Radiotherapy combined with procarbazine, bleomycin, and CCNU in the treatment of high-grade supratentorial astrocytomas

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Twenty consecutive patients with supratentorial Grade III and IV astrocytomas were treated with postoperative radiotherapy, and a simultaneous induction chemotherapy with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), procarbazine, bleomycin, and maintenance chemotherapy with CCNU. They were compared to 32 retrospective control patients selected similarly, who had received postoperative radiation therapy alone. The median survival time was 56 weeks for the combined treatment group, and 51 weeks for the control group. There was no statistical difference in survival in the two groups of patients.

Key Words □9 astrocytoma □9 radiation therapy □9 CCNU □9 procarbazine □9 bleomycin □9 chemotherapy □9 glioblastoma

The treatment of high-grade supratentorial astrocytomas by surgery and radiotherapy is still unsatisfactory, with median survival times between 36\textsuperscript{18} and 50 weeks.\textsuperscript{9} Recently, some chemotherapeutic agents have proven effective in recurrent malignant gliomas,\textsuperscript{16} with the nitrosoureas\textsuperscript{10,14,16} and procarbazine\textsuperscript{7,16} being the most active. Anti-tumor activity was also demonstrated with bleomycin in gliomas of mice\textsuperscript{4} and in a clinical trial;\textsuperscript{11} further, a synergistic effect of bleomycin with radiotherapy was shown in tissue-culture studies.\textsuperscript{5} Bleomycin, having no hematological toxicity, would be an ideal agent to combine with irradiation and hematotoxic cytostatic drugs. Chemotherapy theoretically should be begun early after operation when the tumor burden is the least.

The goal of our study was to investigate whether the addition of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), procarbazine, and bleomycin to radiation therapy early after surgery, and maintenance chemotherapy with CCNU would enhance the effect of postoperative irradiation and prolong the survival time of patients with high-grade supratentorial astrocytomas.

Clinical Material and Methods

Selection of Patients

The study included 52 patients who fulfilled the following criteria: All had histologically confirmed astrocytomas, mixed gliomas, and gliosarcomas Kernohan Grades III and IV, localized supratentorially but without tumors.
of the deep basal ganglia or thalamic areas. All histopathological sections were reviewed and graded by the same neuropathologist (A.Z.). All patients had had maximum feasible tumor resection with a satisfactory recovery after surgery and an expected survival of 8 weeks or more. None had a major medical illness, and all had normal hematopoieses, liver, and renal function.

Twenty consecutive patients presenting between November, 1974, and November, 1975, were included in the chemotherapy group. Thirty-two patients presenting between July, 1967, and September, 1972, who were operated on and irradiated in our departments, and who were followed in our outpatient clinic, served as retrospective controls. Characteristics of both groups are listed in Table 1. There were more Grade IV patients in the control group, but there was no statistical difference in survival between Grade III and IV patients either in the combined treatment group or in the control group. There was no major difference in age and symptom duration between the two groups. Since all patients fulfilled the same selection criteria and pathological diagnosis, and surgery and radiotherapy were carried out at the same institution, we believe that comparison of the two groups is possible.

Treatment

The surgical and postoperative management of the patients in each group was comparable and carried out in the same neurosurgical department. Most of the patients had internal decompression by gross total orsubtotal tumor resection. A needle biopsy specimen was obtained in only one patient in the combined treatment group.

Both groups received radiation therapy at our institution, beginning 2 to 4 weeks after surgery. All the patients irradiated before 1973 received fast-electron therapy, ranging from 25 to 35 MeV, applied with a rotating electron beam. The dose covering the entire tumor volume was 6000 to 6400 rads. In the combined therapy group the total brain was first covered with two to four fields with cobalt-60 to a dose of 5000 rads, and then with the rotating electron beam of the betatron (25 to 35 MeV); the dose of the tumor volume alone amounted to 6400 to 6800 rads. The tumor volume of all patients in both groups was covered with a dose of 6000 to 6800 rads.

In both groups, dexamethasone was used routinely in the pre- and postoperative periods and discontinued 10 to 14 days after surgery. Only four patients in the chemotherapy group required a maintenance dose of 1 to 2 mg/day to control neurological manifestations or raised intracranial pressure. In all other patients in both groups, dexamethasone was resumed only to control recurrent symptoms and was maintained in a dose of 2 to 6 mg/day until further deterioration or death occurred.

Induction chemotherapy consisted of CCNU, procarbazine, and bleomycin (Fig. 1). Three patients who did not tolerate procarbazine well received CCNU, 130 mg/sq m. Because of side effects, bleomycin had to be reduced in some patients; dosage ranged from 105 to 225 mg per patient with a mean dose of 163.7 mg.

Maintenance chemotherapy consisted of CCNU, 130 mg/sq m, administered orally every 6 to 8 weeks depending on the blood count, beginning 4 weeks after the end of the second course of procarbazine (Fig. 1). In recurrent cases, steroids were resumed and CCNU continued, because if recurrence was early the treatment with CCNU was not thought to be adequate. The chemotherapy was stopped if there was clearly further deterioration of clinical status and brain scan after two doses of CCNU. If there was only slow progression, CCNU was continued as long as the patient was able to return to the outpatient clinic. It was stopped after 1 year if the patient's neurological status and brain scan remained normal or stationary.
Radiation with chemotherapy in high-grade astrocytomas

![Diagram](image)

**Radiation Therapy**

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**Weeks after surgery**

Fig. 1. Administration schedule of CCNU, procarbazine, and bleomycin combined with radiation therapy. White circle = CCNU, 75 mg/sq m; black circle = CCNU, 130 mg/sq m, every 6 to 8 weeks; open box = procarbazine, 100 mg/sq m, daily for 2 weeks; comma = bleomycin, 15 mg intramuscularly.

Follow-up studies of the patients who received chemotherapy involved a neurological examination on each return visit and close communication with their general practitioners. Blood counts were done before each course of chemotherapy and at least every 2 weeks. Brain scans were performed at the end of the irradiation and induction chemotherapy, and later on an individual basis as indicated by a change in clinical status. Follow-up data from the control group were collected by means of a questionnaire sent to the patient’s family or his general practitioner, and from the record of the outpatient clinic. At the time of this report all patients had been followed for at least 24 months after operation.

**Results**

**Survival**

Survival time from operation until death was used as a clinical parameter to investigate the effect of the adjuvant treatment after surgery. The survival curves were calculated by computer analysis according to the method of Kaplan and Meier (Fig. 2). The median survival was 56 weeks for the combined treatment group and 51 weeks for the control group. At 18 months after operation, eight (40%) of the combined treatment patients and nine (28.1%) of the control patients were alive. There was no statistical difference in survival between the two groups of patients.

**Performance Status**

The general performance status of the combined treatment group is summarized in Table 2. Because clinical grading of the control group was not possible in all cases retrospectively, only patients who were partially or fully able to work again after therapy were...
TABLE 2
Performance status of chemotherapy group
(20 patients)

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<th>Clinical Grade</th>
<th>Criteria</th>
<th>No. of Cases 3 mos</th>
<th>No. of Cases 18 mos</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Postop</td>
<td>Postop</td>
</tr>
<tr>
<td>0</td>
<td>fully active</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>ambulatory, capable of light work</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>in bed under 50% capable of self-care</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>in bed over 50% limited self-care</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>bedridden</td>
<td>2</td>
<td>2</td>
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compared with the two groups. Six (30%) of the patients treated with the combined treatment, and 11 (34.3%) of the control patients were again capable of work 3 months after surgery.

Toxicity

Toxicity to CCNU was mild and essentially hematological. Only two patients had a drop in platelet counts below 50,000 and of leucocytes below 2000, both in combination with procarbazine and radiation therapy.

Three patients were unable to tolerate procarbazine, two because of uncontrollable vomiting, and one because of an allergic skin reaction. In addition to hematological toxicity in combination with CCNU and radiation therapy, there was one patient with a temporal lobe tumor who showed a psychotic reaction which could be controlled with chlorpromazine. Bleomycin showed the greatest toxicity and had to be discontinued in eight patients, in two because of hyperthermia after drug injection, and in six because of skin reactions. There were no deaths from drug toxicity.

Discussion

Studies have shown that CCNU is effective in recurrent gliomas, but the combination of 1, 3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and procarbazine as chemotherapy for recurrent tumors showed no advantage over each agent used alone. In tissue-culture studies, bleomycin was only slightly active against malignant glial cells, but very toxic against normal cells. In subcutaneously transplanted gliomas in mice significant anti-tumor activity was demonstrated only with large doses of bleomycin. Takeuchi reported effectiveness of bleomycin in the postoperative adjuvant treatment of malignant brain tumors in an uncontrolled study, but he was unable to demonstrate in a more recent paper any difference in survival rate in patients treated or untreated with bleomycin.

In our series, there was no significant difference in the survival of patients who received radiation therapy alone or in combination with CCNU, procarbazine, and bleomycin. For both groups the median survival times were comparable to the survival times of selected patients treated with surgery and radiation alone or in combination with CCNU reported in the literature. The results of our study agree with reports that CCNU and bleomycin have no significant effect when used as an adjunct to radiation therapy. The toxicity of bleomycin was severe; otherwise the chemotherapy was well tolerated, and no patient died from drug toxicity. There was also no difference in general performance status between the two groups 3 months after surgery.

Summary

The survival of patients with supratentorial high-grade astrocytomas treated by postoperative radiation therapy in combination with CCNU, procarbazine, and bleomycin was not significantly longer than the survival of patients treated with postoperative radiotherapy alone.

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References

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