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Temozolomide in patients with advanced non-small cell lung cancer with and without brain metastases: a phase II study of the EORTC Lung Cancer Group (08965)

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Abstract

This study was performed to evaluate the activity of single-agent temozolomide in two groups of chemotherapy-naïve non-small cell lung cancer (NSCLC) patients, with (12 patients) and without (13 patients) brain metastases (BM). Patients in both groups were treated with temozolomide 200 mg/m^2/day, administered orally for 5 consecutive days of a 28-day cycle. Treatment was continued for up to six cycles, disease progression or unacceptable toxicity. The median number of received cycles was only one in the group with and two in the group without BM, and early disease progression was the main reason for treatment discontinuation. Toxicity was moderate—in the group of patients with BM, the most frequently observed grade 3 or 4 side-effects included thrombocytopenia (17%), granulocytopenia (17%), lethargy (17%); other neurological (17%) and other genitourinary toxicity (17%). Patients without BM experienced anaemia (15%), thrombocytopenia (23%), nausea (15%) and lethargy (15%). This trial was designed according to Simon one-sample two-stage testing procedure and both groups of patients were assessed separately. No objective response was observed in either group and the study was closed after the first step of accrual with the conclusion of a lack of therapeutic activity of single-agent temozolomide in patients with stage IV NSCLC.

Keywords: Chemotherapy; Temozolomide; Non-small cell lung cancer; Phase II study; Brain metastases

1. Introduction

Lung cancer remains the leading cause of cancer death in the European Union [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 75–80% of all lung tumours. High rate of distant failures in both operable and advanced NSCLC mandates a continuous search for effective systemic treatment. Brain metastases (BM) occur in approximately 20–30% of NSCLC patients during the course of their disease. Prognosis in these patients is particularly grim, with a median survival of approximately 3–4 months after whole-brain radiation therapy (WBRT) [2,3]. More aggressive treatment of BM with surgery or stereotactic radiotherapy is possible only in a small subset of patients [4]. The role of systemic treatment in patients with BM remains controversial for various reasons. Typically, patients with BM often present neurological symptoms that add to the existing co-morbidities and thus are excluded from many clinical trials addressing the role of chemotherapy in disseminated NSCLC. The penetration of chemotherapeutic agents in the brain is limited by the blood-brain barrier, although this may already be disrupted by the presence of BM and/or treatment with WBRT [5,6].

Temozolomide is a novel imidazole tetrazinone, orally bio-available, groove-directed DNA methylating agent with significant activity in malignant melanoma as well

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as in low and high-grade central nervous system (CNS) gliomas. Both temozolomide and dacarbazine (DTIC) are pro-drugs of the active metabolite—monomethyl triazenoimidazole carboxamide (MTIC) [7,8]. Unlike DTIC, temozolomide has been demonstrated to cross the blood–brain barrier [9,10]. In a phase I clinical trial conducted by the Cancer Research Campaign (CRC), the first 51 patients were treated with temozolomide administered either orally or intravenously using a single-dose schedule [11]. In the subsequent 133 patients, temozolomide was given orally for 5 consecutive days in a 28-day cycle. Dose-limiting toxicity (DLT) was myelosuppression and the maximum tolerated dose (MTD) was set at 1000 mg/m^2. Based on the activity demonstrated in this trial, phase II studies were subsequently conducted by the CRC in high-grade glioma [12], advanced malignant melanoma [13] and low-grade lymphoma [14]. In a phase I pharmacokinetic study of temozolomide and cisplatin in patients with advanced solid tumours, this combination showed some activity in NSCLC patients [15]. The distribution of temozolomide in the brain renders this drug an attractive agent against secondary brain malignancies.

A number of schedules of temozolomide administration have been developed in phase I trials [16–18]. The most frequent and approved for the treatment of high-grade gliomas is a schedule of daily treatment for 5 consecutive days with a daily dose of 200 mg/m^2 (150 mg/m^2 for patients previously exposed to chemotherapy), repeated every 28 days. With this schedule, grade 4 thrombocytopenia and grade 3/4 neutropenia occurred in 10% and less than 5% of patients, respectively. Other toxic effects, e.g. nausea, were mild and easily manageable by standard supportive therapy. The second most frequently used schedule of temozolomide administration has been a continuous treatment for 6–7 weeks with the recommended dose of 75 mg/m^2 daily. With this schedule, the most prominent side-effect was myelosupression and other toxicities were negligible [18].

On the basis of the above data, a phase II study was designed to assess the activity of temozolomide in chemotherapy-naïve, stage IV NSCLC patients, with and without BM. The study was conducted in four institutions of the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Group.

2. Patients and methods

2.1. Study subjects

Patients with histologically- or cytologically-confirmed NSCLC stage IV, with no prior chemotherapy for disseminated disease were enrolled into two separate study groups. Patients had to have at least one bidimensionally measurable lesion and for patients with BM, at least one measurable brain lesion was required. The minimum size of a target lesion was 2.5 cm in the largest diameter outside the brain and 2.0 cm in the brain. In patients without BM, prior palliative radiotherapy was allowed if given at least 4 weeks prior to registration and provided that there was at least one measurable lesion outside of the radiotherapy portals. Patients with brain lesions had to be either asymptomatic or had completed WBRT at least 4 weeks before study entry. Patients were required to be aged between 18 and 70 years old, to have a World Health Organization (WHO) performance status of 0-2 and adequate haematological, hepatic and renal function. No previous malignancies were allowed except for adequately treated *in situ* carcinoma of the cervix or squamous carcinoma of the skin. The trial was approved by the EORTC Protocol Review Committee and Local Ethical Committees of all participating institutions; informed consent had to be obtained before patient registration in the study. In the course of the trial, we discovered that the written informed consent could not be retrieved for 13 included patients (50%). However, all these patients were checked using other source data, and for all these patients, the responsible investigator stated that he/she fully informed the patient orally on all aspects of the trial and certified that each patient agreed to participate in the trial.

2.2. Study design

The primary objective of this non-randomised, multicentre phase II trial was to assess the therapeutic activity of temozolomide in metastatic NSCLC patients, with and without BM.

Temozolomide was administered orally at the dose of 200 mg/m^2 daily for 5 consecutive days of a 28-day cycle, under fasting conditions. Blood counts were assessed weekly during therapy; liver, renal function tests and electrolytes were monitored before each cycle. Temozolomide dose reduction was foreseen on two levels—from 200 to 150 and from 150 to 100 mg/m^2 upon the occurrence of grade 3/4 haematological toxicity or grade 3/4 non-haematological toxicity other than alopecia, nausea/vomiting and elevation of alkaline phosphatase or transaminases. The latter required a dose reduction in cases of grade 2 or more. No dose escalation was allowed. Treatment was continued until disease progression, unacceptable toxicity, patient refusal or for a maximum of six cycles. In the group of patients with BM, continuation of protocol treatment was allowed in cases of disease progression in only one site (brain or target lesions outside brain) and evidence of response in the other sites (mixed responses).

Evaluation of response was performed according to the WHO criteria [19]. Target lesions were assessed by

clinical examination, computed tomography (CT), gadolinium-enhanced magnetic resonance imaging (Gd-MRI), chest X-ray or ultrasound. The initial examinations had to be performed within 14 days prior to registration. Evaluation of target lesions was performed every 8 weeks and response had to be confirmed by a second evaluation performed at least 4 weeks apart.

For toxicity assessment, we used Common Toxicity Criteria (CTC) of the National Cancer Institute (NCI) extended by the National Cancer Institute of Canada (NCIC) [20]. Quality of life or lung cancer symptom assessment was not performed in this trial.

The study was planned as two distinct phase II trials, one for the group of patients with brain metastases and one for the group of patients without brain metastases. In each group, the trial was designed according to the Simon one-sample two-stage testing procedure [21]. Type I error of 10% and type II error of 10% were accepted to test that the response rate was between 10 and 30%. Under these assumptions, the planned total number of eligible patients in each group was 35. The first step of the analysis was performed to check for the lack of drug activity (less than two responses in the first 12 eligible patients in either group). Each group of patients (with and without BM) was evaluated separately. Ineligible patients were excluded from all the analyses.

3. Results

Between September 1997 and March 2001, 12 patients with BM and 14 patients without BM were registered in this study. According to the protocol, the study was temporarily closed for accrual in order to perform the first step analysis. After the response data of all the eligible patients became available, the study was definitively closed in both groups of patients based on the results of this analysis.

Of 26 patients registered in this trial, all except 1 patient without BM were eligible. The lack of lesions suitable as a target for the response evaluation was the reason for the ineligibility of this patient (the lesions were too small and no thoracic CT scan was available). In addition, one protocol violation was noted in the group with BM (low creatinine clearance) and three others were identified in the group of patients without BM (low creatinine clearance; small target lesion which, however, could clearly be assessed for response, and missing baseline bilirubin and brain CT scan).

When considering the 25 eligible patients registered in this study, adenocarcinoma was the most frequent histology (Table 1). 4 patients with a performance status of 2 were enrolled in the group of patients with BM (33%) whereas in the group of patients without BM, only 1 patient with a performance status of 2 was registered (8%). In the group with BM, 9 eligible patients (75%) received at least one prior treatment for NSCLC (mainly surgery and/or radiotherapy, induction chemotherapy was given to 1 patient and palliative brain radiotherapy to 4 patients). In the group without BM, 5 patients (38%) received at least one prior treatment (surgery and/or radiotherapy).

Table 1
Baseline characteristics in 25 eligible patients

Characteristic	Patients with BM ($n=12$) N (%)	Patients without BM ($n=13$) N (%)
Age median (range), years	57 (42–69)	53 (46–68)
Gender		
Male	6 (50)	9 (69)
Male	6 (50)	4 (31)
Performance status		
0	2 (17)	5 (38)
1	6 (50)	7 (54)
2	4 (33)	1 (8)
Histological subtype		
Squamous cell	3 (25)	0 (0)
Adenocarcinoma	7 (58)	8 (62)
Large cell	1 (8)	4 (31)
NSCLC (undetermined)	1 (8)	1 (8)
Baseline leucocyte count		
Median (range), 10^9/l	10 (8.3–40)	9.8 (6.1–25.9)
Baseline haemoglobin		
Median (range), g/l	134 (98.2–150)	131 (79.4–153)
Baseline platelet count		
Median (range), 10^9/l	306 (184–509)	338 (234–999)

BM, brain metastases; NSCLC, non-small cell lung cancer.

In the group of patients with BM, 26 cycles of temozolomide were given to the 12 eligible patients, with a median of only one cycle per patient (range 1–6). In the group of patients without BM, a total of 26 cycles of treatment were given to the 13 eligible patients, with a median of two cycles per patient (range 1–4). A significant proportion of patients received only one cycle of treatment—7 in the group with BM (58%) and 5 in the group without BM (38%). Only 1 patient completed six cycles of treatment as planned by the protocol in the group with BM (8%). The reasons for treatment discontinuation are presented in Table 2.

Table 2
Reasons of treatment discontinuation

Main reason	Patients with BM ($n=12$) N (%)	Patients without BM ($n=13$) N (%)
Progressive disease	8 (67)	11 (85)
Toxicity	2 (17)	1 (8)
Refusal	1 (8)	0 (0)
Completion of protocol therapy	1 (8)	0 (0)
Intercurrent death	0 (0)	1 (8)

Toxicity was moderate and mostly haematological (Table 3). Median granulocyte nadir counts for all cycles were 6.8 and 4.7×10^9/l for patients with and without BM, respectively (range 0.1–16.2 and 0–27.2×10^9/l). For nadir platelet counts, the respective median values were 136 and 242×10^9/l (range 21–430 and 5–429×10^9/l, respectively). In the group with BM, 2 patients discontinued their treatment with temozolomide due to toxicity. In 1 patient, grade 2 anaemia was reported as the reason for treatment discontinuation. In another patient, grade 4 neurological toxicity (confusion and seizures) occurred and was scored as possibly related to temozolomide. This event was also considered as possibly linked to early disease progression. In the group without BM, 1 patient went off treatment due to prolonged febrile neutropenia after 3 cycles.

At the time of this analysis, all eligible patients in both groups progressed and all except one in the group with BM have died. One death occurred as a result of gastrointestinal bleeding that occurred 19 days after the last administration of the third cycle of temozolomide. Platelet count 1 day before the death of the patient was 72×10^9/l. This event was recorded as early death due to other causes, although toxic death due to thrombocytopenia could not be excluded. The remaining patients died due to progression of disease.

In the group with BM, 1 patient was not assessable for response— after receiving one cycle of chemotherapy he stopped treatment due to confusion and seizures. In this group, 3 patients were considered to have stable disease (25%), 4 progression (33%) and 4 died early due to malignancy (33%). In the group without BM, all 13 patients were assessable for response. Stable disease was noted in 3 patients (23%), progressive disease in 7 patients (54%), and early death due to malignant disease in the remaining 3 patients (23%). In both groups of patients, no objective responses were observed.

Table 3
Major toxicities (grades 3 and 4 according to Common Toxicity Criteria extended by National Cancer Institute of Canada, NCIC CTC) in 25 eligible patients

Toxicity	Patients with BM ($n=12$)			Patients without BM ($n=13$)		
	3	4	(% 3/4)	3	4	(% 3/4)
Haemoglobin	1	0	(8)	1	1	(15)
Leucocytes	0	1	(8)	0	1	(8)
Platelets	1	1	(17)	1	2	(23)
Granulocytes	1	1	(17)	0	1	(8)
Febrile neutropenia	0	0	(0)	1	0	(8)
Infection	1	0	(8)	0	0	(0)
Nausea	0	0	(0)	2	0	(15)
Vomiting	1	0	(8)	1	0	(8)
Diarrhoea	0	0	(0)	1	0	(8)
Constipation	1	0	(8)	0	1	(8)
Lethargy	2	0	(17)	2	0	(15)
Headache	1	0	(8)	0	0	(0)
Other neurological	1	1	(17)	0	0	(0)
Pain/cramping	0	0	(0)	1	0	(8)
Cancer pain	1	0	(8)	0	0	(0)
Other genitourinary	2	0	(17)	0	0	(0)
Other cardiovascular	0	0	(0)	1	0	(8)
Haemorrhage	0	0	(0)	0	1	(8)
Other toxicities[a]	0	0	(0)	1	1	(15)

G, grade.
[a] Weight loss G3/Prothrombin G4.

4. Discussion

The response rates of single-agent or combination chemotherapy in disseminated NSCLC remain unsatisfactory and rarely exceed 20%. The bad prognosis of stage IV NSCLC patients, particularly those with BM, and the promising activity of temozolomide in preclinical studies provided a rationale for testing this agent in a phase II trial. According to our knowledge, this is the first phase II study of temozolomide in previously untreated stage IV NSCLC.

Unfortunately, we were not able to demonstrate any therapeutic activity of single-agent temozolomide against NSCLC in stage IV patients, with and without BM. The poor treatment results in the group of patients without BM might, in part, be influenced by selection bias. It is likely that investigators might have been reluctant to offer study treatment to patients who were candidates for more aggressive chemotherapy regimens. At present, two-drug platinum-based combinations are considered as the 'standard of care' in most of the NSCLC population who have a good performance status, no severe weight loss and no major co-morbidities. These regimens have been found to produce BM regressions in up to 50% of patients [22]. In addition, most BM patients require immediate brain irradiation for symptom palliation or to delay the occurence of severe neurological deficits.

A negative conclusion regarding the therapeutic activity of temozolomide in the group of patients with BM in our study should be viewed in the context of three phase II trials performed in patients with metastatic disease to the brain [23–25]. In the first two of these studies, heavily pretreated patients with a variety of primary tumours were included, with NSCLC as the most frequent tumour type. In the study reported by Abrey and colleagues, 41 patients with BM were evaluated including 22 with NSCLC; two partial responses were observed in this study in the NSCLC patients. Another 8 patients in this group were evaluated as having stable disease [23]. In a study by the Hellenic Cooperative Oncology Group, there were 12 NSCLC patients out of a total of 28 patients and the only response, both at primary tumour and in the brain, was noted in this malignancy [24]. As in our study, most of the patients in

the latter study did not complete the planned treatment and died within 2 months after commencement of therapy. A recently reported phase II study compared the response rate of concurrent oral temozolomide (75 mg/m^2 daily) and 40 Gy conventionally fractionated whole brain radiotherapy to radiotherapy alone in patients with BM from solid tumours [25]. NSCLC was the diagnosis in two-thirds of these patients, and most of them did not have any extracranial disease. No information on previous treatment for the primary site and no data on extracranial responses were provided in the report. Patients receiving chemo-radiotherapy were also treated with an additional six cycles of oral temozolomide 200 mg/m^2 for 5 days every 28 days. In this study, a significantly superior objective response rate in the brain (96% versus 67%) and a marked difference in neurological function and the proportion of patients requiring corticosteroids in favour of concomitant treatment were described. No difference in survival was noted, although this was not anticipated with the trial design. This relatively small study supports the hypothesis of useful interaction between temozolomide and radiotherapy in patients with metastatic brain disease. However, in view of the negative results of our study and others [23,24], oral temozolomide should not be accepted as a systemic treatment for NSCLC where there are active first- and second-line therapies.

Early disease progression as the main reason for treatment discontinuation may be considered to be a result of ineffective treatment of NSCLC patients with a particularly bad prognosis. It is possible that a negative selection of patients in our trial might have influenced this high rate of early treatment failure. However, the baseline characteristic of our patients do not substantially differ from the expected population of stage IV NSCLC patients, with or without BM. Most of our patients had relatively good performance status, as well as adequate haematological, renal and liver function.

Similar to the results of another recently completed phase II EORTC Lung Cancer Group trial of single-agent temozolomide given with the same schedule in previously untreated patients with malignant pleural mesothelioma [26], haematological toxicity was mild and dose reductions relatively infrequent. Nausea and vomiting was the most frequent drug-related non-haematological toxicity, and grade 3/4 lethargy was observed in 2 patients with and 2 patients without BM.

In conclusion, we could not demonstrate any therapeutic activity of single-agent temozolomide in chemotherapy-naïve stage IV NSCLC patients, both with and without BM. We do not recommend further testing of this drug as a single-agent in advanced NSCLC patients. Platinum-based chemotherapy remains the 'standard of care' for patients with advanced NSCLC, including those with BM, along with brain radiotherapy for patients with neurological symptoms.

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