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CLINICAL TRIAL REPORT

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High-dose carmustine for high-grade gliomas in childhood

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Abstract Carmustine (BCNU) has proved to be of value against a variety of primary brain tumors. This agent exhibits a steep dose-response curve in in vitro and animal tumor models and has been proposed for use in high-dose chemotherapy as a single agent or in combination. We conducted a phase II study to assess high-dose BCNU in children with high-grade gliomas. A total of 13 children with high-grade gliomas were treated in a phase II study using high-dose BCNU (800 mg/m^2) followed by autologous bone marrow transplantation. Eight patients were newly diagnosed, and five were treated at the time of tumor recurrence. Seven patients had diffuse intrinsic brain-stem gliomas. The response was assessed at 1 month after treatment. Only one objective effect was observed. Five patients had stable disease and seven progressed. The immediate toxicity was mild; however, one patient developed fatal respiratory distress at 50 days after treatment with high-dose BCNU. Dose escalation of BCNU does not seem beneficial in children with high-grade gliomas.

Key words BCNU · Autologous bone marrow transplantation · Child · High-grade glioma.

The present work was done at the Centre Léon Bérard, Lyon, France

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Introduction

Chemotherapy has a questionable role in the management of high-grade glioma [12, 21]. Despite reports of some objective responses to treatment with various agents, the overall lack of success with conventional chemotherapy has led a number of investigators to assess the efficacy of high-dose chemotherapy in adult high-grade glioma [1, 2, 6, 9, 15, 16, 19, 20, 22, 25]. Carmustine (BCNU), a lipid-soluble nitrosourea, easily crosses the blood-brain barrier and has proved to be of value against a variety of primary brain tumors. This agent exhibits a steep dose-response curve in in vitro and animal tumor models. In conventional therapy with carmustine at doses of up to 200 mg/m^2 every 6–8 weeks, myelosuppression is the dose-limiting toxicity [24]. Using autologous bone marrow rescue, phase I studies in adult patients have defined a maximum tolerable dose of 800–1000 mg/m^2 [19]. High-dose chemotherapy using BCNU has been less well investigated in children. At our institution we therefore undertook a phase II study of high-dose BCNU in children with high-grade gliomas.

Patients and methods

A total of 13 patients were entered into this study. Prior to bone marrow harvest and chemotherapy, informed consent was obtained from the parents. The patients' characteristics are listed in Table 1. There were seven boys and six girls, whose ages ranged from 17 months to 16 years (median 6 years). Nine patients had infratentorial tumors (eight in the brain stem and one in the posterior fossa), and four had supratentorial tumors (two parietal and two thalamic). Only six patients had histologically proven high-grade glioma, since seven patients with diffuse intrinsic brainstem tumors had not undergone biopsies. Among those in which histology was undertaken there were four WHO grade III gliomas and two grade IV tumors (glioblastoma multiforme). Surgery was partial in all six patients.

Of the 13 patients, 5 had previously been treated; all 5 had received chemotherapy and 3 had undergone radiation therapy, and all had progressed before receiving high-dose BCNU. Two of the five patients who had received chemotherapy following surgery experienced neurological deterioration that required increasing doses of

Table 1 Patients' characteristics (*NA* Not applicable, *VM* tenoposide, *CDDP* cisplatin, *FU* 5-fluorouracil, *DTIC* dacarbazine, *CPM* cyclophosphamide, *PCZ* procarbazine, *XRT* radiotherapy, *OE* objective effect, *SD* stable disease, *PD* progressive disease, *DOD* dead of disease, *TD* toxic death)

Patient number	Sex/age (years)	Tumor location	Grade	Previous therapy	Landsky scale	Response to BCNU	Additional therapy	Outcome
1	F/2	Thalamus	3	Partial surgery	80	OE	XRT	TD 50 days
2	F/7	Brain stem	NA		60	PD	XRT	DOD 6 months
3	M/9	Parietal	3	Partial surgery	60	SD	XRT	DOD 20 months
4	M/1.5	Brain stem	NA		60	SD		DOD 4 months
5	M/5	Cerebellum	4	Partial surgery	90	PD	XRT	DOD 2 months
6	M/16	Brain stem	3	Partial surgery	90	SD	XRT	DOD 70 months
7	F/5	Brain stem	NA		80	PD	XRT	DOD 10 months
8	F/6	Brain stem	NA		60	SD	XRT	DOD 11 months
9	F/14	Parieto-occipital	4	Partial surgery VM-BCNU-PCZ	40	PD		DOD 12 days
10	M/3	Brain stem	NA	XRT VM-BCNU-PCZ	60	PD		DOD 4 months
11	F/7	Brain stem	NA	XRT VM-CDDP-FU-DTIC-CPM-PCZ	50	PD		DOD 17 days
12	M/6	Brain stem	NA	XRT VM-CDDP-FU-DTIC-CPM-PCZ	70	SD		DOD 11 months
13	M/5	Thalamus	3	Partial surgery VM-BCNU-PCZ	80	PD	XRT	DOD 3 months

steroids. Computerized tomography (CT) scans confirmed tumor progression. The remaining three patients presented with progressive neurological impairment and imaging evidence of progressive disease. Eight patients entered the study at the time of diagnosis (four patients had primary surgery and four had diffuse intrinsic brain-stem glioma). All patients had measurable disease. The postoperative tumor volume was assessed by early CT scan within 72 h following surgery in two patients. In the remaining two postoperative patients the tumor assessment was performed at 28 and 45 days after surgery, respectively. The performance status at the time of study entry was assessed according to the Lansky scale [11] and ranged from 40 to 90 (median 60).

All patients received 800 mg/m^2 of BCNU in a 30-min infusion. Bone marrow was harvested the day before BCNU infusion and was reinfused 2 days after drug administration. The median number of mononucleated cells reinfused was 1.36×10^8/kg (range $0.69-2.61\times10^8$/kg), and the median number of granulocyte/macrophage colony-forming units (CFU-GMs) reinfused was 4.3×10^4/kg (range $0.8-18\times 10^4$/kg). Patients were then either ambulatory or in hospital according to their neurological status, with a full blood count being performed three times a week. Platelets were transfused at a platelet count below 20×10^9/l, and red blood cells were transfused at a hemoglobin level below 8 g/dl.

Assessment of the response was based upon CT or magnetic resonance imaging (MRI) scans, corticosteroid requirements, and neurological evaluation according to the Macdonald criteria [13]. Radiological evaluation took into account the volume of the tumor and the peritumoral odema as well as the presence and the extent of contrast enhancement. A complete response (CR) was defined as the disappearance of all visible tumor, no steroid requirement, an increased or stable Karnofsky scale, and neurological stability or improvement. A partial response (PR) was defined as a decrease of $>50\%$ in tumor size, a stabilization of or reduction in the corticosteroid dose, an increased or stable Karnofsky scale, and neurological stability or improvement. An objective response was defined as a tumor mass reduction of between 25% and 50%, a stabilization of or reduction in the corticosteroid dose, an increased or stable Karnofsky scale, and neurological stability or improvement. Progressive disease (PD) was defined as an increase of $>25\%$ in tumor size or the appearance of any new tumor on any subsequent scan, a stabilization of or increase in the corticosteroid dose, a decreased or stable Karnofsky scale, and neurological stability or deterioration. All other situations were defined as stable disease (SD). Evaluation of the response to therapy was assessed at 1 month after treatment with high-dose BCNU by clinical examination, CT or MRI scan, and corticosteroid requirement.

Results

In all, 11 of the patients who entered the study were evaluable for response and toxicity. Two patients died early (days 12 and 17, respectively) following BCNU therapy. Both presented with progressive neurological deterioration despite increasing doses of steroids. A CT scan performed prior to death in both cases revealed marked peritumoral odema with evidence of tumor progression. Both patients developed pneumonia that was more likely to be secondary to swallowing disturbances than to specific BCNU toxicity. No autopsy was performed. One patient improved clinically and had an objective response as assessed by CT scan. All other patients had either SD (five patients) or tumor progression (five patients). Eight patients received radiotherapy following high-dose BCNU treatment. The median survival time after BCNU infusion was 4 months (range 12 days to 60 months). Only two patients survived for over 1 year; both had grade III glioma and had undergone partial surgery and additional radiation therapy.

The immediate toxicity was mainly gastrointestinal, with nausea occuring in all 11 patients and grade II vomiting, in 6. Two patients developed a cutaneous rash immediately following BCNU treatment which lasted for 24 h. One patient showed a transient increase in gamma-glutamyl transpeptidase (γGT) without displaying any clinical or biological sign of liver failure.

The hematological toxicity was moderate. Seven patients had grade III–IV neutropenia and three each developed grade III and grade IV thrombocytopenia, respectively. Three patients required platelet transfusion and three required transfusion of red blood cells. Two patients developed neutropenic fever requiring antibiotics. One patient died at 50 days after BCNU infusion of progressive respiratory failure. No autopsy was performed.

Discussion

Encouraging results have been obtained through high-dose chemotherapy in various pediatric and adult malignancies [10, 23]. However, most of these tumors also respond to conventional chemotherapy. The most complex problem concerning glioma is the paucity of drugs known to be active against it. The failure of conventional-dose chemotherapy to improve the outcome of patients with high-grade brain tumors has led several investigators to use high-dose chemotherapy in an attempt to overcome the limited benefit seen with conventional-dose therapy, which is due to intrinsic drug resistance as well as the impermeability of the blood-brain barrier. Since nitrosoureas at conventional doses have had a slight effect in phase II studies, dose escalation seemed a promising concept. BCNU is currently the single most effective chemotherapeutic agent in malignant glioma. At conventional doses it provides a small, statistically significant prolongation of survival [3].

The dose escalation of BCNU is limited by myelosuppression. However, the BCNU dose can be increased up to 1000 mg/m^2 when it is given with autologous bone marrow transplantation. More than 200 adult patients with high-grade gliomas have been treated using high-dose BCNU followed by bone marrow rescue. Response rates range from 18% to 60% [1, 2, 6, 9, 10, 15, 16, 19, 20, 22, 25]. Despite these encouraging results, the potential benefit of this procedure remains unclear, since most patients included in these studies were highly selected. This selection bias may explain to a large extent the inconclusiveness of the efficacy of high-dose chemotherapy, since favorable prognostic factors (age, histology, extent of surgery, performance status) in adult patients with gliomas account for significant differences of as much as 2–3 orders of magnitude in survival time [21]. Morbidity of high-dose BCNU has been reported and seems to be enhanced by escalation of the dose. The toxic death rate in adult studies ranges from 5% to 10% and includes infectious complications as well as specific drug-related toxicities such as fatal interstitial pneumonitis, hepatic failure, and progressive neurological deterioration [9, 15, 25].

High-grade gliomas mostly affect adult patients. The rarity of these tumors in childhood makes the development of phase II studies difficult. Pediatrics studies that use high-dose chemotherapy are limited and usually include patients with supra- and infratentorial tumor in their analyses [4, 5, 7, 8, 14]. This was also the main limitation in the present series, which mixed newly diagnosed patients with relapsing patients and supratentorial tumors with brain-stem gliomas. However, only one objective effect was seen in this limited phase II study. Our selection criteria were less favorable than those reported for adult studies. Seven patients had diffuse intrinsic brain-stem gliomas which have a proven resistance to chemotherapy and, hence could explain the lack of response in this trial. This resistance to chemotherapy remains unclear. Several reasons have been advocated: the heterogeneity of these tumors, their natural resistance to nitrosoureas, or a limited diffusion of drug through the blood-brain barrier [17].

The early toxicity was manageable and mainly digestive. The peculiar kinetics of bone marrow toxicity resulting from BCNU infusion permits this treatment to be given in an ambulatory setting. Only three patients required either platelet or red cell transfusions. However, one child died at 50 days after high-dose treatment with BCNU of progressive respiratory failure. This complication was consistent with fatal interstitial pneumonitis reported in adults. Acute and delayed pulmonary fibrosis related to BCNU has also been described in childhood, and a recent report suggests that the risk may be higher in children before puberty [18]. This risk should certainly be considered when the use of this drug with uncertain activity is contemplated in young children with high-grade gliomas.

Several institutions or cooperative pediatric groups are currently developing new protocols for glioma based on high-dose chemotherapy followed by bone marrow or peripheral blood stem-cell rescue [4, 5, 7, 8, 14]. As regimens for high-dose chemotherapy require drugs with proven efficacy, this study precludes the use of high-dose BCNU in such protocols either as a single agent or in combined schedules.

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