Intra-arterial ACNU and Cisplatin Chemotherapy for the Treatment of Glioblastoma Multiforme

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Abstract

Intra-arterial (IA) chemotherapy has achieved no obvious clinical superiority as a treatment for glioblastoma multiforme despite the many theoretical advantages. The clinical courses of 38 patients who underwent surgery and radiotherapy with IA 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU) and cisplatin were reviewed. Tumor regrowth was evaluated by comparison of contrast-enhanced areas on computed tomographic scans. The initial response rate was 19 of 32 patients evaluated, and the median survival time (MST) for all 38 patients was 53 weeks. Local recurrence was observed in 20 patients, and distant recurrence (areas more than 3 cm from the original tumor margin) was observed in 15 patients. The MST was 59 weeks for patients without distant recurrence, and 42 weeks for patients with distant recurrence (statistically not significant). Adjuvant IA ACNU and cisplatin chemotherapy did not improve the survival time. An important clinical feature was the high incidence of distant recurrence, in contrast to experience with other conventional therapy regimens. Distant recurrence, without extended survival, may suggest insufficient control of tumor regrowth.

Key words: glioblastoma, tumor recurrence, ACNU, cisplatin, intra-arterial chemotherapy

Introduction

Glioblastoma is the most malignant primary brain tumor and is presently considered incurable. Patients treated with both surgery and radiotherapy survive for approximately 10 months, and adjuvant chemotherapy with nitrosourea-based regimens achieves a median survival time (MST) of 1 year.14,24,25 However, this improvement is not common to all patients, and is statistically insignificant.25 The limited effect of chemotherapy for glioblastoma is probably partly due to poor delivery of the agents to the tumor.

Experimental and clinical evidence suggests that higher concentrations of drugs may be achieved in tumors by regional chemotherapy based on intra-arterial (IA) drug infusion.4,5,12,13,15,27,28 The relatively short half-life of nitrosoureas provides a rationale for the first-pass benefit of IA infusion. The results of several non-randomized trials have indicated clinical efficacy of IA chemotherapy using nitrosoureas or cisplatin.5,9,12,18,21,28 However, there has been no proof of the clinical superiority of IA chemotherapy over conventional chemotherapy.23 The effect of central neurotoxicity, a major toxic complication of IA chemotherapy, has not been considered on the survival times, so the reasons for the discrepancy between the theoretical advantages and the disappointing clinical results are still unknown.19,23

This retrospective review attempted to clarify the clinical course of patients treated with IA chemotherapy using 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU) and cisplatin to assess the possible complications.

Clinical Materials and Methods

I. Patient population

Thirty-eight consecutive patients with a histological diagnosis of supratentorial glioblastoma...
multiforme were treated with surgery, radiotherapy, and IA ACNU and cisplatin between January, 1983 and December, 1992. The mean age at diagnosis was 46 years (range 16-70 yrs). The mean preoperative Karnofsky performance status (KPS) score was 76 (range 30-100). Two patients had multiple gliomas at diagnosis. All patients with newly diagnosed glioblastoma multiforme were treated according to the protocol described below. Informed consent was obtained from each patient or guardian.

II. Treatment protocol
Radiotherapy was begun within 2 weeks of maximum surgical removal of the tumor. Local irradiation of 60 Gy in 30 fractions, given 5 days a week over 6 weeks, was delivered to a target volume encompassing the tumor plus a 3-cm margin. Alternatively, whole brain irradiation of 40 Gy in 23 fractions was followed by an additional 20 Gy local brain irradiation. The first IA chemotherapy course was performed within 2 weeks of initiation of the radiotherapy. The main feeding artery was identified by computed tomography (CT), magnetic resonance (MR) imaging, or angiography. The ipsilateral internal carotid artery (ICA) was catheterized using the Seldinger method. ACNU (100 mg in 50 ml of physiological saline) was injected at 20 mg/min. Cisplatin (100 mg) was then injected at 20 mg/min. If the tumor was located in the posterior portion of the cerebral hemisphere and partly supplied by the vertebral artery, the ACNU dosage was delivered equally via the ICA and the vertebral artery. Cisplatin was only infused into the ICA because of the potential ototoxic effect when infused into the vertebral artery. This IA chemotherapy regimen was administered a total of three times at 6-week intervals.

III. Evaluation methods
The initial effect of the therapy was evaluated by the change in tumor volume between CT scans obtained postoperatively and 1 month after completion of the first IA chemotherapy. The tumor volume was calculated from the area of enhancement after intravenous administration of contrast material. The responses were classified as complete response (CR), disappearance of the tumor; partial response (PR), a greater than 50% reduction in tumor volume; no change (NC), a less than 50% reduction or less than 25% increase in tumor volume; and progressive disease (PD), a greater than 25% increase in the tumor volume.

Follow-up CT scans were obtained at least every 2 months after completion of the first IA chemotheraphy and radiotherapy. Recurrence was defined as an increase in the contrast-enhanced tumor volume on any follow-up CT scans compared to the postoperative and pre-(radio)chemotherapy contrast-enhanced tumor volume. The location of the tumor was transferred onto tracing paper to compare the pre- and post-treatment tumor locations. We attempted to avoid variation in observer interpretation of tumor volume by having one person perform all tracing in a consistent pattern. All CT scans were investigated randomly by number instead of name, so that initial and recurrence scans from individual patients were not traced sequentially.

The pattern of recurrence was classified into local recurrence and distant recurrence. Local recurrence was defined as tumor regrowth located within 3 cm of the original area of contrast enhancement, including extension outside the 3-cm margin. Distant recurrence was defined as tumor regrowth exclusively outside the 3-cm margin of the original tumor. All evaluations were based on CT scans to provide data comparable to previous studies. However, MR imaging offers more accurate information about tumor location, and was used when available for supplementary evaluation of recurrence. When tumor growth was defined as distant recurrence on CT scans but as local recurrence by MR imaging, the tumor recurrence was classified as local recurrence.

The interval between surgery and the detection of recurrence by CT (time to tumor progression: TTP) was also obtained. The period of survival was the interval between surgery and either death of the patient or termination of this review (June 30, 1993). Data for all 38 patients were subjected to Kaplan-Meier analysis to obtain a survival curve.

IV. Evaluation of complications
The major complications caused by IA chemotherapy are ocular toxicity, encephalopathy, and myelosuppression. Ocular toxicity manifests as complete or partial loss of vision. Encephalopathy is characterized by neurological deterioration several months after IA chemotherapy, with hypodense areas on CT scans in the white matter of the infused territory. The relationship between tumor recurrence and encephalopathy is always difficult to determine, but non-progressive neurological deterioration not accompanied by an enlarged contrast-enhanced area is probably mainly due to encephalopathy. Myelosuppression is clinically significant when the white blood cell count is under 3000 cells/mm³ or the platelet count is under 70,000 cells/mm³.
Results

I. Initial CT response
Six patients could not be evaluated because the postoperative and pre-(radio)chemotherapy CT scan did not reveal a residual tumor. Evaluation in 32 patients found CR in eight patients, PR in 11, NC in 10, and PD in three. The total response rate was 19/32 patients.

II. Patterns of recurrence
At the end of the study, three patients had no recurrence and were still alive. Local recurrence was seen in 20 patients with a TTP of 30 weeks. Distant recurrence had occurred in 15 patients, with a TTP of 36 weeks. Patients with distant recurrence had abnormal enhancement in the ventricular wall and cortical sulci in seven cases, which indicated cerebrospinal fluid dissemination. Representative cases of distant recurrence are shown in Figs. 1 and 2. Distant recurrence was observed in two of nine patients treated with whole brain irradiation and in 13 of 29 patients treated with local irradiation. Eleven of the 15 patients with distant recurrence had lesions in areas into which chemotherapeutic agents had not been infused, while the other four patients had lesions within the infused areas.

III. Survival time
The survival curve for all 38 patients is shown in Fig. 3 upper. The MST was 53 weeks, and the 18-month survival rate was 42%. The MST for the subgroup without distant recurrence was 59 weeks.
while the subgroup with distant recurrence had a MST of 42 weeks. The log-rank test showed that the MST difference was not statistically significant (Fig. 3 lower). There were no statistically significant differences in age, sex, preoperative KPS score, extent of surgery, or irradiation field between the two subgroups (Table 1).

Table 1 Comparison of patients with and without distant recurrence

<table>
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<th>Characteristics</th>
<th>Distant recurrence</th>
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<tr>
<td>No. of cases</td>
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<td>Age (yrs):</td>
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<td>mean range</td>
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There were no significant differences between the two groups in any characteristic.

while the subgroup with distant recurrence had a MST of 42 weeks. The log-rank test showed that the MST difference was not statistically significant (Fig. 3 lower). There were no statistically significant differences in age, sex, preoperative KPS score, extent of surgery, or irradiation field between the two subgroups (Table 1).

IV. Complications

Ocular toxicity was not encountered in the present series, although mild to moderate eye pain with conjunctival hyperemia was observed in nearly all patients. Encephalopathy was encountered in two patients who were both long-term survivors beyond 18 months. Myelosuppression was observed in nine patients, requiring delays in subsequent chemotherapy courses for intervals of up to 7–9 weeks. No clinically significant ototoxicity or nephrotoxicity was encountered. No seizures were observed within 24 hours of chemotherapy.

Discussion

In the present study, adjuvant IA ACNU and cisplatin chemotherapy achieved a favorable CT response rate when compared with reported rates in patients treated with radiotherapy and conventional intravenous (IV) chemotherapy. However, the MST was only 53 weeks, little more than those recorded with the conventional therapy regimens. Similar disappointing results with IA chemotherapy for supratentorial malignant gliomas were reported by the Brain Tumor Cooperative Group, which suggested a rather worse survival rate in the IA group than the IV group. Encephalopathy, the well-known toxic complication of IA chemotherapy, did not affect survival times, as 13 of the 155 patients (8%) who developed significant encephalopathy following IA chemotherapy using 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) had the same survival rate as the total patient group. IA ACNU and IA cisplatin have also been reported to cause encephalopathy, but these drugs are less toxic than BCNU when used via the IA route. The incidence of encephalopathy in our series was acceptably low.

We found that 15 of the 38 patients suffered distant recurrence outside the 3-cm margin of the original tumors. In general, recurrence of glioblastoma after radiotherapy with or without conventional chemotherapy has been found to be overwhelmingly local and continuous with the surgical bed. Encephalopathy, the well-known toxic complication of IA chemotherapy, did not affect survival times, as 13 of the 155 patients (8%) who developed significant encephalopathy following IA chemotherapy using 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) had the same survival rate as the total patient group. IA ACNU and IA cisplatin have also been reported to cause encephalopathy, but these drugs are less toxic than BCNU when used via the IA route. The incidence of encephalopathy in our series was acceptably low.

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An increased incidence of distant recurrence associated with effective local control of tumor regrowth has also been noted in malignant gliomas following brachytherapy. In these cases, dissemination of disease beyond the local tumor often developed in patients with prolonged survival. Since glioblastoma is a highly invasive tumor, any area of the brain tissue can harbor isolated tumor cells in advanced stages of
the disease.\textsuperscript{2,22}} Good control of local tumor regrowth can be expected to result in longer survival times because the isolated tumor cells will take a relatively long time before developing to a symptomatic tumor. However, the present results showed that there is no difference in survival times between the two groups with and without distant recurrence. The development of distant recurrence without an associated longer survival time suggests that IA chemotherapy cannot control either local or distant tumor regrowth. Glioblastoma is refractory to chemotherapy and cisplatin, even as part of an IA chemotherapy regimen.

References


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