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Salvage chemotherapy with temozolomide in primary CNS lymphomas: preliminary results of a phase II trial

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Abstract

Temozolomide is a well-tolerated alkylating agent, that is able to permeate the blood–brain barrier (BBB), and has additive cytotoxicity when given with radiotherapy (RT). A phase II trial assessing temozolomide 150 mg/m^2/day, for 5 days every 28 days in primary central nervous system (CNS) lymphoma (PCNSL) patients with negative human immunodeficienct virus (HIV) serology, Eastern Cooperative Oncology Group (ECOG) performance status (PS)<4, previously treated with high-dose methotrexate-containing (HD-MTX) chemotherapy and/or RT was started. Twenty-three patients were enrolled. Median age was 60 years. Five complete remissions (median duration 6+ months; range 2–36 months), one partial response, four stable disease (median duration 7.2 months, range 2–16.5 months), and 13 progressions were observed. No major toxicities were observed, apart grade 3 vomiting in a single cycle. Main grade 1–2 toxicities were: 15% nausea, 6% vomiting, 9% fatigue and 9% neurological symptoms. This is the first prospective trial assessing single-agent activity in PCNSL at failure. Although some patients had a poor PS and had been heavily pre-treated, temozolomide yielded 26% objective responses and was well tolerated without any major toxicity.

Keywords: Phase II trial; Primary CNS lymphoma; Salvage therapy; Temozolomide

1. Introduction

Despite recent progress, results following treatment for primary central nervous system (CNS) lymphoma (PCNSL) patients remain disappointing, typically producing a 5-year survival rate of 22–40% [1–3]. Chemotherapy followed by radiotherapy (RT) is the cornerstone of first-line treatment for PCNSL [4–7]. The principal drug in the management of PCNSL is high-dose methotrexate (HD-MTX), which yields 30–65% complete responses [8–10]. As no other single agent has been prospectively proven active against PCNSL, it is

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presently, impossible to attribute a therapeutic benefit to any single drug, apart from HD-MTX. Several studies have attempted to improve patient outcome by adding other drugs to HD-MTX, and these drugs were empirically chosen on the basis of their activity against extracerebral non-Hodgkin's lymphomas (NHL) or due to their capability to cross the blood-brain barrier (BBB) [3,11–14]. This strategy has resulted in increased toxicity without improving survival rates [11]. Improving the efficacy of primary chemotherapy therefore remains the most pressing issue. One avenue of investigation is the assessment of the toxicity and activity of new drugs that (if active) could then be subsequently selected for first-line treatment. Temozolomide, is an oral alkylating agent that spontaneously undergoes chemical conversion to the cytotoxic metabolite MTIC (5-(3methyl-1-triazeno) imidazole-4-carboxamide) at physiological pH, without metabolic conversion. Temozolomide depletes the DNA repair enzyme *O*-6 methylguanine-DNA methyltransferase in various cell types. This drug seems to have a sound rationale for clinical study in PCNSL because it is an alkylating agent, and these drugs are one of the mainstays of NHL treatment; it also permeates the BBB; exhibits *in vitro* additive cytotoxic activity with radiotherapy [15]; and is well tolerated. The latter aspect is a relevant one because approximately half of PCNSL patients are over the age of 60 years, and suffer excessive treatment-related toxicities [1]. Temozolomide activity against PCNSL has been anecdotally reported [16–18]. Based on these considerations, a multi-centre phase II trial of temozolomide as salvage therapy for PCNSL was started in January 2000.

2. Patients and methods

2.1. Patient population

Inclusion criteria for this trial were: age 18–75 years, PCNSL failure after previous treatment including HD-MTX and/or RT, histological or cytological diagnosis of NHL, disease limited to the brain, both at diagnosis and at failure, presence of at least one bi-dimensionally measurable target lesion, negative human immunodeficient virus (HIV) serology, Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 4, adequate bone marrow (platelet $\geqslant 100\times10^9$ cells/L, haemoglobin $\geqslant$ 100 g/L, absolute neutrophil count $\geqslant 1.5\times10^9$ cells/L), renal (serum creatinine $\leqslant 2$ times upper limit of normal (UNL)) and hepatic function aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT) $\leqslant 3$ times UNL, bilirubin and alkaline phosphatase ($\leqslant 2$ times UNL), absence of frequent vomiting or medical conditions which could interfere with oral medication intake, and no concurrent treatment with other experimental drugs. Patients with prior malignancy were ineligible for the study, with the exception of those who had basal cell carcinoma of the skin, carcinoma *in situ* of the cervix, or other cancer for which the patient had been disease-free for at least 5 years. The protocol was reviewed and approved by local ethics committees. All participating patients were required to give written informed consent. The study was conducted in agreement with the declaration of Helsinki.

2.2. Treatment plan

Eligible patients received oral temozolomide 150 mg/m^2 day, for 5 days every 4 weeks. Treatment was given until progression of disease (PD), unacceptable toxicity or patient's refusal. In case of clinical progression occurring before the first disease evaluation and not dependent on corticosteroids dose reduction, treatment was discontinued and the response to treatment was assessed as 'early progression'. In case of stabilisation of the disease (SD), the patient was treated for a maximum of 6 cycles. In patients with objective response, at least 2 cycles of temozolomide were delivered after the maximum response. Prophylactic anti-emetics were administered at the discretion of the treating physician.

Dose adjustments were made according to the degree of toxicity. In case of inadequate bone marrow recovery (i.e. absolute neutrophil count $\leqslant 1.5\times10^9$ cells/L, platelets $\leqslant 100\times10^9$ cells/L), on the intended day of re-treatment, the start of the next cycle was delayed for a maximum of two weeks. Thereafter, treatment was discontinued. The dose of temozolomide administered for subsequent cycles was determined according to the nadir neutrophil count or platelet count of the first cycle day 21 and 28 and to non-haematological toxicity. For grade 3 or 4 toxicity, dosage for the subsequent cycle of temozolomide was reduced to 100 mg/m^2. If grade 3 or 4 toxicity occurred on lower doses of temozolomide, the patient was taken off the study. If multiple toxicities were seen, the dose was reduced according to the most severe grade of any single toxicity observed.

The use of anti-emetics, analgesics, antibiotics, anticonvulsants, sedatives, anti-hyperuricaemic agents as well as other therapies to control metabolic and malnutrition disturbances was permitted.

2.3. Study evaluations

Pre-treatment evaluation consisted of a complete medical history, physical examination, neurological evaluation, PS assessment, haematological and biochemical serum profiles, whole body computed tomography (CT) scan, whole brain CT or magnetic resonance (MR) scan, and, when possible, cerebro-spinal fluid examination with cell count and cytology. A clinical examination, neurological evaluation, and haematological

profile were performed immediately before every cycle. Blood counts and a biochemical serum profile were repeated on day 21, or as clinically indicated. Whole brain CT or MR scan was repeated every two cycles of chemotherapy or as clinically indicated. After the end of treatment, if the patients did not progress, the disease was assessed every three months, following the same procedure as during treatment, to evaluate the duration of response or stabilisation.

2.4. Toxicity and response criteria

Toxicity was graded by the National Cancer Institute (NCI) Common Toxicity Criteria (CTC). Response to treatment was assessed on the basis of a maximum of three 'target lesions' selected before the start of the treatment and taking into account measurable change in tumour size, corticosteroid requirements, and the neurological examination [19]. Tumour size was considered the maximum cross-sectional area of the enhancing mass on CT (post-iodinated contrast) or MR (T1-weighted, post-gadolinium) and calculated by multiplying the largest cross-sectional diameter by the largest diameter perpendicular to it. A complete response (CR) was defined as the complete disappearance of all evidence of lymphoma (including non-target lesions) for at least 4 weeks apart, off corticosteroids for at least two weeks and neurologically stable or improved. A partial response type 1 (PR_1) was defined as $\geqslant 90\%$ decrease in tumour size at least 4 weeks apart, corticosteroids dose stable or reduced, neurologically stable or improved. A partial response type 2 (PR_2) was defined as $\geqslant 50\%$ decrease in tumour size (but <90%) at least 4 weeks apart, corticosteroids dose stable or reduced, neurologically stable or improved. Progressive disease was defined as $\geqslant 25\%$ increase in tumour size (including non-target lesions) or any new area of tumour on any follow-up scan, corticosteroids dose stable or increased and neurologically stable or worse. SD was defined as disease that did not meet any of the previous criteria. The best response recorded from the start of the treatment until PD was considered. The duration of response was measured from the date of documentation of response. The time to progression was defined as the interval between the initiation of treatment and the occurrence of PD. Survival was measured from the initiation of treatment to the date of death or to the last follow-up assessment. All eligible patients were considered for the response evaluation. Patients dying before the response assessment were considered as 'early deaths' and classified according to the cause of death: PD, toxicity or disease and drug unrelated. Patients discontinuing treatment before the response assessment were considered as 'early discontinuation' due to PD, toxicity or disease and drug unrelated. Patients not evaluated for any reason were considered as 'not assessed'.

2.5. Statistical analysis

The principal end-point of this trial was the objective response to temozolomide. For statistical purposes, the Simon Minimax two-stage design was used [20]. The maximum response rate of low interest was 15% and the minimum response rate considered of interest was 35%. The sample size was calculated using a type I error of 5% and a test power of 90%. The target enrollment was estimated to be 38 patients. The first stage of the study was to enrol 23 patients, and if $\geqslant 4$ responses were observed, the study would continue until a maximum of 38 patients were entered. Temozolomide would be considered an active agent against PCNSL if >9 objective responses were noted among the 38 enrolled patients.

3. Results

3.1. Patient population

Between January 2000 and December 2002, 23 patients were entered into this study (Table 1). The median time to failure following initial treatment was 18.5 months (range 4–130 months). Previous treatment was heterogeneous (Table 1), consisting of HD-MTX (1.5–8.4 g/m^2/month)-based chemotherapy alone ($n = 4$), or followed by RT ($n = 15$), RT alone ($n = 1$) or associated with high-dose cytarabine-based chemotherapy ($n = 3$). The whole-brain dose ranged between 30.6 and 50.4 Gy (median 44.5 Gy), the tumour bed dose ranged between 30.6 and 59.4 Gy (median 46 Gy). Temozolomide was the first-line chemotherapy in one case, the second-line in 19 cases, the third-line in two patients, and the fifth-line in one patient.

3.2. Treatment summary

Altogether, 77 cycles of temozolomide were delivered. The median number of cycles was two (range 1–12). In no case was the treatment interrupted or the start of a new cycle delayed as a result of toxicity or side-effects. Four patients stopped treatment after the first chemotherapy cycle and before the response assessment due to neurological deterioration attributed to PD. Nine patients stopped therapy after the first ($n = 5$), the second ($n = 3$) or the third cycle because of radiologically confirmed PD. There were no major protocol deviations. Temozolomide was always delivered at the full dose.

3.3. Safety and toxicity

All 23 patients were assessed for toxicity. No haematological grade 3–4 toxicity was observed. One

Table 1
Summary of patient characteristics at baseline

Patient	Age (years)	Gender	PS	Histotype	First line	Number of		RT	Failure	TFTF (months)	OR	Duration (months)	Survival (months)
						Lines	Lesions						
1	66	Male	3	DLC	MVP	2	Single	+	R	5	CR	36.0+	38.0+
2	54	Male	2	DLC	MVP	1	Multiple	+	R	19	PR_2	2.5	2.5
3	61	Female	0	DLC	A	1	Multiple	−	R	10	PD		2.0
4	60	Male	2	DLC	BAVm	1	Multiple	+	R	23	ED		1.5
5	57	Male	3	DLC	MATI	1	Single	−	PD	4	PD		3.5
6	52	Male	3	DLC	CVOD/ BVAM	1	Multiple	+	R	11	ED		1.0
7	62	Female	0	DLC	MATI	1	Multiple	+	R	14	PD		1.5
8	54	Male	1	LP	M	1	Multiple	+	PD	10	SD	16.5	16.5+
9	68	Male	2	DLC	None	0	Multiple	+	R	99	PD		4.5
10	64	Male	1	DLC	MATI	1	Single	+	R	12	SD	2.0	2.0
11	51	Male	1	DLC	MA	1	Multiple	+	R	39	CR	2.0	14.5+
12	54	Female	2	DLC	F-MA-CHOPn	2	Multiple	+	R	130	PD		3.5
13	54	Male	2	DLC	MAI	4	Single	+	R	28	PD		2.5
14	64	Female	1	DLC	MVP	1	Multiple	+	R	24	PD		12.5+
15	61	Female	2	UN	M	1	Single	+	R	19	CR	6.0+	6.5+
16	62	Male	0	DLC	MVP	1	Single	−	R	14	PD		27.5
17	54	Female	1	DLC	VPAL	1	Multiple	+	R	20	SD	9.5	9.5
18	81	Male	1	UN	MVP	1	Single	−	R	44	CR	6.0	22.5+
19	48	Male	2	UN	MVP	1	Multiple	+	PD	6	ED		1.0
20	66	Male	2	DLC	A	1	Multiple	+	R	48	ED		1.0
21	47	Male	0	DLC	A	1	Single	+	R	14	SD	5.0	25.5+
22	69	Male	3	DLC	MA	1	Single	+	R	38	CR	2.0+	4.0+
23	56	Female	3	DLC	MA	1	Multiple	+	R	18	PD		0.5

PS, performance status; DLC, diffuse large B-cells; LP, lymphoplasmacytic; UN, unclassified; M, methotrexate; V, vincristine; P, procarbazine; A, cytarabine; B, carmustine; Vm, teniposide; T, thiotepa; I, idarubicin; F, fluorouracil; O, doxorubicin; D, dexamethasone; Pn, prednisone; L, lomustine; RT, radiotherapy; R, recurrence; PD, progression; TFTF, time to first treatment failure; OR, overall response; CR, complete response; PR, partial response; SD, stable disease; ED, early death; C, cyclophosphamide.

patient developed grade 3 vomiting in a single cycle. Grade 1–2 toxicity mainly consisted of nausea (12% and 3% of cycles, respectively), vomiting (1% and 5% of cycles, respectively), fatigue (5% and 4% of cycles, respectively), neurological symptoms (1% and 8%, respectively), diarrhoea and constipation (both grade 2: 1% of cycles).

3.4. Response and survival

There were five CR and one unconfirmed PR_2 for an objective response rate of 26% (95% confidential interval (CI): 8–44) in 23 evaluable patients. CR occurred after two cycles of temozolomide in 4 patients and after 10 cycles in one patient. Three CR patients received 4 cycles of temozolomide, one patient eight cycles and one patient twelve cycles. Median CR duration was 6+ months (range 2–36). At time of recurrence, all these patients except one (#15) received dexamethasone at a dose of 4–24 mg. CR lasted 36+, 6, and 2+ months after steroid discontinuation, for cases #1, 18 and 22, respectively. In patient #11, steroids were discontinued during the fourth cycle, thereafter contrast-enhancing lesions continued to regress, and CR was obtained after 10 cycles. A PR_2 was observed (#2) after the first cycle of chemotherapy. In this patient an initial response was observed after three weeks of steroids, before the start of temozolomide treatment. In spite of radiological objective response, the patient had neurological deterioration and died 40 days after receiving the second temozolomide cycle, without response confirmation. Four patients had SD lasting 2, 5, 9.5, and 16.5 months (median 7.2 months). One (#21) received salvage HD-cytarabine achieving a CR. Nine patients had radiologically confirmed PD. One of these (# 16) obtained a CR with salvage RT. Four patients died without tumour assessment and were classified as early deaths due to PD. Median time-to-progression was 2 months (range 0.4–36+ months). Fifteen patients died and eight patients are alive (3 without recurrence) at 4–38 months after initial failure (median 16 months). Median survival for all patients was 3.5+ months (range 0.4–43 months). One year overall survival was 38%.

4. Discussion

Currently, the major investigational efforts against PCNSL aim to improve the efficacy of primary chemotherapy treatment with minimal impairment of the patient's quality of life and avoiding neuro-psychological deterioration. Since the activity of single agents against PCNSL has been poorly established, phase II trials testing drug activity in recurrent or refractory PCNSL patients should receive high priority. Temozolomide is a suitable candidate for study because it has limited neurotoxicity, is safe, and is able to cross the BBB [15]. If some activity is shown, another intriguing area of research would be to explore the role of temozolomide in association with HD-MTX as upfront therapy, as consolidation or maintenance therapy after CR, or as a radiosensitiser.

This is the first reported phase II trial assessing single-agent activity in relapsed or refractory PCNSL. Temozolomide yielded 26% (95% CI: 8–46) objective responses (22% CR; 95% CI: 5–39) in 23 patients. Although some patients had a poor PS and had been heavily pre-treated, temozolomide was well tolerated without any major toxicities of note, CR were observed in elderly patients, with poor PS, who had been heavily pre-treated, and had a short time to first treatment failure. The main drawback of this study is the possible impact of steroid exposure on the response assessment. In at least three cases, CR was certainly due to temozolomide because no steroids were given at the time of recurrence (#15), CR occurred after steroid discontinuation (#11), or lasted 36 months (#1), which is very unlikely to be observed following steroid use alone. In the other three responders, the influence of steroid use on the response of patients cannot be ruled out. This bias can not be easily avoided because steroid administration is mandatory in most of patients with PCNSL to reduce oedema and mass effect, and the assessment of its potential impact on response would require, in this rapidly progressive disease, a period of 3–4 weeks of exclusive steroid treatment before the chemotherapy start, with the risk of being unable to deliver any salvage therapy in most of the non-responding patients.

At time of this trial design, no information about the expected response rate of salvage treatment in patients with PCNSL failure was available. We arbitrarily decided to look for a minimum response rate of 35% to consider activity of sufficient interest. To avoid the treatment of a large number of patients with an inactive drug, an interim analysis was planned after the first 23 patients, to stop the trial if less than 4 responses were observed. According to this rule, enrolment will be continued to include a total of 38 patients as per protocol.

Recently, three series of salvage treatment for patients with PCNSL who had failed after first-line HD-MTX-containing chemotherapy were reported [21–23]. Sixteen patients were treated with etoposide, ifosfamide and cytarabine [21]. Patients in this previous study were younger than those in our series (median age 54 years versus 60 years), had a similar PS ($PS \leqslant 1$ in 37% versus 43%) and time to treatment failure (19 versus 18.5 months) [21]. CR was obtained in six cases (38%) with a median duration of 7.5+ months, while no PR was observed [21]. One-year survival was 42% versus 38% in our series [21]. Toxicity consisted of neutropenic fever in 50% of cases, including three cases of sepsis and two cases of pneumonia, and severe encephalopathy in one

case [21]. Another series included 37 patients who were heterogeneously treated at failure with intra-arterial carboplatin, with or without intravenous (i.v.) etoposide, with or without i.v. cyclophosphamide, and followed or not by RT [22]. Their median age was 57.5 years and 76% of the patients had a PS $\leqslant$ 1. CR was observed in 26% and PR in 11%, with a median duration of 9 months and a 1-year survival of 25% [22]. In this series grade 3–4 toxicity was relevant, with 22% of patients experiencing leucopenia, 19% thrombocytopenia, 19% requiring platelets or red cell transfusions, 8% with sepsis, 5% with deep venous thrombosis, and 3% had ototoxicity, cardiac infarction, diarrhoea, pulmonary embolism, pulmonary oedema, aphasia or hip fractures [22]. In another series of 15 patients treated with topotecan followed or not by RT, the CR rate was 20% and the PR rate was 20%, with 13% experiencing neutropenic fever and 13% late neurotoxicity [23]. In all of these series, the role of steroids was not analysed and it is impossible to assess the role of single agents or of RT [21–23]. In our series temozolomide showed a similar activity in terms of the CR rate, response duration and overall survival, to the above mentioned chemotherapy combinations, which however, were associated with more toxicity.

Recently, there has been considerable interest in using temozolomide for CNS lymphoma, and isolated and anecdotal case reports of the successful use of this drug as first-line chemotherapy [16,17] has resulted in what we believe to be undue and premature enthusiasm for temozolomide in this clinical setting. While this information is of interest, it does not provide reliable evidence of activity and it does not constitute an adequate rationale to include temozolomide in poly-chemotherapy trials. Our experience, while promising, suggests that the activity of temozolomide against CNS lymphoma is modest, although still worthy of further study and could be overestimated due to the confounding activity of steroids. A more reliable indication of the activity of temozolomide, based on a larger number of patients and longer follow-up, will only be available at the conclusion of this trial.

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