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A phase II EORTC study of temozolomide in patients with malignant pleural mesothelioma

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Abstract

The aim of this study was to investigate the anti-tumour activity of temozolomide in patients with malignant pleural mesothelioma. 27 chemotherapy-naïve patients with histologically-proven malignant mesothelioma were treated with temozolomide 200 mg/m^2/day, given orally on days 1–5 of each 28-day cycle. Therapy continued up to 10 cycles unless disease progression or excessive toxicity mandated discontinuation. Toxicity, symptom improvement and pain intensity were regularly assessed. With a median relative dose intensity of 97%, toxicity was moderate with grade 3 or more nausea, vomiting, thrombocytopenia, leucocytopenia, neutropenia, febrile leucocytopenia, arthralgia, infection and fever with infection occurring in 13, 13, 10, 3, 7 and 3% of patients for the remaining events, respectively. Overall, 1 objective response was observed (response rate 4%, 95% Confidence Interval (CI): 0.1–19). Median survival was 8.2 months. Symptom assessment showed no improvement and an increase of pain was observed during the study. Thus, oral temozolomide is an inactive agent in malignant mesothelioma.

Keywords: Chemotherapy; Mesothelioma; Phase II study; Pleura; Temozolomide

1. Introduction

Malignant mesothelioma is a nearly invariably incurable tumour, whose appearance is often strongly linked with prior asbestos exposure. Its incidence is expected to further increase in the next few decades in most countries [1]. Its natural history is characterised by a median survival of 9–14 months, with less than 5% 5-year survivors. Several factors predictive of survival have been identified, allowing the classification of patients into prognostic groups [2,3].

At the present time, there is no standard of care for patients with advanced malignant mesothelioma. The current status of chemotherapy based on the literature can be summarised as follows [4,5]. Cisplatin and doxorubicin are considered the most active among the single agents tested. Results of combination chemotherapy do not appear to provide better results than single agents, although response rates have been higher in some studies and combinations. Reports of symptom improvement achieved by chemotherapy are to be confirmed. As part of a continuing programme to develop and evaluate novel drugs in this disease, the European Organization for Research and Treatment of Cancer—Lung Cancer Group (EORTC—LCG)-LCG has assessed the anti-tumour effect of several agents in chemotherapy-naïve patients with malignant pleural mesothelioma during the past decade [6–11].

Temozolomide is an orally bio-available DNA-methylating agent, with significant activity in metastatic malignant melanoma and in patients with primary brain tumours [12,13]. Its mechanism of action, toxicity and

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clinical pharmacology have been extensively reviewed [14]. Adverse events are reported to be mild or moderate in severity, with haematological side-effects occurring in less than 10% of patients [15,16].

We assessed a possible activity of temozolomide in chemotherapy-naïve patients with pleural mesothelioma in a multicentre phase II study.

2. Patients and methods

2.1. Study subjects

As this study was part of a continuing programme of sequential phase II studies, the inclusion criteria of patients are similar to the ones of prior studies [6–11]. Briefly, patients with histologically-confirmed malignant mesothelioma of the pleural cavity, who had received no prior chemotherapy, were accrued into this study. Pathology was centrally reviewed. Tumour extension was classified according to the International Mesothelioma Interest Group (IMIG) and had to be bidimensionally measurable in at least one target lesion [17]. Pleural effusion alone was not accepted as evaluable disease. Previous intracavitary treatment was allowed, provided no cytotoxic drugs or immune modulators were applied. Patients had to be older than 18 years, present with World Health Organization (WHO) performance status of 0 to 2. Furthermore, they had to have an adequate haematological (haemoglobin >97 g/l, granulocyte count $\geqslant 2\times10^9$/l, platelet count $\geqslant 100\times10^9$/l), hepatic (bilirubin <25 μmol/l, alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) $<2.5\times$upper limit of normal (ULN) or $<5\times$ULN in case of liver involvement) and renal (creatinine clearance $\geqslant 1$ ml/s) function. Prior and concomitant radiotherapy was permitted to painful lesions, needle tracks or surgical scars, provided that the indicator lesions were outside the irradiated field. Patients with symptoms or signs of metastases in the central nervous system (CNS) and those with a recent history of body weight loss of $\geqslant 10\%$ were excluded. The Ethical Board of all participating institutions approved the study. Written informed consent from each patient had to be obtained before patient entry.

2.2. Study design

Temozolomide at a dose of 200 mg/m^2/day was given orally on days 1–5 of each 28-day cycle. In general, treatment was administered on an outpatient basis. Patients were asked to fast one hour pre and one hour post administration of temozolomide. Blood cell counts were assessed weekly after administration, and liver/renal function controlled before each cycle. Treatment cycles were repeated every 28 days, provided toxic effects were not prohibitive and there was no clinical evidence of tumour progression. Dose escalation of temozolomide was not permitted. The dose of temozolomide for subsequent cycles was adjusted according to nadir counts with dose levels of 150 and 100 mg/m^2/day, respectively. In cases of grade 3 or greater haematological toxicity, patients were to be treated at the lower dose level. The same applied for non-haematological toxicity, except for alopecia, nausea, vomiting and elevation of transaminases and alkaline phosphatase. In the latter case, any grade 2 elevation of transaminases or alkaline phosphatase had to be resolved to at least a grade 1 prior to repeat dosing; in the following cycle a one dose level reduction was applied. Full haematological recovery was required for retreatment. Patients delayed by more than 2 weeks and/or requiring a dose level reduction to below 100 mg/m^2/day were taken off study. Administration continued up to 10 cycles, unless tumour progression, death, patient refusal or unacceptable toxicity developed or the investigator thought that further treatment was not beneficial.

Tumour response was assessed with target lesions at baseline, every second cycle and at the end of treatment, according to WHO criteria [18]. Target lesions had to be at least 2.5 cm in their largest diameter. Nodular thickening of the pleura was accepted as a target lesion if the thickening was at least 2 cm in its largest perpendicular diameter on at least two contiguous levels of the computed tomography (CT) scan. The use of CT scans was mandatory for evaluation. Objective responses had to be confirmed by two measurements, at least 4 weeks apart, during which time no new lesions could appear and no existing lesion could enlarge by $\geqslant 25\%$.

Toxicity was scored according to the common toxicity criteria of the National Cancer Institute (NCI) extended by the National Cancer Institute of Canada (NCIC) [19]. As part of the protocol, assessment of symptoms was registered. A disease-specific checklist, adapted from the EORTC Quality of Life Core 30 Questionnaire (QLQ-C30) and the EORTC QLQ-Lung Cancer (LC13), was developed for this purpose [20]. The symptoms included in the checklist were dispancea pain, need to rest, insomnia, feeling of weakness, fatigue, pain interfering with daily activities, cough and chest pain. Two overall quality of life (QL) scales were included. The symptom checklist had to be completed at baseline and before each subsequent cycle of treatment, until the end of last treatment. A visual analogue score evaluating the patient's perception of his/her pain intensity during the previous week had to be completed.

Patient suitability for enrolment was determined by the pathological report at the treating institution, and reviewed by the national mesothelioma pathology board. Only patients with an unequivocal histological diagnosis of pleural mesothelioma were considered eligible. Responses had to be reviewed by an independent radiologist.

This study was planned according to the Simon one-sample, two-stage testing procedure, having type I and type II error rates of $<10\%$ each to differentiate between a response rate of 10 and 30% [21]. A first step analysis was planned after 16 patients had been treated, and there was further accrual to a total of 25 eligible patients if more than one objective response was seen. The regimen would be considered for further evaluation if more than four objective responses were seen in the eligible patients. To compensate for ineligibility, some extra-patients were included. The Kaplan–Meier method was used to estimate overall survival of all registered patients [22]. Toxicity and symptom assessment were analysed on all of the registered patients.

3. Results

Between March and October 1998, 30 patients were registered into the study from five institutions in The Netherlands and Belgium. Due to a rapid accrual and the impossibility to evaluate responses in a short time, the original two-step design could not be adhered to. The median interval between diagnosis and treatment start was 5 months (range 1–72 months). 3 patients were considered ineligible: 2 lacked measurable lesions, 1 started chemotherapy before registration. Some major characteristics of prognostic significance in the 27 eligible patients and their tumours are listed in Table 1. In 24 of these, review of the pathologist's report allowed the diagnosis to be confirmed. Pathology review of the remaining cases could not be performed.

Table 1
Patient and tumour characteristics in 27 eligible patients

Characteristic	Patients (*n*) (%)
Sex	
Male	23 (85)
Female	4 (15)
Median age (range), years	57 (42–77)
Performance Status (WHO)	
0	5 (19)
1	20 (74)
2	2 (7)
TNM stage (IMIG)(15)	
I–II	5 (19)
III–IV	22 (81)
Histological subtype	
Epithelial	17 (63)
Non-epithelial	8 (30)
Not specified	2 (7)
Prior treatment	
Pleurodesis	16 (59)
Prior radiotherapy	10 (37)
Surgery	3 (11)
Baseline WBC count	
$<8.3\times10^9$/l	13 (48)
$\geqslant8.3\times10^9$/l	14 (52)
Baseline platelet count	
$\leq350\times10^9$/l	8 (30)
$>350\times10^9$/l	19 (70)
Baseline LDH	
$\leqslant$upper normal limit	23 (85)
$>$upper normal limit	1 (4)
Unknown	3 (11)

LDH, lactate dehydrogenase; WBC, white blood cells; WHO, World Health Organization; IMIG, International Mesothelioma Interest Group; TNM, tumour, node, metastasis.

Temozolomide was administered 419 times in 85 cycles. The median number of cycles per patient was 2 (range 1–8), with 21 patients receiving at least two cycles. A median relative dose intensity of 97% (range 40–100) was reached. 2 patients never completed one cycle due to toxicity, 4 stopped after one cycle and 8 others stopped after cycle 2. Only 1 patient received all eight cycles.

Toxicity was mild and mostly of gastrointestinal origin. Details of severe toxicities (grade 3 or more) are described in Table 2. The median neutrophil nadir count was 4.0×10^9/l (range 0.5–15) and the median platelet nadir count was 236×10^9/l (range 33–776). All severe toxicities were thought to be related to drug administration, except 3 cases of dyspnoea, 1 of lethargy and 1 of paresis at the end of the first cycle. The latter was attributed to progression of disease for which local radiotherapy was administered. 3 patients went off study due to toxicity (nausea, vomiting, malaise and febrile neutropenia) and another 3 patients refused further treatment for reasons related to toxicity.

The compliance of the symptom checklist was at baseline 80%. Fig. 1 details the distribution of symptoms at registration. The dropout of patients thereafter was substantial and mostly due to progression of disease. This attrition highlights the importance of collecting QL questionnaires also after progression [23]. We

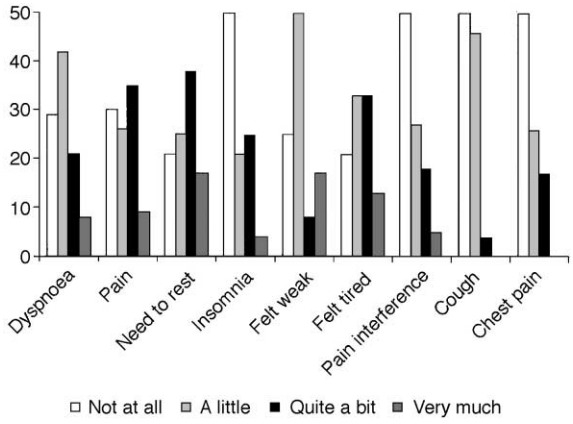

Fig. 1. Distribution of mesothelioma-specific symptoms at baseline as % of all 30 patients on this study.

Table 2
Grade 3 and 4 toxicities (according to National Cancer Institute of Cancer Common Toxicity Criteria (NCIC CTC)) as encountered in all 30 patients[a]

Toxicity (grade)	3	4	% 3/4
Leucocytes	1	–	3
Granulocytes	2	–	7
Platelets	3	–	10
Febrile neutropenia	1	–	3
Infection	–	1	3
Fever w/o infection	–	1	3
Nausea	4	–	13
Vomiting	2	2	13
Arthralgia	1	–	3
Lethargy[b]	1	–	3
Dyspnoa[b]	3	–	10
Neurologic (motor)[b]	1	–	3

[a] The highest CTC grade for each patient is reported.
[b] Considered not-drug related.

grouped patients into two groups: patients who stopped treatment before the fourth cycle versus those who stopped later. The latter tended to have a higher baseline QL score than the former. We can therefore assume that the dropout is not completely at random, i.e. there is selection bias in the inclusion of patients into the QL analysis at later time points. This bias is difficult to assess and to adjust for, as the number of patients is quite small. Therefore, care has to be taken in the interpretation of the following changes. Scores for dyspnoea and pain tended to increase just before patient's dropout. Insomnia tended to decrease after the start of treatment and cough tended to increase after two or three cycles. There is a tendency for a decrease in general QL before stopping treatment. The scores for the other items do not show any clear trend. The QL score by response to treatment show that patients with a high initial QL score are more likely to respond or have stable disease instead of progression.

3 patients (11%) were considered treatment failures since they stopped treatment after the first cycle due to toxicity (2) and refusal (1). 2 patients died of their disease before formal response evaluation was possible. All the other eligible patients were assessable for response. There was one confirmed partial response in a pathology-reviewed patient (response rate 4%, 95% confidence interval (CI) 0.1–19%), observed after two cycles at the site of a soft-tissue metastasis and confirmed after four cycles. Duration of response was 4 months. 11 other patients (41%) were considered to have stable disease, while 10 (37%) showed disease progression during therapy.

At the time of analysis, 19 patients died, all due to progression of disease. Patients still alive at the time of analysis were censored. Median survival from diagnosis was 13.9 months (95% CI: 10.7–21.3) and 8.2 months (95% CI: 3.9–11.0) from trial registration (Fig. 2).

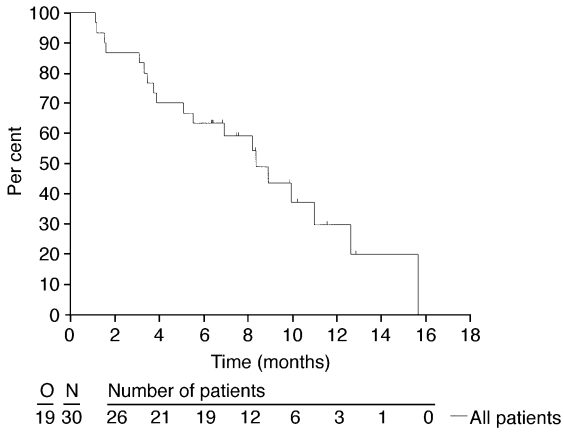

Fig. 2. The overall survival (Kaplan–Meier plot) for the 30 patients registered on this study. O, observed; N, number.

Progression-free survival and survival estimates at 6 months were 20% (95% CI: 6–34%) and 63% (95% CI: 46–80%), respectively. The corresponding estimate for the 1-year survival was 30% (95% CI: 10–50%).

4. Discussion

Experts in the field of mesothelioma treatment agree that the results of available clinical studies justify the current policy of continuing to investigate new single agents in patients with this refractory tumour type [24]. The rationale for choosing temozolomide as an agent for phase II testing in malignant mesothelioma was the observed activity in other chemo-resistant solid tumours such as brain tumours and melanoma [12–16].

In this study, only very limited therapeutic activity of single agent temozolomide against mesothelioma was observed at a dosage and schedule that are commonly employed in untreated patients [15,16]. Compared with other studies the median number of cycles per patient was low. We speculate that this could be the reason for the low observed activity and QL benefit. The patient and tumour characteristics and prognostic factors were indeed similar to those of previous EORTC studies [2].

Haematological toxicity was mild resulting in few dose reductions and hence a high median dose-intensity. Non-haematological toxicity was a major reason for treatment discontinuation due to gastrointestinal side-effects, clearly related to drug intake and resolved after stopping treatment. Several investigators have observed important clinical benefit and symptom improvement with chemotherapy, even in patients without objective response [25,26]. Unfortunately, we were not able to objectify this in this study, as the response rate was low and the rate of dropout high. As the rapid accrual made a two-step design not feasible, future EORTC phase II studies in this disease should be designed according to Fleming's single stage procedure.

In conclusion, this trial excludes at 90% power a response rate of greater than 30% for single agent temozolomide at the prescribed dosage and schedule in chemotherapy-naïve patients with malignant pleural mesothelioma. Temozolomide was only moderately tolerated and no symptomatic improvement was observed. We do not recommend further testing of the drug as a single agent in this disease.

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