Controlled study of CCNU and radiation therapy in malignant astrocytoma

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The authors report 63 patients with biopsy-proved malignant (Grades 3 and 4) astrocytomas who were randomly placed in one of three treatment schedules within 2 weeks of surgery. One group (22 patients) received radiation therapy alone; the second group (22 patients) received 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) orally at intervals of 8 weeks; and the third group (19 patients) received combined radiation and drug therapy. Patients who received radiation therapy, with or without the drug, had a significantly longer survival than did those who received the drug alone. There was no difference in survival between the two groups who received radiation. The nitrosourea derivative CCNU does not seem to be an effective agent in the therapy of primary malignant brain tumors.

KEY WORDS · malignant astrocytoma · glioblastoma multiforme · CCNU · nitrosourea · radiation therapy

The poor prognosis for survival of patients with glioblastoma multiforme (astrocytoma Grades 3 and 4) has been well documented in the literature. Direct comparison of statistical data from different institutions, or even from one institution at different times, is of questionable validity for a number of reasons. These include variations in patient selection, diagnostic criteria, surgical and postoperative management, and methods of collecting and presenting the statistical data. The evaluation of any new therapeutic modality requires that these variables be controlled if small but perhaps significant effects of the treatment on prognosis are to be detected.

Chemotherapy has been employed in the treatment of glioblastoma for more than two decades. The literature relating to this subject has been thoroughly reviewed through 1968 by Shapiro and Ausman.9 Despite encouraging comments by some investigators, there is no supportable evidence that any agent, administered by any method or route, improves the life expectancy or quality of survival in these patients as compared with patients treated by the conventional modes of surgery and postoperative radiation.

To our knowledge, this is the first randomized controlled study that compares the effect of a chemotherapeutic agent with conventional therapy carried out at one institu-
tion. The agent used was 1-(2-chloroethyl)-3-
cyclohexyl-1-nitrosourea (CCNU) (NSC 79037), a lipid-soluble compound that
probably acts as an alkylating agent. It has
been shown to be effective against experi-
mental murine gliomas of various types, and some
preliminary but uncontrolled studies in
human patients have suggested that the drug
is active against glioblastoma multiforme.

Clinical Material

Selection of Patients

The study was designed as a controlled ran-
domized study of the relative effects of three
treatment programs on a uniform group of
patients with supratentorial astrocytomas of
Grades 3 and 4. Patients were selected from
among those with pathologically confirmed
tumors who were operated on at the Mayo
Clinic between November, 1970, and
December, 1972. In addition to pathological
confirmation of the tumor, patients were in-
cluded in the study only if their mental and
physical conditions permitted them to under-
stand and to carry out the requirements of the
study and if there was no evidence of other
serious illness.

When a patient met these criteria and con-
ented to participate in the study, the treat-
ment program was selected by a random
procedure. Therapy was started within 2
weeks of surgery. The three treatment
programs were radiation therapy alone,
chemotherapy alone, and combined radiation
and chemotherapy.

A total of 75 patients were randomized in
the study. Of the 75 patients, 12 were ex-
cluded from analysis because of major
protocol violations (2 had incorrect diagnoses
and 10 failed to receive the designated
therapy). Data on the remaining 63 patients
form the basis of this report. Radiation
therapy alone was given to 22 patients, 22
received CCNU alone, and 19 received com-
combined therapy.

Treatment

The two groups receiving radiation therapy
were encouraged to receive their therapy at
our institution in order to ensure a uniform
treatment program. All but seven of the 41
patients in these groups did so. These patients
received whole-brain irradiation which used
supervoltage equipment (60Co or 4- or 6-MeV
linear accelerators). A midplane dose of 5000
rads was delivered in 25 to 28 fractions over
30 to 39 days by parallel opposed lateral
fields.

The two groups who received chemo-
therapy were given an initial dose of CCNU,
130 mg/m² by mouth, preceded by an anti-
emetic. This dose was repeated at intervals of
8 weeks for as long as the patient was able to
return to our clinic, unless a reduction in
dosage was dictated by persistent myelo-
suppression.

Follow-up involved a neurological ex-
amination at each return visit as well as close
communication with the patient, his family,
and his home physician. Patients receiving
CCNU were given a letter for their local
physician after each course of therapy which
requested that leukocyte and platelet counts
be taken at weekly intervals. The patient
brought the results of these tests with him at
each return visit. Other laboratory or special
clinical investigations were performed as in-
dicated on an individual basis.

The surgical and immediate postoperative
management of the patients in each group
was comparable. Most of the patients had a
subtotal tumor resection, with some gross
evidence remaining of tumor. Gross total
resection was achieved in seven cases, and
only a biopsy specimen was obtained in eight.
Most of the patients in each group received
dexamethasone for the first 7 to 10 post-
operative days. Only four patients received
dexamethasone for longer than 2 weeks—the
longest period was 50 days.

Follow-up was maintained on all 63
patients. Sixty-one patients had died by
April, 1975. The two who were still alive had
survived longer than any of the others (29 and
36 months as of last scheduled observations).
Four patients had received additional therapy
because of evidence of tumor recurrence some
months after their initial treatment program:
three underwent reoperation at 7, 12, and 14
months, and one had begun procarbazine
therapy at 5 months. In the analysis of data,
these four patients were included and ex-
cluded, in order to determine if their data
were crucial to the findings.

Pathological follow-up was incomplete.
Four patients died at our institution, and
complete postmortem examinations were ob-
ained. The brain, or portions of it, was ob-
tained in four other cases in which autopsies were done elsewhere.

Results

Treatment Groups

Radiation Therapy Alone. Of the 22 patients in the group receiving radiation therapy alone, 15 were treated at our institution and seven received documented courses of radiation at other centers. The patients ranged in age from 31 to 70 years, with a mean of 52.3 years. One patient was alive at 36 months after surgery. Postoperative survival of the remaining patients ranged from 2.7 to 25.1 months. The median survival was 11.5 months, and the mean was 13.8 months. Assessment of the course of the neurological disability was more difficult in this group because the patients did not have the same motivation to return for periodic examinations as did the patients who were given the drug. However, an evaluation of the quality of survival, in terms of either return to gainful employment or enjoyment of active recreational activities, was possible for 16 patients. Of these, four had no period of good-quality survival. The other 12 patients had 3 to 22 months of useful survival before a recurrence or an increase in neurological deficit forced them to abandon productive or enjoyable activity. The median time was 7 months.

Chemotherapy Alone. The 22 patients who received chemotherapy alone ranged in age from 22 to 70 years, with a mean of 53 years. The number of courses of CCNU given to these patients ranged from one to eight, with an average of 3.4. One patient in this group was alive 29 months after surgery. Postoperative survival of the remaining 21 patients ranged from 1.4 to 24.9 months. The median survival was 6.6 months, and the mean was 9.1 months. An assessment of the quality of survival was possible for 21 of these patients. Five had no period of useful activity after surgery. The period of good-quality survival in the remaining 16 ranged from 2 to 21 months. The median period of good-quality survival was 4 months.

Combined Radiation and Chemotherapy. The ages of the 19 patients in this group ranged from 45 to 77 years, with a mean of 58 years. All 19 received their radiation therapy at our institution. The number of courses of CCNU administered to these patients ranged from one to 10, with an average of 3.4. None of these patients was alive at the end of 1974. Survival ranged from 1.9 to 28.7 months after operation, with a median survival of 12.0 months and a mean of 12.7 months. Five patients had no period of good-quality survival. The period of useful survival in the remaining 14 ranged from 4 to 25 months, with a median of 7 months.

Statistical Analysis of Survival Time

A description of the survival of patients under the three treatments has been shown in summary form in Table 1 and Fig. 1. Statistical significance was determined by rank-sum tests because of the wide departure of the data from the normal distribution. In general, the results are as follows: the group of patients who received chemotherapy without radiation survived for a statistically significant shorter time (p = 0.02) than did the group that received radiation alone or the group that received radiation and chemotherapy. The latter two groups had survivals that did not differ significantly.

The data, excluding the three patients who underwent reoperation and the one patient who received procarbazine, were analyzed. The statistical results were the same; that is, a significantly shorter survival was noted for patients who were not irradiated.

Further exclusions were also made. Only patients described by the operating surgeon as having subtotal resections were included. The results then became inconclusive. Although the two radiation groups appeared to have a better survival than did the group that received chemotherapy alone, there was no statistical significance (p = 0.10). This last result suggests the loss of ability to detect real differences because of reduction in sample size.

Drug Toxicity

The most consistently observed side effect was that of gastrointestinal toxicity. All patients experienced some nausea, and many vomited. The nausea was always of short duration, and it usually disappeared the day after treatment. Various antiemetics were employed, but none was uniformly effective in preventing nausea and vomiting. Hematopoietic toxicity was frequently encountered. Leukocyte counts of less than 3000/mm³
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were found in 24 of 41 patients (59%), and in this same group, platelet counts of less than 100,000/mm³ were found in 35 patients (85%). No complications of infection or bleeding were seen as a result of leukopenia or thrombocytopenia. We did not consider hematopoietic toxicity as a contraindication to continued drug therapy, although in a few patients who had significant hematopoietic depression, the subsequent dosage schedule was reduced slightly.

Discussion

In experimental trials, CCNU has been effective in significantly increasing the duration of survival of mice with intracerebrally implanted, carcinogen-induced ependymoblastoma, glioma 261, and glioma 26.5 In addition, preliminary uncontrolled clinical trials have suggested that the drug has some activity against malignant gliomas in humans. Hansen and Muggia² noted “dramatic responses” in three of six bedridden patients who had astrocytomas of Grades 3 and 4. Rosenblum, et al.² treated 26 patients who had various brain tumors, including 17 patients with glioblastoma multiforme. In their series, the time from diagnosis to the start of drug therapy ranged from 1 to 31.5 months, with a mean of 5.3 months. Of the 17 patients, four showed improvement of symptoms and signs after the initial course of CCNU. Seven of the 17 patients were alive at the time of the study 8 to 44½ months after initial surgery. Ten patients died between 6.5 and 19 months after operation, with a mean survival of 10.2 months. Two of the patients who were alive and four of the patients who died also had received radiation therapy. Thus, the experimental and initial clinical trials with this drug indicated that a controlled study of its clinical usefulness was warranted.

In our series, there was no significant difference in the survival of patients who received radiation therapy with or without the drug (Table 1). The median survival times for these two groups were comparable to the survival times of patients treated with surgery and radiation reported in the literature. At 6 months after operation, the proportion surviving (55%) among patients treated with CCNU alone was significantly (p < 0.05) less than the proportion surviving among patients treated by radiation alone (86%) or patients

![Fig. 1. Probability of survival by months after start of treatment among 63 patients with supratentorial astrocytomas of Grades 3 and 4 who were treated with CCNU, radiation, or a combination of CCNU and radiation.](image-url)
treated by the combination of radiation and CCNU (84%).

The results of our study do not support the hypothesis that CCNU has any significant antitumor effect in patients with malignant astrocytoma, when used either alone or as an adjunct to radiation therapy. Although the 1-year survival rate of 18% in the group treated by the drug alone is slightly better than the results of surgery alone reported in the literature, we had a highly selected group of patients who were likely to survive the first few postoperative months with no additional therapy. Despite these negative results, nitrosourea compounds remain, on theoretical and experimental grounds, among the most promising chemotherapeutic agents against neoplasms of the central nervous system. Two other nitrosoureas, methyl-CCNU and BCNU (1, 3-bis(2-chloroethyl)-1-nitrosourea), are currently being evaluated in a national cooperative study.

References

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