14</td>
<td>Payne, et al., 1982</td>
<td>MG</td>
<td>157/168</td>
<td>RT: 200 rads/day in 25 Fx + CCNU &amp; HU RT: 200 rads 4 x 1 day in 40 Fx + CCNU &amp; HU</td>
<td>MTP 48, 22% 2-yr Sv MTP 48, 16% 2-yr Sv</td>
<td>relative biological effect of RT thought to be equivalent hyperfraction RT no advantage</td>
</tr>
<tr>
<td>15</td>
<td>Jellinger, et al., 1983</td>
<td>astro III &amp; astro IV</td>
<td>226</td>
<td>supportive care RT: 4000–6000 rads COMB (CCNU, PCZ, VCR, &amp; MTX) RT &amp; COMB</td>
<td>MTP 19, MTP 28 MTP 30, MTP 51 MTP 50, MTP 53</td>
<td>historic controlled study RT alone (p = 0.05); toxicity in multimodality therapy</td>
</tr>
<tr>
<td>16</td>
<td>Afra, et al., 1983</td>
<td>GBM MG</td>
<td>84/91</td>
<td>RT: 5000–6000 rads RT + DBD &amp; DBD alone RT + DBD + CCNU &amp; DBD</td>
<td>MTP 40 MTP 57 MTP 60</td>
<td>DBD during &amp; after RT adds significantly to survival (p = 0.002); CCNU did not add further improvement</td>
</tr>
</tbody>
</table>

* Abbreviations: astro = astrocytoma (grade in roman numerals); GBM = glioblastoma multiforme; RT = conventional radiotherapy (unusual doses only are noted; Fx = fractions; ret = radiation absorbed dose); MG = malignant glioma; AnaA = anaplastic astrocytoma. For drugs see Definitions of Abbreviations table; COMB = combination drug regimen.

† Number of cases evaluated/number entered in the study.

‡ MST = median survival time (in weeks); MTP = median time to progression (in weeks); % Sv = percent survival rate; CR = complete remission; PR = partial remission.
Chemotherapy for malignant gliomas

### TABLE 1 (continued)*

<table>
<thead>
<tr>
<th>Study No</th>
<th>Authors &amp; Yr</th>
<th>Tumor Type, % Incidence</th>
<th>No. of Cases†</th>
<th>Treatment</th>
<th>Results‡</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Green, et al., 1983</td>
<td>MG 527/609</td>
<td>RT</td>
<td>RT: 6000 rads + mepred</td>
<td>MST 40</td>
<td>BCNU &amp; PCZ additive to RT (p = 0.009 &amp; 0.003); mepred has no effect on survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT + BCNU &amp; mepred</td>
<td>MST 41</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT + PCZ</td>
<td>MST 47</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT + BCNU</td>
<td>MST 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Ushio, et al., 1984</td>
<td>GBM AnaA 60</td>
<td>RT only</td>
<td>MST 31</td>
<td></td>
<td>bleomycin does not add to RT while MeCCNU does (p = 0.05); combination no more effective than MeCCNU alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT + bleomycin</td>
<td>MST 42.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT + MeCCNU</td>
<td>MST 56</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT + bleomycin+MeCCNU</td>
<td>MST 73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Green, et al., 1984</td>
<td>GBM 84% AnaA 14%</td>
<td>557/603</td>
<td>RT: 6000 rads + BCNU</td>
<td>MST 45, 18% 18-mo Sv</td>
<td>RT equivalent to 1700 rads either Fx RT nor radiosensitizers improved survival advantage of BCNU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT + 2 Fx/day +BCNU</td>
<td>MST 48, 24% 18-mo Sv</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT &amp; miso + BCNU</td>
<td>MST 40, 18% 18-mo Sv</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT + streptozocin</td>
<td>MST 42, 24% 18-mo Sv</td>
<td></td>
<td>streptozocin as effective as BCNU</td>
</tr>
<tr>
<td>20</td>
<td>Green, et al., 1985</td>
<td>GBM 46% MG 36% other 17%</td>
<td>139/152</td>
<td>AZQ</td>
<td>MST 39</td>
<td>controlled Phase II study: all patients had prior RT; PCNU significantly better than AZQ (p = 0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCNU</td>
<td>MST 67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Abbreviations: astro = astrocytoma (grade in roman numerals); GBM = glioblastoma multiforme; RT = conventional radiotherapy (unusual doses only are noted; Fx = fractions; ret = radiation absorbed dose); MG = malignant glioma; AnaA = anaplastic astrocytoma. For drugs see Definitions of Abbreviations table; COMB = combination drug regimen.

† Number of cases evaluated/number entered in the study.

‡ MST = median survival time (in weeks); MTP = median time to progression (in weeks); % Sv = percent survival rate; CR = complete remission; PR = partial remission.

the drug is then given at a time when the patient shows clinical evidence of tumor regrowth and frequently after the employment of surgery, radiotherapy, and in some cases after prior chemotherapy. These studies are single-drug trials carried out in patients with recurrent malignant gliomas (Table 2). In addition, a series of multiple chemotherapeutic treatment studies have been published (Table 3). Finally, the radiation-sensitizing drugs will be considered as another type of chemotherapeutic agent (Table 4).

In order to update the information relevant to the current status of brain-tumor chemotherapy, a detailed review of the last 5 years’ results has been prepared. In this review, the individual drugs are considered separately and then the overall results are summarized. It is important to note that in the past 5 years no remarkably effective new agents have been discovered; there has been no “breakthrough” in the development of a curative regimen. What has been accomplished is a far greater understanding of the variables that influence the results of clinical trials. The influence of such factors as age, neurological status, and stage of diagnosis has been carefully evaluated. The role of corticosteroids in patient survival has been considered and put in proper perspective. The format of the Phase III clinical trial is now fully established as it relates to the determination of efficacy of new agents.

**Theoretical Concepts of Chemotherapy in Brain Tumors**

Before considering the specific chemotherapy agents and their results, it is important to discuss certain critical variables that influence the success or failure of chemotherapy for brain tumor. The first group of variables includes clinical factors such as age, neurological status, and stage of the disease at diagnosis. It has...
become clear that older patients have a poor prognosis and are less likely to respond to chemotherapy. The neurological status of the patient prior to embarking on chemotherapy is particularly crucial. It is unrealistic to expect that a patient who is in a poor neurological condition will respond well to chemotherapy. The stage of the disease at diagnosis is of obvious importance. A patient with a bihemispheric lesion is clearly less likely to have a good result with chemotherapy. The location of the lesion influences the direct benefit of ease of surgical resectability and it also has an indirect effect: a lesion that is difficult to debulk offers less time for chemotherapy to be effective. These clinical variables have influenced the way in which patients are now entered into clinical trials.

One concept that is particularly relevant to achieving success in chemotherapy of malignant glioma has been the appreciation that if an agent results in positive responses in only a relatively small percentage of the patient population and if that response is only of modest proportions, then that agent used alone will not prove effective in a proper Phase III trial. This concept makes clear that a combination of agents either in sequence or together will be required to achieve a shift in the overall response rates in a patient population, and then offer an effective result in a Phase III trial. This greater degree of responsiveness can be achieved by designing treatment programs with a rational combination of synergistic agents or by preselecting the agent that would be most effective for a specific patient. This type of insight is now being gained through studies at the cellular level.74,75,92 There are presently two types of assays under investigation for use in predicting individual response. The first of these assays, the so-called

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**TABLE 2**

*Phase II single-drug trials in recurrent malignant gliomas involving non-nitrosourea chemotherapy*

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Authors &amp; Yr</th>
<th>Tumor Type</th>
<th>No. of Cases†</th>
<th>Treatment</th>
<th>Results‡</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Garbino &amp; Gorgon-Firing, 1984</td>
<td>GBM</td>
<td>19</td>
<td>VM-26</td>
<td>MST 90</td>
<td>historic control: MST 58 (p = 0.05); &quot;useful;&quot; mild toxicity</td>
</tr>
<tr>
<td>2</td>
<td>Feun, et al., 1984</td>
<td>primary BT</td>
<td>25/41</td>
<td>AZQ</td>
<td>PR 24%, MTP 54</td>
<td>“further studies indicated;” delayed progressive thrombocytopenia</td>
</tr>
<tr>
<td>3</td>
<td>Stewart, et al., 1983</td>
<td>astro, recurrent</td>
<td>31</td>
<td>CDDP</td>
<td>CR 6%, PR 6%, S 6%</td>
<td>“further studies planned;” mild GI toxicity</td>
</tr>
<tr>
<td>4</td>
<td>Andersen, et al., 1984</td>
<td>GBM</td>
<td>21</td>
<td>prednimustine</td>
<td>MST 38</td>
<td>“limited effectiveness;” hematological toxicity</td>
</tr>
<tr>
<td>5</td>
<td>Djerassi, et al., 1983</td>
<td>astro III &amp; IV (ped + adult)</td>
<td>10</td>
<td>very high-dose MTX with atrasorune rescue</td>
<td>PR 80%, MST 56</td>
<td>seizures in 3 patients hepatic &amp; septic complications</td>
</tr>
<tr>
<td>6</td>
<td>Pazdur, et al., 1984</td>
<td>MG recurrent</td>
<td>14</td>
<td>AZQ</td>
<td>R 28%</td>
<td>“active agent;” “requires further investigation”</td>
</tr>
<tr>
<td>7</td>
<td>Carapella, et al., 1984</td>
<td>MG</td>
<td>16</td>
<td>lonidamine</td>
<td>R 25%</td>
<td>indications of activity</td>
</tr>
<tr>
<td>8</td>
<td>Decker &amp; Al-Sarraf, 1983</td>
<td>astro, recurrent</td>
<td>AZQ</td>
<td>R 25%, P 63%</td>
<td>indications of “improvement”</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Curt, et al., 1982</td>
<td>astro III &amp; IV, recurrent</td>
<td>AZQ</td>
<td>R 26%, S 26%, P 39%</td>
<td>active in end-stage glioma</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Feun, et al., 1983</td>
<td>primary BT, recurrent</td>
<td>22/30</td>
<td>RT &amp; CDDP + CDDP</td>
<td>MTP 24, MST 53</td>
<td>tolerable &amp; feasible, ototoxicity encountered</td>
</tr>
<tr>
<td>11</td>
<td>Feun, et al., 1985</td>
<td>primary BT, recurrent</td>
<td>15/16</td>
<td>mitoquazone</td>
<td>S 27%</td>
<td>no response seen</td>
</tr>
<tr>
<td>12</td>
<td>Schold, et al., 1984</td>
<td>primary BT, recurrent</td>
<td>16</td>
<td>AZQ</td>
<td>CR + PR 44%</td>
<td>19% unequivocal response; “AZQ is effective in some patients”</td>
</tr>
<tr>
<td>14</td>
<td>Eagan, et al., 1983</td>
<td>astro, recurrent</td>
<td>DAG + VP-16</td>
<td>R 33%</td>
<td>“an alternative treatment”</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Stewart, et al., 1984</td>
<td>GBM</td>
<td>21</td>
<td>CDDP followed by AraC</td>
<td>CR 8%, S 24%, PR 40%, P 7%</td>
<td>“no major potentiation of CDDP;” dose-limiting GI toxicity; some neurotoxicity</td>
</tr>
<tr>
<td>16</td>
<td>Eagan, et al., 1983</td>
<td>primary BT</td>
<td>29</td>
<td>AZQ</td>
<td>R 17%</td>
<td>“worthy of further study;” myelosuppression was only toxicity</td>
</tr>
</tbody>
</table>

* Abbreviations: GBM = glioblastoma multiforme; BT = brain tumor; astro = astrocytoma (grade in roman numerals); MG = malignant glioma; GI = gastrointestinal; RT = radiation therapy. For drugs see Definitions of Abbreviations table.
† Number of cases evaluated/number entered in study.
‡ MST = median survival time (in weeks); PR = partial remission; S = stabilized disease; MTP = median time to progression (in weeks); P = progressive disease; R = response to treatment; CR = complete remission.
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“clonogenic” or “stem-cell” assay, provides very valid survival data for measuring response. Its major limitation has been the relatively low plating efficiencies and the difficult task of establishing growth in a moderate percentage of patients. A second approach involves the monolayer technique in which cultures are established from individual patients and then a variety of direct and indirect cell counting techniques are used to determine responsiveness. The technique is efficient and works in the vast majority of patients, but it lacks the cell-survival study type capabilities and also raises a question of whether all of the cells present in the cultures are relevant tumor cells. It is of great interest, however, that investigators using both sets of techniques have arrived at remarkably similar conclusions in regard to the nitrosoureas. In both techniques, a nonresponder to BCNU in vitro was virtually 100% unlikely to respond clinically. Conversely, an in vitro responder to BCNU had about a 67% chance of responding clinically.

Among the biological variables that influence the efficacy of chemotherapy are: cell-cycle kinetics, the blood-brain barrier, the microenvironment, heterogeneity, and development of drug resistance.

Cell-Cycle Kinetics

The kinetics of brain tumors have been elucidated only partially. Of particular note is the fact that normal glia do not replicate in adults or older children. Cerebral vasculature and some of other supporting elements do replicate, but at comparatively slow turnover rates. Brain tumors, on the other hand, have some cells at least that are by their very nature actively going through the cell cycle. Low-grade astrocytomas have been demonstrated to have extremely few cells undergoing active proliferation, whereas high-grade gliomas appear to have a greater but nevertheless still small percentage of cells actively replicating. A very wide distribution of kinetic parameters has been found. Thus, the labeling index is on the order of 0% to 10%, the S phase is approximately 7 to 10 hours, and the growth fraction is 0.30 and extremely variable. Birth rate of tumor cells is between 0.5%/hr and 1.7%/hr. The estimated turnover time is therefore between 3 and 7 days. If a computed cell loss factor of 85% is included, the more common clinically accepted doubling time of 6 to 8 weeks can be obtained. This has had clear implications for chemotherapeutic considerations.

Blood-Brain Barrier

The brain is traditionally thought to be protected by the blood-brain barrier. This pharmacological-physiological entity has been located in the endothelium of the majority of cerebral capillaries. Pentalaminar fusions of endothelial cell membranes from relatively continuous zones obstruct the passage of substances having a molecular weight (MW) greater than 200 daltons. Drugs that have high lipid-solubility and thus are capable of crossing cell membranes generally are considered to pass through the blood-brain barrier. Drugs must either be non-ionized or have readily reversible ionization equations in order to pass through the blood-brain barrier. Although the blood-brain barrier has traditionally been cited as one of the more important factors in the choice of chemotherapeutic agents for the treatment of malignant brain tumor, it is both pharmacologically and histopathologically not intact in the midst of the tumor. Capillary endothelial cells within tumor tissue have been shown to have abnormal or discontinuous tight junctions. Computerized tomography (CT) and radionuclide scanning, both of which are dependent upon the entrance into the area of tumor of large protein molecules that are isotope-labeled, are able to attain contrast differential between tumor and normal brain by virtue of leaks in the blood-brain barrier. Studies using an extracellular peroxidase marker and horseradish peroxidase (MW 44,000 daltons) in experimental tumor systems have demonstrated the discontinuous nature of the endothelium of brain-tumor vasculature. Thus, the role of the blood-brain barrier remains unclear in human brain-tumor therapy.

Microenvironment

Recently, the concept of a “microenvironment” of brain tumor has evolved and includes a number of factors. First, the brain is devoid of lymphatic drainage and, therefore, one of the major paths of egress of drugs (and metabolites) from extracellular fluid is not available. Such lack of drainage also has implications for formation of edema as well as drainage from the extracellular space into the cerebrospinal fluid. Second, histological study of most brain tumors frequently reveals areas of necrosis in the center of the tumor and an actively proliferating edge of tumor which is well vascularized and that intermingles with an outer zone, the so-called “brain adjacent to tumor.” Each of these areas is believed to have a different pharmacological environment, contains viable tumor cells (in very different proportions), and has different kinetic considerations for the cells in each of these zones.

Heterogeneity

There is increasing evidence of diverse biological heterogeneity in brain tumor. Studies evaluating the chromosomal content, number, and karyotyping of freshly explanted, serially transplanted brain tumors have provided evidence of marked changes in tumor characteristics within a matter of a few cell generations. Thus, what appears histopathologically as a single type of brain-tumor cell, may in fact have extremely different kinetic, immunological, and metabolic activity and response to therapy.

Development of Drug Resistance

With the wide variety of kinetics seen and the marked heterogeneity of cell populations, the therapist is faced with an extraordinarily difficult problem in that a
mostly radio- or chemo-therapeutically sensitive tumor today may be replaced by its resistant variant within a short time. The development of strains of bacteria resistant to antibiotic drugs is well known. However, it takes many generations before resistance becomes apparent, and this may well not be an analogous phenomenon. Recent data have shown the cell population most likely to be resistant (to BCNU, for example) are the diploid cells.\textsuperscript{74,85}

**Cytotoxic Agents**

*The Nitrosoureas*

The use of the chloroethyl nitrosoureas is the most prominent and frequent form of chemotherapy for brain tumor. These agents are also considered among the most effective. The nitrosoureas as a class are considered highly lipid-soluble and essentially non-ionized, and they readily cross the blood-brain barrier. They rapidly degrade once administered into two reactive compounds, one with carbamylation activity, and the other into an alkylating agent. Various modifications upon the basic nitrosourea moiety have led to differences in solubility, the amount of alkylation or carbamylation activity present, and the amount of toxicity encountered.

**Carmustine (BCNU).** Since the original report of the efficacy of BCNU by the Brain Tumor Study Group, a series of additional controlled trials have been carried out. Studies 4, 5, 8, 11, and 12 (Table 1)\textsuperscript{62,68,86,95} all utilized BCNU in a controlled setting. In these series, BCNU was always employed following surgery and radiation therapy, and median survival times improved to between 51 and 73 weeks when compared to control patients receiving irradiation alone (median survival time approximately 35 weeks). The two large cooperative group studies (Studies 5 and 8, Table 1)\textsuperscript{62,95} both demonstrated an increase in median survival time as well as in the proportion of 18-month survivors who were treated by BCNU. Several other studies either found BCNU to be equivocal in its efficacy or failed to demonstrate any value at all.\textsuperscript{86} Some of these studies had comparatively small numbers of patients and hence were prone to error, whereas others demonstrated the variability which has been so characteristic in the treatment and management of malignant glioma and which makes the need for controlled studies self-evident.

Ultra-high doses of BCNU, such as used in efforts to cause total bone marrow destruction with autologous bone marrow rescue, have been given in an attempt to increase the therapeutic index of BCNU (Study 2, Table 3);\textsuperscript{66} this therapy is discussed later in this review.
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Another attempt to potentiate the efficacy of BCNU utilized metronidazole (Study 6, Table 3). No potentiation was demonstrated and the treatment was not recommended. Therefore, BCNU remains the most effective single agent. It is limited in its efficacy by virtue of cumulative bone marrow toxicity, hepatic dysfunction, and increasing incidence of pulmonary fibrosis when a total cumulative dose of more than 1400 mg is exceeded.

A major question which as yet is not fully resolved relates to the timing of BCNU therapy. In most studies, radiotherapy is given and completed prior to the first dose of BCNU. There are both logistical and theoretical arguments which would favor giving the first dose of BCNU prior to radiotherapy. From a logistical standpoint, losing 6 weeks of time before giving the first dose of chemotherapy in a disease associated with such a short average survival time means that precious time is being lost. One of the reasons for the relative lack of efficacy with chemotherapy in glioblastomas is that the patient's demise all too often precedes the administration of enough of the dose of drug required to evaluate whether it has been effective. There is also evidence that radiotherapy produces vascular changes which limit the penetration of a drug into the tumor tissue; thus, giving the first dose of chemotherapy prior to radiotherapy may enhance its delivery. Presently, studies are under way to evaluate this timing sequence more carefully.

A further issue in regard to timing involves the overall sequence of therapy. It might be advantageous to deliver chemotherapy as a primary treatment modality and reserve irradiation as a secondary modality. To date, studies with BCNU have not supported this hypothesis and have suggested the synergy of irradiation and BCNU as being critical for success. Another issue related to timing is based on the observation that in many instances responses of recurrent tumors to BCNU are more dramatic than the response of the original neoplasm. Thus, reserving BCNU until recurrence and using only radiotherapy as the initial modality has been of some interest.

At present, the most commonly followed approach is to use irradiation and BCNU as a combined modality for initial treatment. One may prefer to initiate the first dose of chemotherapy prior to beginning radiotherapy. It is hoped that in the next few years more data will be available to facilitate a more scientific resolution of the issue of timing of BCNU therapy.

Lomustine (CCNU). Lomustine (CCNU) has been compared to several different agents including other nitrosoureas (Studies 1, 4, 6–8, and 13–15, Table 1)\(^{11,28,36-51,62}\). In the majority of these trials, CCNU was found to be relatively ineffective when utilized alone or in combination with other drugs or when compared to radiotherapy alone. Only one study (Study 7, Table 1)\(^{11}\) found CCNU to be superior to radiotherapy alone or to radiotherapy plus BCNU and that study had only 30 patients in each treatment group. Several studies have used CCNU in a wide variety of combination therapies, many of which utilized procarbazine and/or vincristine (Studies 8, 13, and 15, Table 1 and Study 8, Table 3)\(^{28,36,51,62}\). An investigation has also been carried out with CCNU and dibromodulcitol as well as CCNU and VM-26 (teniposide). The specific role of CCNU in the treatment of gliomas of the basal ganglia has been described. The majority of these studies have yielded equivocal results. In addition, the radiosensitizer metronidazole was tried as a potentiator for CCNU and showed minimal effects (Study 8, Table 3).\(^{36}\) The dose-limiting side effects of CCNU are myelosuppression with thrombocytopenia being the predominant finding, and there has been a report of significant nephrotoxicity following CCNU therapy for gliomas.

There are theoretical reasons why CCNU may be less effective than BCNU in the therapy of malignant gliomas. The inconsistencies of absorption through the gastrointestinal tract and the uncertainties of patient compliance with an orally administered agent limit the precise regulation of the blood levels achieved with given dosages. The pharmacokinetics of CCNU are also not as favorable as those of BCNU. Despite these concerns, there remains a role for CCNU in those patients in whom the use of BCNU is made difficult by such reasons as venous access or patient acceptance. In an experience now totalling over 400 patients (PL Kornblith, unpublished data), CCNU has been found to have approximately the same response rate as BCNU (30% to 40%), to be well tolerated, and to have far greater acceptance on the part of patients who find the logistics of receiving intravenous agents difficult.

In terms of fully established efficacy, only BCNU has withstood the scrutiny of a Phase III trial.

Semustine (MeCCNU). Methyl-CCNU was the third of the nitrosoureas to be brought into clinical usage and was selected for its extreme lipid-solubility, oral utilization, and preliminary evaluation in animal test systems. In a large cooperative study (Study 5, Table 1),\(^{93}\) MeCCNU was used following surgery with and without radiation therapy and was compared to radiation therapy alone, and radiation therapy and BCNU. Methyl-CCNU was not effective independently, nor did it enhance the effects of radiation therapy. The combination of MeCCNU and DTIC (imidazolcarboxamide) was found to be no more effective than BCNU; however, the combination was highly toxic and is not further recommended (Study 12, Table 1).\(^{10}\) Only one study (Study 18, Table 1)\(^{95}\) found that MeCCNU in combination with radiotherapy increased median survival times from 31 to 56 weeks. This study had only 60 patients randomized among four treatment arms and thus may have had insufficient numbers of patients. In summary, MeCCNU, although highly lipid-soluble and orally administered, has not been shown to have any advantage over other nitrosoureas and in a prospective controlled study,\(^{95}\) was not additive to radiation.
therapy. It is not presently used in clinical chemotherapy due to its toxicity and lack of therapeutic advantage.

**PCNU.** The nitrosourea PCNU was chosen as it was reasonably lipid- and water-soluble and thus might have improved distribution and penetration characteristics. A single controlled study (Study 20, Table 1) compared PCNU with aziridinylbenzoquinone (AZQ) in patients with recurrent brain tumors, and found PCNU to be significantly better than AZQ. On the basis of this, PCNU will be incorporated into future controlled studies. In an uncontrolled study (Study 3, Table 3), PCNU demonstrated a 44% partial response rate with additional stabilization of disease in 40% of patients. This drug is considered active in brain tumors and has been shown to have the usual cumulative delayed myelosuppression characteristics of the nitrosoureas. While PCNU has considerable activity, it has thus far not been shown to be either more effective or less toxic than BCNU.

**Streptozocin.** Streptozocin is composed of 1-methyl-1-nitrosourea combined with glucose, which has modified its pharmacological characteristics and toxicity. Streptozocin was evaluated in a controlled study (Study 19, Table 1) and found to be as effective as BCNU and radiotherapy. Because no additional advantage for streptozocin has been found, it has rarely been employed in other protocols.

**Other Nitrosoureas.** Hara, et al., reported using ACNU in very high doses with autologous bone marrow rescue (Study 4, Table 3). Their preliminary results were considered as showing efficacy and acceptability. Combination studies have evaluated ACNU with fluorouracil (5-FU) demonstrating a response rate of 36% (Study 9, Table 3). An additional variation of the nitrosourea molecule (MeCCNU) was also reported as having suggestive efficacy (Study 1, Table 3). While there are at least 10 variations on the nitrosourea moiety, the initial observation by the Brain Tumor Study Group of the primary efficacy of BCNU has stood the test of time and no other nitrosourea compound has been shown to be consistently better. The search for additional nitrosoureas with the faint hope that they may be more efficacious or less toxic is probably not worthwhile. Therefore, efforts have been turned toward evaluating methods of delivering higher concentrations of BCNU directly to the tumor bed, modifying toxicity, or utilizing other dose schedules. Radiotherapy and BCNU continue as the benchmark for comparison of all other treatments.

**Procarbazine**

Procarbazine (Matulan or Natulan) requires hepatic metabolic activation, has the activity of an alkylating agent, and has been studied both alone (Study 20, Table 1) and in combination with other drugs (Studies 8, 13, and 15, Table 1). In the single controlled randomized study where procarbazine was evaluated as an independent agent (Study 17, Table 1), the mean survival time of patients following radiation therapy was 47 weeks, which was comparable to a 50-week mean survival time for the reference control group receiving BCNU. Procarbazine was reasonably well tolerated although nausea and vomiting are not infrequent complications. Procarbazine has also been utilized in association with several drug combinations, most notably CCNU and vincristine (Studies 8, 13, and 15, Table 1). In most instances, the dosage of procarbazine is lower in order to avoid combined toxicity, and no advantage in combining it with CCNU was demonstrated. The study by Jellinger, et al., (Study 15, Table 1) represents a partially controlled investigation in that a comparable historic control group was selected for comparison with patients who received radiotherapy and CCNU, procarbazine, vincristine, and methotrexate (COMB). This combination resulted in statistically improved survival times versus those achieved with radiotherapy or supportive care alone; however, it was believed to be highly toxic and limited in duration of effectiveness.

**Hydroxyurea**

Hydroxyurea (Hydrea) has been used both as a radiosensitizer and for its own intrinsic antineoplastic activity (Studies 3, 8, and 14, Table 1). Only one study directly compared the addition of hydroxyurea to radiotherapy and BCNU; only a modest improvement was found in patients with glioblastoma multiforme but not in those with lower-grade gliomas. That observation has not been substantiated by others. The results reported in Studies 8 and 14 (Table 1) did not show further improvement following the addition of hydroxyurea to radiotherapy and the nitrosoureas PCNU or CCNU. Hydroxyurea used as a radiosensitizer or as an antitumor agent demonstrates little activity and does not add significantly to success in combination chemotherapy.

**Dianhydrogalactitol**

Dianhydrogalactitol (DAG) was evaluated in a small controlled study (Study 2, Table 1). There was an increased survival time for those patients so treated; however, the radiotherapy dose used in the study (5000 rads) was comparatively low and some patients were given BCNU following recurrence of tumor, thus making survival a difficult endpoint to interpret. Studies 14 (Table 2) and 5 (Table 3) also evaluated DAG in uncontrolled investigations in combination with VP-16 (terazanate) or BCNU. Both studies reported DAG to be as effective as the nitrosoureas and therefore acceptable.

**Teniposide**

Teniposide (VM-26, epipodophyllotoxin) is a modestly active podophyllotoxin which has been further evaluated in an uncontrolled study (Study 1, Table 2) where it was compared with historic controls and be-
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AZQ is believed to be effective as a single agent. However, in controlled studies (Studies 6 and 10, Table 1), 2,4 when VM-26 was added to CCNU and compared to radiotherapy alone, no survival advantage was seen. Thus, VM-26 appears to have little future in the treatment of malignant brain tumors.

**Bleomycin**

Bleomycin was compared alone and in combination with other drugs in carefully regulated studies (Studies 9 and 18, Table 1). 3,9 It was shown not to be effective either as a single agent following radiation therapy or as additive therapy with MeCCNU. The significant incidence of pulmonary fibrosis further limits its role.

**Imidazolcarboxamide**

Imidazolcarboxamide (DTIC) was used in combination with MeCCNU in a controlled study (Study 12, Table 1); however, the results were not found to be superior to those of radiotherapy alone and extreme toxicity was encountered, requiring dose reduction and active treatment of the toxic side effects. From this observation and previous studies with DTIC, this agent appears too toxic to be of value.

**Dibromodulcitol**

Dibromodulcitol (DBD) has been used alone and in combination with CCNU in a controlled study (Study 16, Table 1). 1 The treatment schedule included the use of DBD during radiotherapy with continued DBD or CCNU plus DBD upon the completion of radiotherapy. It was considered that DBD significantly added to radiotherapy whereas the addition of CCNU to the DBD regimen failed to demonstrate further improvement. Although DBD appears to be of some value, further confirmatory studies need to be carried out.

**Aziridinylbenzoquinone**

The alkylating agent AZQ has been evaluated in Phase I and II studies. 3,5,12,13,19,22,26,29,32,45,56,63,64,79,80,82,91 Virtually all of these studies have reported that AZQ appears to be an "active" agent in the treatment of malignant gliomas or that it is at least effective in some patients, and therefore worthy of further study. In a typical study as applied to recurrent primary anaplastic brain tumors (Study 12, Table 2), 2,1 a phase II study of the role of AZQ in high-grade glioma, 31 patients were treated with AZQ and responders were measured by serial CT scanning. Of 28 evaluable patients, six (21%) had limited improvement (10% to 40% reduction of tumor size), 10 (36%) had disease stabilization, and 12 (43%) had progressive disease. It is of interest that in the latter study, as in all other studies, the drug was well tolerated clinically with minimal acute toxicity, and 50% or more of total AZQ exposure occurred during the actual infusion period. A recent small study (Study 20, Table 1) 2,1 compared AZQ to PCNU and demonstrated that PCNU was significantly better. In the various dose schedules used, AZQ was well tolerated, with delayed progressive thrombocytopenia as the major toxicity.

The role of AZQ is still not clear. The results in early Phase II studies were encouraging. It does appear that AZQ is effective in achieving partial responses in 20% of patients. The use of AZQ as a secondary agent in patients who have failed BCNU/CCNU therapy is worth considering. Although AZQ shares the effect of alkylation with the nitrosoureas, it has a highly specific effect on mitochondrial function that may make it capable of destroying nitrosourea-resistant cells. 6 From the data available at the present time, AZQ with its low toxicity and low (20% range) response rate is useful in only selected patients. Development of a predictive assay of response may make it possible to determine in which patients this relevantly low-yield drug would be efficacious. 27 At this time, AZQ cannot be considered as a primary treatment agent.

**Cisplatin**

Cisplatin (CDDP, Platinol), a heavy metal compound which inhibits DNA (deoxyribonucleic acid) synthesis, is highly biologically active. It is remarkably effective for testicular, ovarian, and head and neck cancers. Cisplatin has been evaluated in recurrent brain tumors (Studies 3 and 10, Table 2). 3,8 Both studies suggested efficacy, reasonable tolerance of the drug, and that further studies were indicated. One study (Study 15, Table 2) 9 attempted to potentiate CDDP by the use of cytosine arabinoside (AraC), but no major potentiation was demonstrated. Cisplatin is a highly potent chemotherapeutic agent. Its role in the treatment of a variety of pediatric brain tumors has been suggested but not conclusively proven. No Phase II or III study has been completed showing consistent efficacy. The ototoxicity and pronounced vomiting that often accompany cisplatin have limited enthusiasm for this agent. At present, its role is still that of an experimental drug. It is under detailed investigation for use in intra-arterial therapy. From reports of successful use in individual patients, it may be considered a potential backup agent in the treatment of medulloblastoma or malignant astrocytoma in childhood.

**Noncytotoxic Agents**

In addition to the cytotoxic chemotherapy agents, there are two other types of therapy adjuncts that deserve mention. These are the radiosensitizers which have theoretical potential for enhancing the effect of radiotherapy on tumor but not on normal brain, and the corticosteroids which have a significant effect on peritumor edema.
TABLE 4
Phase II trials of radiosensitizers for malignant glioma*

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Authors &amp; Yr</th>
<th>Tumor Type, % Incidence</th>
<th>No. of Cases†</th>
<th>Treatment</th>
<th>Results‡</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kapp &amp; Wagner, 1981</td>
<td>GBM IV</td>
<td>18</td>
<td>metronidazole with RT: 600 rads/7 fx</td>
<td>very large dose of RT</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Russo, et al., 1983</td>
<td>GBM</td>
<td>12</td>
<td>BUdR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Carabell, et al., 1981</td>
<td>astro III &amp; IV</td>
<td>54</td>
<td>mison, then RT: 400 rads</td>
<td>MST 39</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Aiken et al., 1984</td>
<td>metastatic</td>
<td>76/151</td>
<td>metronidazole 6 gm/sq m/4 hrs before RT: 600 rads</td>
<td>neurological function, CT scan, clinical state, steroid dependence unchanged</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Kurup, et al., 1985</td>
<td>GBM</td>
<td>25</td>
<td>2.5 gm miso/sq m/4 hrs then 3.0 Gy fast-neutron RT: 1/wk x 6</td>
<td>MST 52, 25% 18-mo Sv</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>EORTC, 1983</td>
<td>GBM 39% AnaA 37% other 29%</td>
<td>163</td>
<td>RT + miso</td>
<td>MTP 30, MST 44</td>
<td>double-blind placebo-controlled</td>
</tr>
<tr>
<td>8</td>
<td>MRC, 1983</td>
<td>astro IV 58% astro III 42%</td>
<td>384/436</td>
<td>RT: 4500 rads + placebo</td>
<td>MST 36, 28% 12-mo Sv</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Stadler, et al., 1984</td>
<td>astro III &amp; IV</td>
<td>45</td>
<td>RT + miso</td>
<td>MST 33, 25% 12-mo Sv</td>
<td>RT dose competitively low; mison 4–5 hrs before RT</td>
</tr>
<tr>
<td>10</td>
<td>Fulton, et al., 1984</td>
<td>GBM 70% AnaA 30%</td>
<td>128</td>
<td>RT: 5800 rads daily fx RT 3 daily fx RT 3 daily fx + miso</td>
<td>MTP 21, MST 29</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: GBM = glioblastoma multiforme; RT = radiation therapy (fx = fractions); CT = computerized tomography; astro = astrocytoma; AnaA = anaplastic astrocytoma. Tumor grade in roman numerals. For drugs see Definitions of Abbreviations table.† Number of cases evaluated/number entered in study.‡ MST = median survival time (in weeks); MTP = median time to progression (in weeks); % Sv = percent survival rate.

Radiosensitizers
Although not strictly chemotherapy agents, radiation-sensitizing drugs may be considered as chemotherapy agents that modify the effects of radiation therapy (Table 4). The goal of radiosensitizers is to improve the radiation biological effect of external-beam radiotherapy. A variety of agents have been studied with some initially encouraging results, but as yet none has proved to be of significant value in controlled studies. Two general classes have been studied: the nitroimidazole group and the halogenated pyrimidines.

Misonidazole. Misonidazole has been administered to patients prior to large doses of radiotherapy on a weekly basis. This drug is a synthetic nitroimidazole which has radiosensitizing properties and has been evaluated in pilot studies (Studies 3 and 5, Table 4) and in extensive controlled studies (Studies 11 and 19, Table 1, and Studies 6 to 10, Table 4). Misonidazole was thought to be of potential value in view of the theoretically "hypoxic" central care of gliomas. Early studies for tolerance and effect utilizing both conventional radiotherapy fractions and fast neutrons have indicated some clinical efficacy. In addition, uncontrolled studies using metronidazole (Studies 1 and 4, Table 4) were also thought to show some transient value; however, considerable toxicity was encountered.

The total dose of misonidazole that can be delivered is limited. A series of controlled studies have been carried out utilizing various radiotherapeutic treatment fractions with the intent of delivering high doses of radiotherapy during the time when high plasma levels of misonidazole can be anticipated and lesser doses of radiotherapy in between. Two studies were placebo-controlled (Studies 7 and 8, Table 4).
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was able to demonstrate any therapeutic gain for the addition of misonidazole over radiation therapy alone. One of these utilized a comparatively low total dose of radiotherapy (4000 rads) while the other used a more conventional total cumulative dose of 6000 rads. Other studies have examined misonidazole either alone or with subsequent chemotherapy. The Brain Tumor Study Group, evaluating 557 patients, did not show that misonidazole improved survival times when added to 6000 rads of radiotherapy followed by BCNU. Thus, this agent, which was thought to be very promising for the treatment of malignant gliomas, has not been shown to be effective. It is of interest that recent data from positron emission tomography evaluation of the oxygen content in the central portion of gliomas has shown that there is ample oxygen present in these tissues and this may explain why radiosensitizers are not effective (DGT Thomas, personal communication).

Halogenated Pyrimidines. Halogenated pyrimidines have been studied for some time as potential radiosensitizers. In the initial studies 5-bromodeoxyuridine (BUdR) was given via the intra-arterial route. The limited technology of intra-arterial therapy in that era led to serious delivery problems. 83 A recent evaluation of the role of this group of agents has been carried out by the National Institutes of Health (NIH) radiation therapy and neurosurgical groups. 54 The nonhypoxic cell sensitizers primarily used were BUdR and 5-ido-2-deoxyuridine (IUdR). Whereas BUdR produces significant toxicities and minimal clinical benefits, IUdR has less toxicity and may have greater value. Inasmuch as relatively little of these data have appeared in the neurosurgical literature as yet, the information about this new work is presented in somewhat more detail.

Certain information has been learned in the course of this study. It had been previously shown that BUdR was an effective radiosensitizing agent in rapidly dividing cells. 71 Further studies showed that when BUdR is given intravenously satisfactory blood levels are attained. Twelve patients were treated with continuous intravenous (24-hour) infusions of BUdR at 650 or 1000 mg/sq m/day for up to 2 weeks. Myelosuppression, especially thrombocytopenia, was the major systemic manifestation of toxicity and limited the infusion period to 9 to 14 days. However, bone marrow recovery occurred within 7 to 10 days, allowing for a second infusion in most patients. Local toxicity (within the radiation field) was minimal. An anti-BUdR monoclonal antibody and immunohistochemistry were used to demonstrate BUdR incorporation into normal skin and tumor cells in vivo in biopsies from three patients; substantially less cellular incorporation was found in normal skin (less than 10%) than in tumor (up to 50% to 70%). The local and systemic toxicity of continuous infusion of BUdR at 1000 mg/sq m/day for approximately 2 weeks is tolerable. The observed normal tissue toxicity is comparable to that found in previous clinical experience with intermittent (12 hours every day for 2 weeks) infusions of BUdR. Theoretically, a constant infusion should allow for greater incorporation of BUdR into cycling tumor cells and thus for further enhancement of radiosensitization. 53

The NIH study also evaluated IUdR. 54 Initial findings described the clinical pharmacology and metabolism of this drug during and after a 12-hour infusion. The kinetics of IUdR were linear at doses between 250 and 1200 mg/sq m. The plasma drug concentration reached steady-state levels in less than 1 hour. Total body clearance of IUdR was 750 ml/min/sq m and the disappearance t1/2 at the end of the infusion was less than 5 minutes. 55

In a clinical trial, 24 patients with locally advanced (19 patients) or metastatic (five patients) tumors were treated in a Phase I study combining constant intravenous infusions of IUdR and hyperfractionated radiation therapy. In most patients, IUdR was given as a constant infusion for 12 hrs/day for two separate 14-day infusion periods. The dose of IUdR was escalated from 250 to 1200 mg/sq m/12-hr infusion in this study. The tumor volume was treated with an initial total dose of 45 Gy (1.5 Gy twice daily for 3 weeks) followed by a cone-down boost to a total of 20 to 25 Gy (1.25 Gy twice daily for 2 weeks) after a planned 2-week break. The IUdR infusion preceded the initial and cone-down irradiation by 1 week. Local acute toxicity (within the radiation volume) was uncommon and few patients required an alteration of the planned treatment schedule. Two patients developed late local toxicity: one showed clinical signs of radiation hepatitis and the other developed a large bowel obstruction that required surgical bypass. Dose-limiting systemic toxicity was confined to the bone marrow with moderate to severe thrombocytopenia developing 10 to 14 days after institution of IUdR infusions at 1200 mg/sq m/12 hrs. Mild stomatitis and partial alopecia occurred in some patients at this dose level. No systemic skin toxicity was seen. Pharmacology studies revealed steady-state arterial plasma levels of IUdR of 1 to 8 × 10⁻⁸ M over the dose range used. In comparison to the earlier experience with intravenous BUdR, this Phase I study of IUdR showed less systemic toxicity (especially to skin), higher (two- to threefold) steady-state arterial levels, and comparable in vivo tumor cell incorporation. 54 These agents, particularly IUdR, merit further Phase II trials, some of which are now in progress.

Corticosteroids

The use of corticosteroids in the clinical management of patients with brain tumors is widely accepted. However, the apparent increase in the quality of life observed in many patients has led to a controversy as to whether the results obtained with these agents represent merely the effect on cerebral edema or whether these agents could have an oncolytic effect.
Methylprednisolone

Very large doses of methylprednisolone (Solu-Medrol) were employed in a controlled prospective study in order to evaluate the efficacy of this drug alone and in combination with BCNU when compared to radiotherapy alone or with BCNU (Study 17, Table 1). In that study, methylprednisolone was not shown to be additive to radiation therapy by itself or in combination with BCNU; thus an oncolytic effect has not been shown. Corticosteroids may be utilized in controlled therapy protocols without fear of contamination of results when the endpoint of survival is utilized. However, when median time to progression or other response factors dependent upon clinical observations are employed, the use of corticosteroids may in some cases make the endpoint less certain.

Dexamethasone

Results with dexamethasone (Decadron) have been essentially similar to those observed with methylprednisolone. Both agents remain as useful tools in clinical management but do not appear to have an oncolytic effect.

Alternative Approaches to Chemotherapy

As it has become apparent that systemic delivery of currently available agents has not yielded highly satisfactory results, considerable effort has been expended in developing alternative routes of delivering chemotherapy to malignant gliomas. Two alternative approaches deserve comment: intra-arterial therapy and bone marrow transplantation. The most effort so far has been directed to the use of intra-arterial chemotherapy via the carotid artery, usually by transfemoral catheterization.

In the studies with BCNU, problems of brain toxicity have been quite serious. Cisplatin and AZQ have also been studied. All trials are still at too early a stage to evaluate definitively.

Intra-Arterial Therapy

Systemically delivered drugs are distributed throughout the body as well as to the brain, so by the time a drug has entered the cerebral circulation, its plasma concentration has been diluted to a considerable extent. Intra-arterial chemotherapy therefore might possess considerable advantages. Studies in the dog using intracarotid infusion of radiolabeled substances (inulin, antipyrine, and pentobarbital) produced concentrations of drug in the normal brain between 1.5 and 3 times greater than with a similar intravenous infusion. Intracarotid infusion of BCNU in the monkey achieved between 1.9 and 2.8 times greater delivery of nucleic acid-bound drug to the brain than was achieved with intravenous infusion. Most studies have been focused on BCNU and cisplatin, but a few authors have reported results with AZQ. As an example of a small positive study, Safdari, et al., reported in 1985 on 10 patients treated primarily by intra-arterial BCNU following partial tumor resection and 1 month after completion of radiotherapy. Total doses of 270 to 280 mg/sq m were given in two sessions separated by a 24-hour interval, and this was repeated every 8 to 10 weeks; no other chemotherapy was given. Four patients underwent three courses, and the other six had two courses of treatment. The major adverse effect observed was transient ipsilateral periorbital erythralgia in six patients and episcleral vasodilatation in all patients. No long-term sequelae were found, although there was transient myelodepletion in one patient. Of the 10 patients, one had a striking improvement, five improved moderately, and four remained unchanged. One patient died of possible long-term neurotoxicity 13 months after diagnosis of the brain tumor. Another patient apparently died from regrowth of the tumor outside the area of treatment. The other eight patients are alive 8 to 14 months after diagnosis. This report is not necessarily typical of the majority of reports related to BCNU therapy.

There are major concerns in virtually every report regarding the toxicity of BCNU given intra-arterially. When given below the origin of the ophthalmic artery, retinal damage has been commonly observed. In attempts to give superselective therapy above the ophthalmic artery, significant numbers of patients have developed neurotoxicity. Foo, et al., noted in 1985 that leukoencephalopathy was seen in four of five cases several weeks after the second infusion of a BCNU dose of 300 to 400 mg/sq m. Greenberg, et al., noted that only seven in a series of 36 patients developed white matter changes on CT scans. Serious questions exist concerning whether the toxicity is related to BCNU itself, a combination of radiotherapy and BCNU, or possible effects of the alcohol diluent. Cisplatin also has been noted to be neurotoxic but is associated with a lower incidence of retinal problems. In an interesting approach to intra-arterial therapy, Oldfield and colleagues have used techniques of drug removal such as extracorporal bypass or exchange columns to remove the drug from the systemic circulation. These techniques appear highly successful in minimizing systemic toxicity such as myelosuppression and could allow much higher doses of BCNU or cisplatin to be given with more systemic safety. Obviously, however, these approaches alone do not alter neurotoxicity.

Attempts to analyze potential neurotoxicity due to mechanical delivery techniques have led to the proposition that the patterns of streaming induced by the actual injection may play a role in the development of neurotoxicity.

A recent series of papers have addressed the various issues of intra-arterial chemotherapy and superselective chemotherapy in terms of toxicity (nausea and vomiting), description of neurotoxicity, preliminary results, and superselective delivery.

It is clear that the intra-arterial therapy route has many theoretical and practical advantages. A series of
Chemotherapy for malignant gliomas

**TABLE 5**

*Ongoing studies on chemotherapy of medulloblastoma*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Patient Population</th>
<th>No. of Cases†</th>
<th>Pre-Chemo Conditions</th>
<th>Treatment Groups</th>
<th>Results‡</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Bloom (SIOP)</td>
<td>randomized (preliminary)</td>
<td>postop</td>
<td>191</td>
<td>surgery</td>
<td>RT, RT, VCR, &amp; CCNU</td>
<td>MTP 2 yrs MTP 3+ yrs</td>
<td>slight benefit to chemotherapy (p = 0.408)</td>
</tr>
<tr>
<td>Evans (CCSG)</td>
<td>randomized (preliminary)</td>
<td>postop, age 2–16 yrs</td>
<td>128/144</td>
<td>surgery</td>
<td>RT vs. RT + VCR, CCNU, &amp; prednisone</td>
<td>69% 2-yr Sv no significant difference</td>
<td></td>
</tr>
<tr>
<td>Crafts</td>
<td>Phase II</td>
<td>recurrent &amp; symptomatic</td>
<td>16/17</td>
<td>surgery &amp; RT</td>
<td>PCZ + VCR + CCNU</td>
<td>72% 2-yr Sv stable 31% progression 6%</td>
<td>moderately acceptable toxicity</td>
</tr>
<tr>
<td>Cangir</td>
<td>Phase II</td>
<td>recurrent &amp; progressive</td>
<td>10</td>
<td>surgery &amp; RT</td>
<td>nitrogen mustard + VCR + PCZ + prednisone</td>
<td>response 80%, MST 11 mos; no response 20%, MST 2 mos</td>
<td></td>
</tr>
<tr>
<td>Rosenstock</td>
<td>Phase II</td>
<td>recurrent</td>
<td>4</td>
<td>surgery &amp; RT</td>
<td>VCR</td>
<td>response 75%</td>
<td>VCR used alone</td>
</tr>
<tr>
<td>Thomas</td>
<td>Phase II</td>
<td>recurrent</td>
<td>8</td>
<td>surgery &amp; RT</td>
<td>VCR, BCNU, dexamethasone, &amp; MTX (IV &amp; IT)</td>
<td>response 100%</td>
<td>IT MTX &amp; BCNU stopped during RT as very toxic when used early (4 deaths)</td>
</tr>
</tbody>
</table>

*Abbreviations: RT = radiation therapy; IV = intravenous; IT = intrathecal. For drugs see Definitions of Abbreviations table.

† Number of cases evaluated/number entered in study.

‡ MTP = median time to progression; % Sv = percent survival rate; MST = median survival time; MDR = mean duration of response.

cemia 10 days after receiving 1400 mg/sq m of BCNU. All patients experienced transient emesis; four developed transient elevation of hepatic enzymes, two exhibited reversible interstitial pulmonary infiltrates, and two who received 1400 mg/sq m of BCNU suffered irreversible cortical damage. Eight patients receiving 600 to 1200 mg/sq m demonstrated reconstitution of polymorphonuclear leukocytes and platelets within at least 30 days after treatment. With a follow-up time of up to 19 months, four patients improved, three stabilized, and three deteriorated and died. The median survival time was 7 months. Computerized tomography performed on patients receiving constant corticosteroids showed diminished contrast enhancement and mass effect in eight patients.48

**Bone Marrow Rescue with Chemotherapy**

A second novel approach to the delivery of chemotherapy involves the use of bone marrow transplantation to overcome the small therapeutic index of BCNU which limits the total amount of drug that may be delivered at any one time. The critical dose-limiting organ for the nitrosoureas is the bone marrow and, thus, if one could protect the marrow from the comparatively brief pharmacological effects of BCNU, it might be possible to deliver considerably higher concentrations of drug to the tumor.

In a study of this approach,48 11 patients with recurrent malignant glioma were treated with single high doses of BCNU ranging from 600 to 1400 mg/sq m. To prevent the characteristic late myelosuppression observed after conventional doses of BCNU, autologous bone marrow harvested just before drug treatment was infused 24 to 36 hours after therapy. Higher doses of BCNU caused earlier and more profound myelosuppression; one patient died of pancytopenia, breakdown of the gut epithelium, and *Clostridium* septi-

**Pediatric Brain Tumors**

The main focus of this review has been directed toward the chemotherapy of malignant gliomas of adults. The management of malignant brain tumors in the pediatric age group is in itself a very complex and difficult issue. There is relatively little that can be said about chemotherapy for an ependymoma except that the nitrosoureas may be tried as an adjunct. There is certainly no conclusion that primary neuroectodermal tumors can be effectively treated with chemotherapy.

The major thrust in the management of pediatric tumors is in the area of medulloblastoma. The many clinical trials of medulloblastoma therapy are summarized in Table 5.58 It is not yet clear how effective the
various protocols may be. It is clear that serious consideration for adjunctive therapy in cases of medulloblastoma is indicated. Care must be taken to follow a sequence of therapy in such a way that neuraxis radiation and consequent bone marrow destruction do not occur, especially with myelosuppressant chemotherapy. At present, the largest experience in medulloblastoma chemotherapy has been with a combination of procarbazine, vincristine, and CCNU; this appears to have value in extending the life of some patients with medulloblastoma.

Summary

At present, the role of chemotherapy for malignant gliomas is adjunctive. There is no evidence that any current form of chemotherapy can be used in lieu of surgery and/or radiotherapy. The most effective agent remains BCNU when delivered intravenously following surgery and irradiation.

Clearly, despite the great amount of effort, there still are no agents in hand with sufficient potency or specificity, used singly or in combination, that are capable of producing a therapeutically useful response in a sufficient percentage of patients with malignant gliomas. The challenge therefore is to encourage the development of agents or combinations that can achieve the desired effects and to explore the possibilities of other routes of delivery as a means of achieving a higher concentration of agents at the tumor site. Much work has been carried out at the cellular level, and insights gained from these results may offer the possibility of selecting the appropriate agent for a given patient based on objective criteria rather than waiting for an extrapolation from the responses of a large population of patients.

In interpreting the data presented in this review it is important to place in perspective the issue of controlled versus uncontrolled studies. To date, the only large controlled studies presenting Phase III data that confirm efficacy for chemotherapy in the treatment of gliomas involve the use of the nitrosoureas, especially BCNU. The clinician responsible for the management of a patient who has failed a program of surgery, radiation therapy, and BCNU is faced with the difficult task of sorting through a rather voluminous literature of uncontrolled studies of a variety of agents, and then choosing to enter the patient in one of the many ongoing Phase I or II trials.

Until such time as further drugs are added to the list of those showing efficacy in Phase III trials, it is difficult to support the use of other specific agents. This observation makes clear the absolute necessity for pooling patient data and developing collaborative trials on a broad base so that more data can be rapidly obtained.

Acknowledgment

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Chemotherapy for malignant gliomas

Radiat Oncol Biol Phys 10:1713–1717, 1984

Manuscript received March 27, 1986.
Accepted in final form September 28, 1987.
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