Cancer Chemother Pharmacol (1991) 27: 481–483
034457049100043Z

Cancer Chemotherapy and Pharmacology

Activity and toxicity of carboplatin and iproplatin in relapsed high-grade glioma

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Received 15 May 1990/Accepted 29 August 1990

Summary. A total of 15 patients with relapsed high-grade glioma were treated with carboplatin (400 mg/m^2) or iproplatin (300 mg/m^2). All had received previous radiotherapy, and 12 had previously undergone chemotherapy. One of the ten patients treated with carboplatin and one of the five treated with iproplatin achieved a partial remission as determined by repeat computerised tomographic (CT) scan. Myelosuppression was considerable, as three patients developed grade IV neurotoxicity, which was fatal in one case. Although carboplatin and iproplatin showed activity against malignant glioma, the study was closed because of unacceptable toxicity.

Introduction

The prognosis for patients with high-grade glioma who have been treated with surgery and radiotherapy remains poor, with only 5%–10% surviving for 2 years. Adjuvant chemotherapy with nitrosoureas probably improves survival [10], but the benefits are small. Cisplatin (*cis*-diamminedichloroplatinum) penetrates brain tumours [11] and responses have been reported both in childhood brain tumours [2, 5] and in adults with malignant glioma [6, 12]. However, cisplatin is particularly toxic in these patients [14]. There is an urgent need for active, well-tolerated chemotherapeutic agents.

Carboplatin [*cis*-diammine-1,1-cyclobutane dicarboxylate platinum(II), JM8] and iproplatin [*cis*-dichloro-*trans*-dihydroxy-bis-isopropylamine platinum(IV), JM9] are second-generation platinum analogues that are active against extracerebral human tumours and less toxic than cisplatin [3, 15]. Both carboplatin and iproplatin have shown activity against malignant gliomas in vitro [4]. The aim of this study was to evaluate the activity and toxicity of carboplatin and iproplatin in the treatment of patients with high-grade gliomas.

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Patients and methods

Characteristics of our patients on entry to the study are shown in Table 1. All had histologically proven high-grade (Kernohan grade III or IV) gliomas. They showed clinical and computerised tomographic (CT) evidence of relapse following prior treatment with surgery and adjuvant treatment with either radiotherapy alone (3 patients) or radiotherapy and chemotherapy comprising a combination of vincristine, lomustine (CCNU) and procarbazine (12 patients). None had previously received platinum chemotherapy. All patients had normal plasma electrolytes and normal renal function with a WBC count of $>4\times10^9$/l and a platelet count of $>100\times10^9$/l on entering the study. Informed consent was obtained after discussion with the patients and their relatives. The study had been approved by the institution's ethical committee.

In all, 10 patients received 21 courses of carboplatin and 5 received 13 courses of iproplatin (Bristol-Myers Company). The study was initially part of an international randomised comparison between carboplatin and iproplatin in adult cancer patients. Iproplatin was withdrawn during the study. However, after the international study had ended and cisplatin had been withdrawn, five additional patients were treated with carboplatin, to which another patient had previously responded. The planned starting dose for carboplatin was 400 mg/m^2 and that for iproplatin, 300 mg/m^2; both prepared in 250 ml 5% dextrose and given as intravenous infusions over 30 min.

Treatment was repeated every 4 weeks unless the blood count had not recovered, in which case treatment was delayed. Full blood counts were taken weekly and doses were adjusted according to the nadir blood count obtained during the previous course of chemotherapy. Dexamethasone was given when clinically indicated to reduce intra-cranial pressure, but the dose was reduced after the start of chemotherapy. All patients received prophylactic anti-emetic treatment, in most cases a combination of intravenous lorazepam, dexamethasone and metoclopramide. In the absence of severe toxicity or clinical deterioration, all patients received two courses of chemotherapy. Patients with stable or responding disease continued treatment and received a maximum of six courses.

Clinical response and toxicity were assessed before each course of treatment. Radiological response was assessed by serial CT scan after the second, fourth and sixth courses of treatment. A complete remission (CR) required the disappearance of all evidence of disease as determined by CT scan. A partial remission (PR) was a reduction of at least 50% of the product of the largest diameters of contrast-enhancing disease as determined by CT scan. Stable disease (SD) was defined as any lesser

Table 1. Patients' characteristics on entry to the study

	Carboplatin ($n = 10$)	Iproplatin ($n = 5$)
Median age	44 (range, 32–59) years	53 (range, 22–67) years
Median Karnofsky performance score	60% (range, 50%–70%)	60% (range, 50–80%)
Histology:		
Glioma, Kernohan grade III	6	3
Glioma, Kernohan grade IV	3	2
Metastatic ependyoma	1	–
Previous treatment		
Surgery and radiotherapy	1	2
Surgery, radiotherapy and chemotherapy	9	3

response and progressive disease (PD), as either an increase of at least 25% in existing lesions or the appearance of any new lesions. In patients who responded, the response duration was defined as the period from the first course of chemotherapy to the time of documented disease progression. Treatment toxicity was assessed according to WHO criteria [7].

Results

All 15 patients were evaluated for both response and toxicity, although 5 received only a single course of chemotherapy (1 toxic death, 1 case of prolonged thrombocytopenia, 1 pulmonary embolus, 1 perianal abscess and 1 case of treatment refusal). One subject who had previously been treated postoperatively with both radiotherapy and chemotherapy achieved a PR with carboplatin. A second patient, who had received only cranial irradiation after surgery, achieved a PR with iproplatin. The response durations were 9 and 4 months, respectively. The neurological symptoms of both of these patients improved following chemotherapy.

Treatment toxicity was significant. Eleven patients had episodes of WHO grade III vomiting (6 were receiving carboplatin and 5 iproplatin). Three subjects treated with iproplatin, 1 of whom had received no prior chemotherapy, experienced WHO grade III or IV thrombocytopenia; and 1 patient required repeated platelet transfusions. There were no episodes of WHO grade III or IV leukopenia or infection.

At <24 h after receiving their first course of chemotherapy, three patients became comatose (WHO grade IV neurotoxicity). Before treatment, all had shown clinical features of raised intra-cranial pressure but were alert and their clinical condition was stable. Two who received 400 mg/m^2 carboplatin vomited after chemotherapy and their conscious level deteriorated, and one of them developed generalised hypertonia with hyperflexia. Serum electrolytes remained normal, but a repeat CT scan showed extensive cerebral oedema. After further intravenous dexamethasone and the administration of mannitol, both patients recovered. The third patient, who had a history of grand mal fits, vomited following the administration of 270 mg/m^2 iproplatin; he had a generalised tonic/clonic fit and developed a decerebrate posture. A repeat CT scan revealed no new abnormalities, but the serum sodium level fell to 117 mmol/l (normal range, 137–145 mmol/l). Despite further intravenous dexamethasone and mannitol, the patient died 48 h after chemotherapy. Accrual to the clinical study stopped because of the neurological toxicity and severe thrombocytopenia.

Discussion

These results suggest that carboplatin and iproplatin have activity against relapsed adult glioma. One of the ten patients treated with carboplatin and one of the five subjects treated with iproplatin showed objective (UICC, International Union Against Cancer) responses to chemotherapy. Similar results have been reported for carboplatin in adults with glioma by Walker et al. [14]. Carboplatin has also been reported to show activity against childhood brain tumours, including brain-stem glioma [1]. No reports have been published on iproplatin in adults with glioma, and no responses were seen in the single study of childhood brain tumours [9].

This study was closed because of unacceptable toxicity. Three patients treated with iproplatin developed prolonged, severe thrombocytopenia despite a reduction of the iproplatin dose in two subjects who had previously been treated with a combination of CCNU, procarbazine and vincristine. The iproplatin regimen that we used may therefore not be appropriate in patients who have previously received myelosuppressive chemotherapy. We also observed severe neurological deterioration in two patients who were treated with carboplatin and in one subject who received iproplatin. The most probable explanation for this deterioration is acute neurotoxicity secondary to this treatment regimen. Acute neurological deterioration, which may be fatal, has previously been reported in patients with brain tumours who were treated with cisplatin [5, 6, 13]. This has been attributed to the vigorous hydration regimens that are required during cisplatin treatment, but increased blood flow associated with seizures may be a contributory factor. Vigorous hydration is not required during treatment with cisplatin analogues and was not used in this study. Moreover, in an animal model carboplatin has proved to be less neurotoxic than cisplatin or iproplatin [8].

We conclude that carboplatin and iproplatin show activity in patients with relapsed malignant glioma, although too few patients were treated in the present study to enable the determination of response rates. Further evaluation is necessary and we recommend that it be carried out in patients who have not received prior chemotherapy and who have a good performance status. It may be possible to avoid serious neurotoxicity by pre-treating these patients with mannitol, even though they would not receive intensive hydration. For the reduction of myelosuppression, a further precaution might be to start treatment at lower doses and to increase the dose only in the absence of severe toxicity.

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