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The activity of raltitrexed (Tomudex®) in malignant pleural mesothelioma: an EORTC phase II study (08992)

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Abstract

We investigated the activity and toxicity of raltitrexed (Tomudex®) as a single agent treatment in patients with Malignant Pleural Mesothelioma (MPM) in a multicentre phase II European Organization for Research and Treatment of Cancer (EORTC) study. This study enrolled chemonaïve patients with histologically-confirmed measurable MPM. Raltitrexed was administered at the dose of 3 mg/m^2 intravenous (i.v.) bolus on an outpatient basis every 3 weeks. A maximum of eight cycles was planned in cases with an absence of progression or unacceptable toxicity. 24 patients received a total of 104 courses. 5 patients (20.8%, 95% confidence interval (CI) 7.1–42.2%) had a partial response (PR), which was confirmed by an independent radiology committee. Toxicity was mild, with diarrhoea, nausea, vomiting, fatigue and neutropenia as the major side-effects, but not exceeding grade 3 toxicity. We conclude that raltitrexed has activity as a single agent in the treatment of MPM, and that further studies with this drug in MPM are warranted.

Keywords: Malignant Pleural Mesothelioma, Tomudex, Phase II, EORTC

1. Introduction

In the next two decades, the incidence of Malignant Pleural Mesothelioma (MPM) is expected to rise in a number of Western countries. MPM is known for its resistance to chemotherapeutic agents. Many researchers have been challenged to find an active compound or combination therapy in this disease. In the last 10 years, the European Organization for Research and Treatment of Cancer Lung Cancer Group (EORTC LCG) has carried out a large phase II programme to screen the single agent activity of new anticancer agents using a stringent and consistent methodology including pathology review, computed tomography (CT)-based response assessment and extramural response review. We have completed over seven different phase II single agent studies in this disease, but, unfortunately, all of the tested agents had an antitumour activity of $\leqslant$15% [1–3].

A review of the literature indicates that there are only few compounds that show modest response rates [4,5], including cisplatin, doxorubicin and methotrexate. Methotrexate and its analogues interfere with the folate acid metabolism in MPM cells. Scandinavian studies have indicated that an overall response rate of up to 40% can be achieved in patients with the epithelial type

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of MPM using folate inhibitory drugs (with or without interferon) [6,7].

Raltitrexed (Tomudex®) is a quinazoline folate analogue, which acts as a pure and specific inhibitor of thymidylate synthase, which is one of three enzymes involved in the synthesis of DNA [8]. It is also a substrate for the enzyme folylpolyglutamate synthase, which converts raltitrexed into its polyglutamate forms. The polyglutamate forms are retained for long periods of time within the cell and are up to a 100-fold more potent inhibitors than the parent compound. The effectiveness of raltitrexed has been shown in a number of studies in Gastro Intestinal (GI) tumours with response rates of up to 20–25% for doses of 3.0 mg/m^2 administered intravenously (i.v.) every 3 weeks [9,10]. The major dose-limiting toxicities are leucopenia, diarrhoea and fatigue. An increase in liver enzymes has also been reported. Raltitrexed has been tested in MPM in combination with oxaliplatin by French investigators. In a phase II study of 30 patients with MPM a response rate of 30% (9/30) was observed [11]. However, single agent activity of raltitrexed in MPM is unknown.

To complete the overall spectrum of activity in chemonaive patients with MPM, the EORTC LCG decided to perform an open phase II study of single agent raltitrexed.

2. Patients and methods

Eligible patients had biopsy-proven and confirmed malignant mesothelioma of the pleura. Patients were chemonaive and pleurodesis with cytotoxic drugs was not allowed. Prior surgery or local radiation to the entrance ports was allowed, but evidence of progression had to be documented and the interval between radiation and registration had to be at least 4 weeks. Eligible patients had to be older than 18 years, had to have a performance score of 0-2 according to the Eastern Cooperative Oncology Group-World Health Organization (ECOG-WHO) scale and at least one target lesion that could be accurately measured in at least one dimension. Written informed consent was obtained from all patients. The Response Evaluation Criteria in Solid Tumours (RECIST) [12] criteria were applied in this study to assess the objective response. The target lesion had to be at least 2 cm thick in its longest diameter. Since it is difficult to determine the 'longest' diameter of pleural lesions, during radiology response review it was decided to take the maximum rind thickness as the 'longest' diameter. However, during the extramural response review, responses were also assessed according the WHO criteria to confirm reliability of the modified RECIST criteria applied in this study. The tumour extension was classified according to the International Mesothelioma Interest Group (IMIG) [13]. Patients had to have the following laboratory requirements: haemoglobin $\geqslant$6.2 mmol/l (100 g/l), white blood cells (WBC) $\geqslant 4.0\times10^9$/l, absolute neutrophil count (ANC) $\geqslant 2.0\times10^9$/l, platelets $\geqslant 100\times10^9$/l, bilirubin $<$25 μmol/l, albumin $\geqslant$30 g/l, creatinine $<$150 μmol/l (1.69 mg/dl), creatinine clearance $\geqslant$1.08 ml/s (measured or calculated), alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) $<2.5\times$ the upper limit of normal (if known liver involvement $<5\times$ULN). Malignant pleural effusion was not considered measurable and radiotherapy or minor surgery could be given to lesions other than the indicator lesions. Patients with symptoms or signs of brain metastates were not eligible.

Raltitrexed (Astra Zeneca Inc) 3.0 mg/m^2 was administered on day 1 of each cycle in a 15-min i.v. infusion every 3 weeks in an outpatient setting. A minimum of two cycles was administered before evaluation. In the absence of disease progression, unacceptable toxicity or patient refusal, a total of eight cycles were administered. Disease evaluation was based on both clinical and radiological evaluation (CT scan and standard chest X-ray). Side-effects were graded according to the International Common Toxicity Criteria (CTC), version 2.0.

Dose delays were planned in cases of incomplete haematological recovery (WBC $<3.0\times10^9$/l, ANC $<1.5\times10^9$/l, platelets $<100\times10^9$/l), bilirubin $\geqslant$25 μmol/l, ALAT and ASAT $\geqslant 2.5\times$ULN (or $>5\times$ULN if known liver involvement). Additionally, diarrhoea and stomatitis had to be fully recovered for at least 3 days without medication and all non-haematological toxicities should be recovered to CTC grade $<$2 before recycling. If the calculated creatinine clearance was $<$65 ml/l on the day of recycling, the treatment was postponed for 1 additional week. In the absence of recovery, a dose reduction and a 4-weekly dose interval were mandatory. For any delay exceeding 2 weeks, the patient went off the study.

Dose reductions were based on the worst grade of toxicity during the previous cycle and was mainly based upon a combination of haematological toxicity (ANC count and platelet count) and diarrhoea. Any grade 2 diarrhoea (with or without haematological toxicity $<$grade 4) resulted in a 25% dose reduction of raltitrexed and in a 50% dose reduction in cases of grade 3 diarrhoea. The same dose reduction scheme applied for grade 3 and grade 4 haematological toxicity (with or without diarrhoea $<$grade 3). Any occurrence of grade 4 diarrhoea at any moment was a reason to stop further treatment, as well as grade 3 diarrhoea in combination with grade 4 haematological toxicity. Following a dose reduction, the recurrence of grade 3 or 4 toxicity was also a reason to stop further treatment.

Tumour response and acute toxicity were the main end points of this study. The response of the target lesion was evaluated every two cycles with a contrast-enhanced CT scan of the thorax and upper abdomen and compared with a baseline CT scan. In cases of

complete or partial response (CR or PR), confirmation after at least 4 weeks was required. In the case of stable disease (SD), the CT scan had to be repeated at an 8-week interval, during which time no new lesions should appear. Responders were reviewed by two independent radiologists. Pathological review by an expert panel was performed retrospectively.

Statistical analysis was performed using the Fleming's one-stage testing procedure [14]. Type I and II errors were set at 0.1, P_0 (largest response probability which if true implies that the therapeutic activity does not warrant further investigation of the drug) and P_1 (lowest response probability which if true implies that the therapeutic activity warrants further investigation of the drug), were set at 10 and 30%, respectively. Under this hypothesis, the sample size was 24 patients. If $\leqslant 4$ responders were observed, the drug was considered ineffective. In the case of >4 responders, it was concluded that further investigation of the drug was indicated. All results presented are based on eligible patients.

3. Results

Between November 1999 and June 2001, a total of 25 patients were registered in this phase II study by five European institutions. At the time of analysis, all patients had terminated the protocol treatment. One patient was considered ineligible because of the lack of a histologically-proven diagnosis of MPM. Pathological review was performed in 21 out of the 24 eligible patients. For 1 patient, no data of local nor central pathology were received by the time the analysis was performed. For the 2 other patients, only local pathological information was available. Out of the 21 centrally reviewed cases, 18 were confirmed as being 'definitive' or 'probable' MPM. In 2 cases, central pathological review considered diagnosis to be 'possible' MPM; furthermore, both patients had a history of asbestos exposure and radiological findings were compatible with MPM. For the last patient, despite diagnosis of definite MPM by a local pathologist, the central pathology could not confirm this as such, probably due to non-representative slides (the slides only contained fibrous pleural plaque). The major characteristics of the patients and the histological subtypes are presented in Table 1. The clinical staging according to the IMIG is presented in Table 2.

A median number of three cycles were administered with a range of 1–8 cycles. 2 patients received only one cycle and 5 completed the planned eight cycles. Two cycles were given to 7 patients, three cycles to 3 patients, four and five cycles each to 1 patient and six cycles to 5 patients. Reasons for going off the treatment before completion of eight cycles were disease progression in 11 patients, toxicity in 3 patients, patient refusal in 1 patient and other reasons in 2 (psychological/anorexia and misinterpretation of the protocol). 2 patients received only six cycles since there was no response occurring and continuation was not considered to be in the best interest of the patient.

Treatment compliance was violated in 9 patients. There was over-treatment in 7 patients who had a grade 2 increase in ASAT/ALAT levels and should have been dose delayed. In 1 of these patients, grade 2 diarrhoea

Table 1
Patient and tumour characteristics of 24 eligible patients

Characteristics	No. (%)
Sex	
Male	19 (79)
Female	5 (21)
Age (years)	
Median (range)	63 (34–75)
Performance status	
0	5 (21)
1	15 (63)
2	4 (17)
Histologically-proven diagnosis (local pathologist)	
Definite	20 (83)
Probable	3 (13)
Possible	1[a] (4)
Histological subtype (local pathologist)	
Epithelial	21 (88)
Sarcomatous	1 (4)
Mixed	1 (4)
Unknown	1 (4)
Asbestos exposure	
No	7 (29)
Yes, possible	6 (25)
Yes, definitive	11 (46)

[a] This patient was initially registered by error as 'possible' MPM, but the local pathological report as well as the central pathology review stated the histological diagnosis as 'probable' MPM.

Table 2
Tumour staging according to the IMIG [13] ($N=24$ eligible)

Category	No. (%)
Clinical T category	
T1	1 (4)
T2	9 (38)
T3	5 (21)
T4	9 (38)
Clinical N category	
N0	18 (75)
N2	5 (21)
N3	1 (4)
Clinical M staging	
M0	20 (83)
M1	4 (17)

IMIG, International Mesothelioma Interest Group.

also occurred for which no dose delay was given. No additional toxicity in these patients was observed due to the overdosing. 2 patients with a grade 2 increase in ASAT/ALAT levels were under-treated as their dose was reduced instead of delayed. There were no other severe protocol violations or toxic deaths observed. The median relative dose intensity was 100.8% (95% Confidence Interval (CI): 64.3–105.2%).

Details of the haematological and other toxicities are presented in Table 3. Haematological toxicity was mild. One patient experienced a grade 4 anorexia but this occurred at the time of disease progression, probably not drug-related. Another grade 4 toxicity occurring in this trial (shortness of breath) was also associated with disease progression.

3.1. Responses

Of the 24 eligible patients, five PRs were observed and confirmed by two independent radiologists using the modified RECIST criteria (response rate: 20.8% with a 95% CI of 7.1–42.2%). There was no difference between the modified RECIST and WHO criteria in the assessment of response, therefore we agreed to use the modified RECIST criteria for the response measurement. 8 patients experienced SD and 8 patients progressed during treatment. One patient died prematurely due to progressive disease and for 2 patients the response could not be assessed due to an early discontinuation of the protocol treatment after one cycle (toxicity and patient refusal). The mean duration of response was 9.4 months, the median survival of the whole group was 7 months (95% CI: 5.5–18.7 months).

Table 3
Grade 3 and 4 toxicities according to the International CTC ($N = 24$ eligible)

Grade NCIC	Grade 3	Grade 4	Grade 3-4 (%)
Haemoglobin	–	–	0
Leucocytes	1	–	4
Platelets	–	–	0
Neutrophils	3	–	13
Fatigue	2	–	8
Febrile neutropenia	1	–	4
Weight loss	1	–	4
Diarrhoea (grade 2: 4 patients)	1	–	4
Anorexia	–	1	4
Nausea	1	–	4
Vomiting	1	–	4
Other neurological toxicity	1	–	4
Chest pain	1	–	4
Pleuritic pain	2	–	8
Other pain	2	–	8
Cough	1	–	4
Shortness of breath/dyspnoea	1	1	8
Other toxicities[a]	1	–	4

CTC, Common Toxicity Criteria; NCIC, National Cancer Institute of Canada; ASAT/ALAT, aspartate aminotransferase/alanine aminotransferase.

[a] Hepatic function (ASAT/ALAT) after two cycles.

4. Discussion

The objective of this study was to evaluate the activity and toxicity of raltitrexed as a single agent in the treatment of MPM. This phase II study, as well as the currently ongoing EORTC phase III study comparing cisplatin with cisplatin–raltitrexed, were based on promising results obtained in two consecutive phase II studies with the combination of raltitrexed and oxaliplatin [11]. However, to our knowledge no single agent raltitrexed trial has ever been reported in MPM. Our study indicates that single agent raltitrexed is active in the treatment of patients with advanced untreated MPM. This is the first study in the EORTC LCG in which a single agent achieved an objective response rate of 20%. Previous studies, using stringent response criteria, have reported response rates of 0–15% and further studies of the tested agents was not considered useful.

The current study indicates that raltitrexed is not only active as a single agent, but also has a safe toxicity profile in this patient population. The patients in this study are a representative group from the MPM patients in Europe with respect to demographics, stage and performance score. Grade 3 toxicities were observed in only a small number of patients and were easily manageable. No grade 4 toxicities were observed which were drug-related. The relative dose intensity was 100.8%. A slight elevation of the ASAT and ALAT levels to grade 2 was considered by one centre not to be a reason for dose delay. A total of 5 (20.8%) patients actually received all of the eight planned cycles of raltitrexed. After two cycles, only 15 (67.5%) continued with the treatment. Reasons for early discontinuation were primarily disease progression (7 patients), nausea/vomiting and fatigue grades 2 in 1 patient and one patient refusal.

From this study, we can conclude that the activity of raltitrexed in MPM is in line with the reports of the other antifolates. Recently, a phase I study combining pemetrexed and carboplatin showed objective responses in patients with MPM [15]. The responders were observed in all of the dose groups tested. During the ASCO meeting in 2002 the results of multinational phase II and III trials of another inhibitor of the folate metabolism were presented. In the phase II study, pemetrexed (a multitarget antifolate) yielded a 16% response rate as single agent among 82 previously untreated MPM patients [16]. In the phase III trial, the same agent was combined with cisplatin and compared with cisplatin alone in patients with MPM [17] (see *EJC* news [18]). The activity of the combination was superior

to the single agent in terms of response rate and median survival, although the toxicity was higher.

The response rate of 20.8% in this study was promising since this was the first time that a response rate exceeding 20% was observed in the EORTC phase II testing for MPM. Due to the small size of this phase II study, a median survival time with a very large CI was observed, which makes it difficult to compare this with previous results.

Currently, an intergroup trial with raltitrexed and cisplatin compared with cisplatin alone is nearing completion in the EORTC and NCI Canada. This trial should further clarify the role of raltitrexed and antifolates in the treatment of MPM and help us in determining the 'optimal' chemotherapy treatment in this disease.

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