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Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy: EORTC Brain Tumor Group phase II study 26972

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Background: Oligodendroglial tumors are chemosensitive, with two-thirds of patients responding to PCV combination chemotherapy with procarbazine, lomustine (CCNU) and vincristine. Temozolomide (TMZ), a new alkylating and methylating agent has shown high response rates in recurrent anaplastic astrocytoma. We investigated this drug in recurrent oligodendroglial tumors (OD) and mixed oligoastrocytomas (OA) after prior PCV chemotherapy and radiation therapy.

Patients and methods: In a prospective non-randomized multicenter phase II trial patients were treated with TMZ 150 mg/m^2 on days 1–5 in cycles of 28 days for 12 cycles. Eligible patients had a recurrence after prior PCV chemotherapy, with measurable and enhancing disease as shown by magnetic resonance imaging. Pathology and all responses were centrally reviewed.

Results: Thirty-two eligible patients were included. In four patients the pathology review did not confirm the presence of an OD or OA. Twelve of 24 patients [50%, 95% confidence interval (CI) 29% to 71%] evaluable for response to first-line PCV chemotherapy had responded to PCV. Temozolomide was in general well tolerated; the most frequent side-effects were hematological. One patient discontinued treatment due to toxicity. In seven of 28 patients (25%, 95% CI 11% to 45%) with histologically confirmed OD an objective response to TMZ was observed. Median time to progression for responding patients was 8.0 months. After 6 and 12 months from the start of treatment, 29% and 11% of patients, respectively, were still free from progression.

Conclusions: TMZ may be regarded as the preferred second-line treatment in OD after failure of PCV chemotherapy. Further studies on TMZ in OD are indicated.

Key words: chemotherapy, oligoastrocytoma, oligodendroglioma, recurrent, second line, temozolomide

Introduction

Although 60–70% of patients with oligodendroglial (OD) tumors respond to PCV chemotherapy [procarbazine, lomustine (cyclohexylchloroethylnitrosourea; CCNU) and vincristine] [1, 2], most responding patients relapse within 12–18 months [1, 3, 4]. For these patients second-line chemotherapy is often the only remaining treatment option. Besides, although PCV in general is considered to be well tolerated, CCNU induces a cumulative myelosuppression that frequently requires dose reductions and delays, and discontinuation of treatment before the intended six cycles of treatment have been given. Nausea and weight loss are other side-effects that limit treatment in a significant number of patients. New active agents and treatment regimens that do not inversely affect quality of life are therefore necessary.

Temozolomide (TMZ) is a new oral alkylating and methylating agent, which has shown good tolerance and promising activity in astrocytic tumors. A large phase II trial on first- and second-line chemotherapy with temozolomide in 162 patients mainly with recurrent anaplastic astrocytoma showed an objective response rate of 35% [5]. Because of these results we initiated two European Organisation for Research and Treatment of Cancer (EORTC) studies in recurrent OD tumors after radiation therapy, one investigating TMZ as first-line chemotherapy and the other as second-line chemotherapy. Here we present the results of the EORTC 26972 study which investigated second-line chemotherapy with TMZ.

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Patients and methods

Patients who were eligible for this study met the following criteria: (i) recurrent or progressive OD or mixed oligoastrocytomas (OA) after radiation therapy and PCV chemotherapy (either adjuvant or at first recurrence); (ii) measurable disease requiring a contrast enhancing lesion with a diameter of ≥1 cm on magnetic resonance imaging (MRI) or computed tomography (CT) scan; (iii) adequate hematological, renal and hepatic function; (iv) World Health Organisation (WHO) performance status of 0, 1 or 2; and (v) written informed consent from the patient. Patients undergoing surgery for the present recurrence were eligible provided they had measurable disease (enhancing lesions with a diameter >1cm) on imaging obtained within 3 days of surgery. Patients were included based on the diagnosis made by the local pathologist, with subsequent central histology review (J.M.K.). Prior to the activation of the study all centers required approval of their ethics committee.

The primary end point of the study was response. Secondary end points included toxicity, estimation of time to tumor progression (TTP), overall survival (OS) and response duration. Response rate and 95% confidence interval (CI) were calculated by pooling the complete response (CR) and partial response (PR) patients. Time to tumor progression and OS were measured from the start of chemotherapy. Overall survival was measured until the date of death or otherwise at the last follow-up examination. Time to tumor progression was measured until the first sign of radiological or clinical progression appeared (whichever came first) or otherwise the date of the last follow-up visit. Overall survival and TTP were estimated using the Kaplan–Meier method [6].

Patients were registered at the EORTC Data Center in Brussels according to the two stage Minimax Simon Design [7]. As a first step, 19 patients were entered. If no response was observed in this group the study would be stopped. One responding patient in this cohort assures, with 95% power and a type I error of 10%, that a minimal response rate of 5% was reached and in that case 16 more patients would be registered in order to evaluate if the true response rate is 25%. If so, the drug would be recommended for further research in a phase III study.

Patients were treated with TMZ 150 mg/m^2 on days 1–5, in cycles of 28 days for a maximum of 12 cycles. To avoid treatment heterogeneity no dose increase to 200 mg/m^2 was foreseen. Dose reductions were made as previously described [5]. Hematological parameters were assessed at baseline and on days 21 and 28 of each cycle. Electrolytes, renal and hepatic function were assessed at baseline and on day 28 of each cycle. The primary end point of the study was response to treatment. Response was evaluated every two cycles for the first six cycles, thereafter at every three cycles. Response was measured according to the criteria of Macdonald et al. [8]. Scans of all patients in which a response (CR or PR) was reported (either to first-line PCV or to second-line TMZ) were centrally reviewed. Toxicity was assessed according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC), December 1994 version.

Results

Thirty-five patients were enrolled by 10 institutions from April 1998 to February 2000. Three patients were not eligible: one patient was registered after the start of treatment, one patient did not have measurable disease and one was subsequently diagnosed with radiation necrosis. The main patient and pretreatment characteristics of those that were eligible are summarized in Table 1. Of the 24 patients evaluable for response to prior PCV chemotherapy, 12 had responded to PCV: five CRs and seven PRs (objective response rate to PCV 50%, 95% CI 29% to 71%). At central pathology review four patients were diagnosed with a non-oligodendroglial tumor: pure astrocytic tumors (three patients) and pilocytic astrocytoma (one patient). At the time of this analysis 24 patients have died and all but one have progressed.

Table 1. Characteristics of eligible patients

No. of patients	32
Age, years	
Median	43.6
Range	27–56
WHO PS at start of treatment	
0	8
1	12
2	12
Histology (at central review)	
Oligodendroglioma	17
Oligoastrocytoma	11
Other	4
Interval since prior PCV chemotherapy	
Median, months (range)	6.5 (1–55)
Response to prior PCV chemotherapy	12
CR + PR	10
SD + PD	2
Not evaluable adjuvant	8

CR, complete response; PCV, procarbazine, lomustine and vincristine; PD, progressive disease; PR, partial response; SD, stable disease; WHO PS, World Health Organization performance status.

A total of 176 cycles were administered (median, five cycles; range 1–16). Treatment was in general well tolerated. In 84% of patients treatment was delivered at >90% of the intended dose intensity. Only five cycles were dose reduced (2.8%; three patients) and 23 cycles (13.1%; 11 patients) were dose delayed (but in 14 cycles/seven patients this was not related to toxicity). Grade 3/4 nausea and/or vomiting was observed in three patients (four cycles), and in subsequent cycles was easily managed with prophylactic anti-emetics. In two patients (three cycles) treatment was complicated by a grade 3 granulocytopenia and thrombocytopenia. One patient developed grade 3 dysphagia and esophagitis, which did not recur despite continuation of treatment at the same dose level. One patient discontinued treatment because of prolonged thrombocytopenia, with subsequent uneventful recovery. In another patient with a borderline performance status at the start of treatment, TMZ was discontinued after five cycles because of a lack of clinical improvement in spite of a radiological partial response.

Seven patients responded to TMZ: a response rate of 22% (7/32; 95% CI 9% to 40%) in all eligible patients. In patients with verified oligodendroglial pathology the response rate was 25% (7/28; 95% CI 11% to 45%). In these patients the median TTP was 3.7 and 8.0 months in responding patients (CR and PR). At 6 and 12 months, respectively, 29% and 11% of patients were still free from progression; the median overall survival in this group

was 12.3 months. Of the 24 patients who were evaluable for response to PCV, four responded to TMZ: three of 12 responders to PCV responded to TMZ.

Discussion

This is the first series on second-line chemotherapy with TMZ in recurrent OD using strict criteria for response including central response review and central pathology review. We observed a response rate of 25% in patients in which the central pathology review confirmed the presence of an OD tumor. In this study, 24 patients had been evaluable for response to first-line PCV chemotherapy; 12 (50%) of them had responded to PCV. This is somewhat less than observed in historical series in which 60–70% response rates were reported [1, 3]. In this small number of patients, no apparent difference was noted in response rate to TMZ between responders to first-line PCV and the total study population.

As noted before, treatment with TMZ was well tolerated [5, 9]. The toxicity of this oral treatment was mild and 85% of the treatment cycles were administered at the intended dose intensity. Furthermore, most of the dose delays were due to non-medical reasons. The only grade 4 treatment-related toxicity observed was vomiting, which was easily managed in subsequent cycles with anti-emetics. All grade 3 toxicities resolved without sequelae. Only one patient had to discontinue treatment for (reversible) toxicity (thrombocytopenia).

Our results are consistent with the response rate to TMZ observed in patients with recurrent anaplastic astrocytoma and mixed OA after prior radiation therapy and chemotherapy [5, 10]. Two other series have investigated second-line TMZ chemotherapy in recurrent OD, but in less stringent trials. In a retrospective multicenter series, van den Bent et al. [9] reported an objective response rate of 26%, with 44% and 27% remaining free from progression at 6 and 12 months, respectively. In a prospective single center trial, Chinot et al. [11] observed a higher response rate (44%), but with similar percentages of patients remaining free from progression at 6 and 12 months (51% and 24%, respectively). These studies differ though in their response rate to prior PCV chemotherapy, suggesting an important selection bias. In the present study, 50% of patients responded to first-line PCV chemotherapy, whereas in the study by Chinot et al. [11], 83% of patients had responded to PCV. The latter response rate is remarkable, being superior to the ~65% response rate of OD to PCV observed both in this and center other studies [1, 3, 12]. This difference appears to be due to the exclusion of patients progressive under PCV chemotherapy in the latter study (O. Chinot, personal communication, 2002). Whether indeed a relationship between response to PCV and response to TMZ exists remains to be established. Two previous studies did not find a clear correlation between response to PCV and response to TMZ [9, 11].

One of the problems faced by studies on OD is the fact that criteria for its diagnosis are poorly defined and poorly reproducible, and they have been widened to include less typical cases due to the reported chemosensitivity of OD [13]. As a consequence, patient selection is likely to affect outcome in trials on chemotherapy in OD tumors. This might be reflected in the slightly lower response rate to PCV in our study as compared with historical controls. Recent studies have shown that, in particular, OD with combined loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) are sensitive to PCV chemotherapy, with 95–100% of patients responding to PCV [14, 15]. Approximately 55–70% of OD tumors do have combined loss of 1p/19q. Thus, genetic testing may allow a better identification of OD tumors that are likely to respond to chemotherapy.

Data on other second-line treatment regimens in OD tumors are limited. Cisplatin/etoposide [16], paclitaxel [17], irinotecan [18] and carboplatin [19] have all shown some activity in second-line treatment of OD in small phase II studies. Carboplatin treatment was complicated by significant myelosuppression. In brain tumor patients the use of both paclitaxel and irinotecan is complicated because of interactions with many anti-epileptic drugs through cytochrome P450 induction. Currently available data suggest that TMZ may provide better results as second-line treatment in OD tumors. Because of ease of oral administration, good tolerance to TMZ and absence of interactions with anti-epileptic drugs, TMZ is therefore to be regarded as the drug of choice for progressive OD tumors during or after PCV chemotherapy. However, as only a limited number of patients respond or remain stable for a more prolonged period of time, further improvement of second-line treatment is clearly indicated.

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