Treatment of newly diagnosed glioblastoma multiforme with carmustine, cisplatin and etoposide followed by radiotherapy. A phase II study

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Summary

A meta-analysis and several studies of patients with grade III and IV gliomas have indicated that the addition of nitrosurea based chemotherapy to surgery and radiation may improve survival. We performed a phase II study of pre-irradiative chemotherapy with BCNU, cisplatin and etoposide. This implies a short total treatment duration and a reliable response evaluation.

The treatment schedule was three cycles of BCNU 200 mg/m² i.v. on day 1, cisplatin 20 mg/m² i.v. on day 1–5 and etoposide (VP-16) 100 mg/m² i.v. on day 1–5, given every five weeks and followed by localized radiation, 60 Gy in 30 fractions. Twenty-nine patients with newly diagnosed glioblastoma multiforme (GBM), mean age 50 (27–66) and performance status (PS) 0–2 were included.

Using the Macdonald criteria 33% had partial remission (PR), 41% stable disease (SD) and 26% progressive disease (PD) after chemotherapy. After additional radiation 44% had PR, 37% SD and 19% PD. Non-hematological toxicity and leukopenia was mild, but thrombocytopenia (TP) frequent. Grade III and IV TP occurred in 25% and 57% respectively, and grade III bleeding in 45%. No severe or fatal complications was seen. Median time to progression (TTP) was 7.6 months (6.0–9.1) and median survival was 11.4 months (10.1–12.7).

We conclude that this regimen is effective and feasible in patients with GBM. The short course pre-irradiatory chemotherapy may be less cumbersome than adjuvant chemotherapy and the regimen may be even more active in grade III gliomas.

Introduction

Surgical resection of glioblastoma multiforme (GBM) is essential for diagnosis and symptom control and the extent of resection is of prognostic significance [1,2]. Even though gross total resection is possible a complete radical resection cannot be achieved and additional treatment is necessary to prolong survival. With whole brain radiotherapy (WBRT) in patients with grade III and IV gliomas in doses of 60 gray (Gy) or more the median survival increases from 14 to 36 weeks [3] compared with results obtained with surgery alone. A meta-analysis of the effect of radiotherapy with or without chemotherapy has demonstrated that adjuvant chemotherapy significantly increases survival [4]. The estimated benefit for GBM was 7.1% at 12 months and 12% at 24 months and it was concluded that chemotherapy should be considered standard after radiotherapy. Most included trials were based on nitrosureas. The planned treatment was often of long duration or until progression. Additionally, most trials were rather small and without complete information on the distribution of prognostic factors. In many trials a mixture of patients with anaplastic astrocytomas (AA) and GBM was included and it seems that the activity of chemotherapy is higher in AA than in GBM [4].

Several drug combinations have proven significant activity in chemotherapy naive patients with recurrent high grade gliomas. These include regimens with cisplatin and epipodophyllotoxins [5–9]. The combination of cisplatin and etoposide is used in the treatment of a variety of cancers, including small
cell lung cancer and germ cell tumors. The use of these drugs is therefore a routine in most oncology departments.

We decided to evaluate the activity of a combination of BCNU, cisplatin and etoposide in patients with newly diagnosed GBM. Our pilot studies of patients with recurrent gliomas have indicated that this regimen is tolerable and feasible.

Response evaluation is complicated by early radiologic changes induced by surgery or radiation and also by side effects [10]. In the present study the efficacy of the proposed chemotherapeutic regimen was evaluated prior to radiotherapy, using the Macdonald response criteria [11]. Since cisplatin, among other drugs, may have radiosensitivity effects [12] this sequence of modalities may theoretically prove advantageous. However, the optimal timing of chemically effective radiosensitization by pretreatment with cytostatic agents is not achieved by the present treatment program.

**Patients and methods**

The entry criteria were histologically confirmed GBM, age ≥18 and <70 years, no prior chemotherapy or radiotherapy, WHO performance status 0–2, and normal bone marrow, renal and hepatic function.

All patients underwent surgery at the Department of Neurosurgery, Rigshospitalet, Copenhagen. Surgery included gross total resection, partial resection, or biopsy. Chemotherapy was initiated two to four weeks after surgery and administered during five days hospitalization every five weeks. The regimen consisted of BCNU 200 mg/m² i.v. on day 1, cisplatin 20 mg/m² i.v. on day 1–5 and etoposide (VP-16) 100 mg/m² i.v. on day 1–5. Three cycles were administered unless the patient had progressive disease during treatment, unacceptable toxicity or refused further treatment. Radiotherapy was initiated four weeks after the last cycle of chemotherapy with a total dose of 60 Gy, 2 Gy per fraction with five fractions every week. The target volume included the preoperative tumor volume defined on contrast enhanced CT or MRI and the surrounding edema with a margin of 1.5 cm. A contrast enhanced CT was performed for therapy planning, and this volume was used if it was greater than the preoperative volume. If the volume included more than 50% of the brain the radiotherapy was altered to whole brain radiation in a reduced total dose, 20 Gy in four fractions of 5 Gy.

Patients received anticonvulsives if they had experienced seizures, and corticosteroids were administered at the discretion of the physician according to symptoms from increased intracranial pressure.

Measurable disease was determined with a CT or MRI with contrast enhancement performed just prior to initiation of chemotherapy. An immediate postoperative scan could not be obtained within the local scanning facilities at the time of the study. Evaluation including CT or MRI, neurological examination and medical records was repeated prior to each cycle and again three months after radiotherapy. After treatment the patients were followed regularly, and imaging was repeated if the patients deteriorated.

The Macdonald response criteria were used [11]. This considers the largest cross-sectional product of tumor contrast enhancement with CT or MRI, neurological status and dose of corticosteroids. A complete remission (CR) requires disappearance of all contrast enhancing tumor, neurologically stable or improved and no use of steroids. Partial remission (PR) is ≥50% reduction of the product of the largest perpendicular diameters of contrast enhancement, neurologically stable or improved and stable or reduced steroids. Progressive disease (PD) is ≥25% increase in tumor size or neurological deterioration and steroids stable or increased. Stable disease (SD) reflects all other situations.

Second line treatment was optional. At the time of PD all patients were considered for surgery which was performed based on clinical symptoms as well as the size and location of the recurrent tumor. None of the patients in this study entered trials with second line chemotherapy and no patients received stereotactical radiotherapy at relapse.

The WHO toxicity criteria for hematological and non-hematological toxicity was used. All patients had physical examination, blood cell counts and chemistry profiles prior to each cycle of chemotherapy. Blood cell counts were measured every week during both chemotherapy and radiotherapy. If hematological toxicity was greater than grade II blood samples were collected more frequently. All patients had $^{51}$Cr-EDTA clearance for renal function prior to each cycle and an audiometry before and after chemotherapy.

**Endpoints and statistical considerations**

The primary endpoint was response to chemotherapy, but also overall response to chemotherapy and