A randomized trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low-grade gliomas: a Southwest Oncology Group study

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Sixty adult patients with incompletely excised low-grade gliomas were randomly assigned to receive radiotherapy (55 Gy over a total of 6 weeks) either alone or with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU; 100 mg/mq every 6 weeks). Pathological review showed that six patients were ineligible for the study. Evaluation of patient age, extent of surgery, tumor grade, and performance status showed no significant differences between the treatment arms. The response rate, as judged by the disappearance or reduction in size of the tumor on computerized tomography scans, was 79% for radiation therapy alone versus 54% for irradiation plus CCNU. The median survival time was 4.45 years for all patients, with no significant difference between treatment arms ($p = 0.7$). For the group as a whole, patient age and performance status were the most important prognostic parameters. The majority of patients receiving chemotherapy experienced moderate hematological toxicity. This study demonstrates that CCNU chemotherapy does not improve the results of radiation therapy in the treatment of incompletely excised low-grade gliomas.

**KEY WORDS** • glioma • radiation therapy • chemotherapy

Low-grade gliomas account for 10% to 15% of primary adult brain tumors. While complete surgical resection can be curative, the location, size, and/or degree of infiltration of these tumors often prevents total excision. The behavior of these tumors can be quite variable. Many patients, particularly younger individuals who present with seizures and no other neurological deficit, can survive for extended periods of time. Median survival times of 3 to 5 years, with 20% of patients surviving 10 years, have been reported. However, incompletely resected gliomas are usually fatal despite their slow growth. It is well recognized that a substantial proportion of these tumors will undergo dedifferentiation to a more malignant histology. Müller, et al., determined that, at the time of recurrence, only 14% of low-grade gliomas were pathologically unchanged whereas 86% were histologically more malignant.

Because of the small incidence of low-grade gliomas, almost all studies evaluating treatment are retrospective. These investigations uniformly support complete resection when possible. However, there are conflicting recommendations concerning the optimum treatment for patients with incomplete resection. The majority of studies support the use of postoperative radiation therapy. The only prospective controlled trial evaluating treatment of low-grade gliomas was part of a large study including all histological tumor grades, and patients were randomly assigned to receive 6000 cGy with or without chemotherapy. The Brain Tumor Cooperative Group, Southwest Oncology Group, and Radiation Therapy Oncology Group are conducting an intergroup prospective randomized trial of immediate irradiation versus irradiation delayed until the time of disease progression.

Previous investigations of chemotherapy for recurrent low-grade gliomas in adults have reported response rates similar to those seen in high-grade tumors. The most active drugs appear to be the nitrosoureas, with procarbazine, methiotrexate, vincristine, dihydralacti-
Clinical Material and Methods

**Patient Population**

From February, 1980, through March, 1985, 23 institutions entered 60 patients for study. Eligibility requirements included the histological diagnosis of a grade I or II primary brain tumor, classified according to Kernohan and Sayre,\(^1\)\(^2\) with incomplete surgical resection. Median patient age was 36 years (range 22 to 73 years) for the irradiation-only arm and 39 years (range 17 to 72 years) for the irradiation plus chemotherapy arm. No patients with cystic cerebellar astrocytoma were included. Patients were required to begin radiotherapy with or without chemotherapy within 6 weeks of tumor resection. All patients were notified in writing of the investigational nature of the study, and no patient was registered without written informed consent in accordance with institutional policy. The study was closed early as a result of a decision by the data monitoring committee. Slow accrual and a rejection of the hypothesis of a 50% improvement in the survival time of patients receiving chemotherapy were the principal reasons for closure.

Pretreatment parameters recorded for analysis included patient age and sex, diagnosis (astrocytoma grade I or II), extent of surgery (biopsy or partial resection), performance status, and results of neurological examination studies. At the time of entry into the study, each patient was stratified by the degree of tumor resection and by their performance status, classified according to the Southwest Oncology Group grading system: Grade 0 = fully active, able to carry on all predisease performance without restriction; Grade 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; Grade 2 = ambulatory and capable of all self-care but unable to carry out any work activities; Grade 3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours; Grade 4 = completely disabled, cannot carry on any self-care, totally confined to bed or chair; Grade 5 = dead. Each patient was then assigned to one of the two treatment arms.

**Histological Grading**

A review of the histology of the resected tumor determined whether patients were considered to have either a grade I or a grade II astrocytoma. Grade II tumors included pilocytic astrocytomas, gemistocytic astrocytomas, mildly anaplastic astrocytomas, mixed gliomas, oligodendrogliomas, and gangliogliomas.\(^23\)\(^24\) According to the original description by Kernohan and Sayre,\(^1\)\(^4\) grade I astrocytomas demonstrate a mild increase of relatively normal-looking astrocytes with some increase in nuclear size, increased cytoplasmic processes, mild pleomorphism, and lack of giant cells or mitotic figures. Grade II astrocytomas show an increase in the number of astrocytes with larger and more hyperchromatic nuclei and with thicker processes than are seen in grade I tumors. No giant cells or mitotic activity are seen. The walls of some blood vessels might be slightly thickened, but the tumors do not have necrosis.

Tumors were also classified using the three-tiered system of astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme. No patient with glioblastoma was included. Those with anaplastic astrocytoma had much less cellular tumors that exhibited less pleomorphism than did those described as "typical" anaplastic astrocytomas, which are included in high-grade brain tumor series. Using current criteria, a wide spectrum of cellularity is seen in anaplastic astrocytomas; for the most part, in this study, those tumors labeled as anaplastic astrocytoma demonstrated only mild pleomorphism and cellularity.\(^\)\(^3\)\(^2\)\(^1\)

**Treatment**

Radiation therapy was given using megavolt apparatus with a minimum peak energy of 1 MeV and a target distance (source to skin or axis distance) of 80 cm. The target volume was defined as the primary tumor, as identified on computerized tomography (CT) scans, with a 2-cm margin. Field arrangements were left to the discretion of the radiation oncologist, with an attempt to achieve a homogeneous dose across the target volume. A total of 55 Gy was delivered to the target volume in 32 fractions, given 5 days per week over a total of 6\(^{1/2}\) to 7 weeks. Port films for each patient were reviewed at the Southwest Oncology Group Quality Assurance Center.

Chemotherapy was begun 2 days prior to the onset of radiation therapy. Those patients randomly assigned to the chemotherapy plus irradiation arm received CCNU at a dose of 100 mg/sq m every 6 weeks. Doses of chemotherapy were modified according to standard Southwest Oncology Group guidelines based on the nadir white blood cell and platelet counts. As clinically indicated during the initial course of therapy, patients were treated with dexamethasone in divided doses, beginning at 10 mg/sq m and tapered and/or discontinued as appropriate. If the patient had a partial or complete response, CCNU was continued for a total period not to exceed 2 years.

The parameters monitored to determine response to therapy included tumor size as measured on CT scans, neurological function, and performance status. Patients were evaluated as having complete remission, partial remission, no change, or increasing disease. "Complete remission" was defined as complete disappearance of all measurable central nervous system (CNS) disease, normal neurological function (or abnormalities due solely to surgery), and absence of symptoms related to the tumor; "partial remission" was defined as a 50% or greater decrease in the product of perpendicular diameters of measurable CNS disease on CT scans, com-

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TABLE 1
Characteristics of 54 eligible patients by treatment arm

<table>
<thead>
<tr>
<th>Factor</th>
<th>Radiotherapy</th>
<th>Radiotherapy + CCNU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
</tr>
<tr>
<td>total cases</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>age (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>36.0</td>
<td>39.0</td>
</tr>
<tr>
<td>minimum</td>
<td>22</td>
<td>17</td>
</tr>
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<td>maximum</td>
<td>73</td>
<td>72</td>
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<tr>
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<td>6</td>
<td>32</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>white</td>
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<td>89</td>
</tr>
<tr>
<td>black</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>other</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>extent of surgery</td>
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</tr>
<tr>
<td>biopsy only</td>
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<td>37</td>
</tr>
<tr>
<td>partial resection</td>
<td>12</td>
<td>63</td>
</tr>
<tr>
<td>grade of tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>18</td>
<td>95</td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>performance status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>15</td>
<td>79</td>
</tr>
<tr>
<td>2-4</td>
<td>4</td>
<td>21</td>
</tr>
</tbody>
</table>

* For definition of Southwest Oncology Group grading system, see Materials and Methods.

bined with improvement in neurological function and in tumor-related symptoms; "no change" was defined as a steady state of measurable disease without progression of symptoms; and "increasing disease" was defined as a 25% or more increase in the size of the CNS tumor on CT scans with deterioration of neurological function or worsening of tumor-related symptoms. Since survival time was the most important parameter in this study, investigators were required to follow each patient until death, and to report the death on a supplementary off-study form.

Statistical Methods

Survival curves were estimated by the method of Kaplan and Meier, comparisons between the curves were made by log-rank tests. Response rates were compared by chi-squared tests.

Results

Sixty patients were entered in this study. Six patients were not included in the final analysis after review of the pathology, which determined that five had high-grade gliomas (glioblastoma multiforme) and one patient had no confirmed tumor. The 54 remaining patients were all considered fully or partially evaluable and were included in the analysis of response and survival data.

Study Entrance Characteristics

A comparison of the characteristics of patients at the time of entry into the study is shown in Table 1. Stratification of patients by extent of surgery (biopsy vs. partial resection) and performance status (0-1 vs. 2-4) assured that patients in each treatment arm would be comparable with respect to these characteristics. Pathological review of the surgical material demonstrated comparable numbers of patients with a grade I astrocytoma and a grade II astrocytoma, as well as comparable numbers of mildly anaplastic astrocytomas, mixed gliomas, and oligodendrogliomas in each group. Data also indicate that patients were comparable with respect to age, sex, and race. The study was designed to result in an equal distribution of treatment assignments between radiation therapy alone and radiation therapy plus CCNU. However, by chance more patients were assigned to receive radiation therapy plus CCNU.

Response Rates and Survival Times

The response rates by treatment regimen are shown in Table 2. The complete plus partial remission rates equalled 79% for irradiation alone versus 54% for irradiation plus CCNU. The difference between these response rates is not statistically significant.

The survival curves by treatment regimen for all evaluable patients are shown in Fig. 1. No statistically significant difference in survival time is seen between the two treatment groups (p = 0.7). The median survival time for patients who received irradiation alone was 4.5 years and that for patients who received irradiation plus CCNU was 7.4 years. The survival curve of the latter

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group reached a plateau at just above 50% at 2.9 years. Survival comparisons were made for all eligible patients distributed by age (Fig. 2). The median survival time in patients less than 30 years of age was greater than 8 years, in patients between 30 and 50 years of age was 5.5 years, and in patients older than 50 years was 1.6 years (p = 0.001). The survival distribution by performance status is illustrated in Fig. 3. Patients with a performance status of 0 to 1 had a median survival time of 7.4 years, while those with a performance status of 2 to 4 had a median survival period of 1.6 years (p = 0.002). Comparison of survival distribution according to the extent of surgery performed is depicted in Fig. 4. Patients who underwent biopsy only demonstrated a median survival time of 2.6 years, compared to 5.5 years for those who underwent partial resection (p = 0.38). Evaluation of survival based on gender (Fig. 5) showed a trend toward improved results for women (p = 0.07). When survival was evaluated according to either pathological classification, there were no differences between groups (data not shown).

Toxicity of Treatment

Treatment toxicity was assessed in accordance with standard Southwest Oncology Group criteria. All patients experienced toxicity, usually as a result of radiation therapy, with alopecia and mild skin reactions to radiation. Of the 32 evaluable patients receiving CCNU, 59% experienced mild to moderate leukopenia and/or thrombocytopenia and 41% experienced mild to moderate gastrointestinal upset. Twelve percent of patients had severe or life-threatening hematological toxicity; one experienced life-threatening leukopenia and three had severe cytopenia. No fatal toxicity was observed. These data are shown in Table 3.

Discussion

This study is the first prospective randomized controlled trial in the United States evaluating the treatment of patients with incompletely excised low-grade gliomas. Retrospective studies assessing the use of radiation therapy for such patients suggest potential benefits. However, this remains controversial, with recent reports suggesting that earlier diagnosis with CT or magnetic resonance imaging results in a better prognosis than is reported in the older series. Thus, the potential benefits of radiation therapy remain unclear.

This trial demonstrates no significant benefit to a combined regimen of radiation therapy plus CCNU when compared to radiation therapy alone. Patients in each treatment group were judged to be comparable for the multiple prognostic parameters evaluated.
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**TABLE 3**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Radiotherapy (18 cases): Degree</th>
<th>Radiotherapy + CCNU (32 cases): Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 or 2 3 or 4</td>
<td>0 1 or 2 3 or 4</td>
</tr>
<tr>
<td>hematological (%)</td>
<td>83 17 0 28 59 12</td>
<td>83 17 0 56 41 3</td>
</tr>
<tr>
<td>gastrometastital (%)</td>
<td>94 6 0 97 3 0</td>
<td>94 6 0 97 3 0</td>
</tr>
<tr>
<td>alopecia (%)</td>
<td>6 83 11 3 97 0</td>
<td>6 83 11 3 97 0</td>
</tr>
<tr>
<td>weight loss (%)</td>
<td>100 0 0 94 3 3</td>
<td>100 0 0 94 3 3</td>
</tr>
</tbody>
</table>

* Degree of toxicity: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = life threatening.

Our study confirms the need to control for a number of important prognostic parameters in any future comparative clinical trial. These include age, performance status, and extent of surgery.36 We failed to demonstrate a difference in survival time when comparing patients with grade I versus grade II astrocytomas, or with the distinction of astrocytoma versus mildly anaplastic astrocytoma or mixed tumor.37,38 There was an unexpected finding which suggests that women with low-grade glioma might survive longer than do men with this malignancy. We are unaware of a good explanation for this finding, but it certainly should be evaluated further in any proposed study.

It is possible that advances in technology will enable us to select a subpopulation of patients with low-grade astrocytoma who should receive adjuvant chemotherapy. Those patients with a high proliferative rate determined with the monoclonal antibody Ki-67 might be predicted to respond to chemotherapy.34 In addition, it has recently been reported that positron emission tomography scanning of these patients may reveal a subgroup of tumors with a high rate of metabolism.35 If these preliminary studies are confirmed, then perhaps only patients whose tumors have these poor prognostic factors should be considered for adjuvant chemotherapy.

Future evaluations of treatment for this patient population should include an assessment of initial irradiation versus delayed irradiation, including quality of life assessment, which is currently being assessed in a prospective intergroup trial coordinated by the Brain Tumor Cooperative Group. Further refinement of surgical procedures has occurred and should be continued. The usefulness of interstitial irradiation boosts and other experimental procedures should also be evaluated.1,2,11

References


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