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Limited efficacy of imatinib mesylate in malignant mesothelioma: A phase II trial

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Received 7 March 2005; received in revised form 26 April 2005; accepted 27 April 2005

KEYWORDS
Malignant mesothelioma;
Treatment;
Imatinib;
PDGF;
c-Kit;
Anti-cancer agents

Summary Twenty-five patients with histologically proven malignant mesothelioma participated in a trial of imatinib mesylate (Glivec) with a starting dose of 400 mg per day taken orally, up to a maximal dose of 800 mg. No responses were observed in the patient group, while three patients showed prolonged (> 6 months) stabilization of disease. The median survival time was 398 days (range 88—840); the median time to progression was 63 days (range 29—275). Side effects of the medication were mild and included edema, nausea, constipation and diarrhea. We conclude that further investigation with monotherapy imatinib in mesothelioma is not warranted.

1. Introduction

Malignant mesothelioma (MM) is a rare neoplasm of the pleura with an extremely poor prognosis [1]. It is associated with exposure to asbestos fibers, particularly of the crocidolite variety. While the exact pathogenesis of mesothelioma is still unclear, it is thought to arise from the mesenchymal cells of the pleura. Abestos fibers are inhaled and subsequently accumulate in the pleura, where years of reactive processes around the fibers are thought to contribute to the disease [2].

Despite the recent positive results reported with a new multitargeted antifolate, Pemetrexed [3], this malignant condition of pleura or peritoneum resists most oncological treatment and long-term survival long-term survival is very uncommon. Therefore, the investigation of new agents, especially those with novel working mechanisms, merits high priority in mesothelioma research.

Many patients with MM experience a sharp increase in their thrombocyte counts, which is thought to be the result of increased platelet derived growth factor (PDGF) secretion (angiogenic activity) associated with the disease [4]. It has not yet been settled whether the PDGF activity is autocrine or paracrine in nature, but in any case PDGF appears to be an important factor in pathogenesis. Another potentially important signaling pathway in MM is c-Kit: in a series of MM patients, one-third was shown to express this oncogene [5].

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0169-5002/$ — see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2005.04.010

These findings stress the importance of clinical studies with agents inhibiting c-Kit and PDGF receptor tyrosine kinases.

Imatinib mesylate (Glivec) is such an agent. It is a 2-phenylaminopyrimidine tyrosine kinase inhibitor known to affect both c-Kit and the PDGF alpha and beta receptors. This drug has been shown to be effective in treating chronic myeloid leukaemia (CML) [6] and gastrointestinal stromal tumors (GIST) [7], and is specific. For instance, it does not affect Ser/Thr kinases, nor other members of the Type III RTK family such as Flt-3 and Fms [8].

2. Patients and methods

Patient selection criteria were: a diagnosis of malignant mesothelioma (pleural or peritoneal) backed up by histological evidence, at least one target lesion, no prior non-palliative radiation therapy given at the target lesion(s), adequate organ function and hematological status (total bilirubin $< 1.5 \times$ ULN, SGOT and SGPT $< 2.5 \times$ ULN, creatinine $< 1.5 \times$ ULN, ANC $> 1.5 \times 10^9\,L^{-1}$, platelets $> 100 \times 10^9\,L^{-1}$), a performance status (ECOG WHO) of less than 3, age over 18 years and a signed informed consent form. Prior chemotherapy was permitted, but patients were non-eligible if they had received any investigational agent in the month before enrolment.

The drug was to be administered orally at an initial daily dose of 400 mg. Patients were required to keep a diary to monitor the side effects and adherence to the treatment. In case there was no excessive toxicity and the cancer did not respond to the medication, the study protocol permitted escalation of the daily dose to 600 mg 8 weeks after enrolment and 800 mg 16 weeks after enrolment.

Patients were to be taken off the treatment in case of progression, or if they experienced high toxicity (grade 2 or higher according to WHO criteria).

The clinical measurements to be performed before the start of treatment included hematology lab values (hemoglobin, WBC and platelet counts), an ECG, assessment of organ function by serum chemistry, and a CT-scan to evaluate the status of the disease. Every 2 weeks, the serum lab values were to be measured again. On finding abnormal lab values (ANC $< 1 \times 10^9\,L^{-1}$, or platelet count $< 50 \times 10^9\,L^{-1}$), the imatinib dose could be reduced (from 800 mg to 600 mg, 600 mg to 400 mg), or the treatment interrupted until the toxicity resolved. A CT-scan was scheduled to monitor the course of the disease every 8 weeks.

The study was set up as a single-center phase II trial following Fleming's single stage design. Response was to be evaluated using the RECIST [9] criteria, while the WHO criteria were adopted to assess toxicity.

3. Results

From May 2002 to September 2003, 25 patients were included in the trial. Table 1 presents patient and disease characteristics at entry. The majority of the patients were male, and the main histological subtype was epithelial. All but two of the cases were pleural. Two patients had received prior therapy (suramin and thalidomide).

The median treatment duration was 63 days (range 8—245). Dose escalation to 600 mg was performed in seven patients, and subsequently the dose was increased to 800 mg in two of these patients. Treatment was discontinued in 15 patients due to progression of the disease and in the 10 remaining cases due to side effects.

Table 2 presents the worst degree of toxicity during treatment. No grade 4 toxicity was observed. The main side effects were edema (ankles, face, genitals and lungs) sometimes causing exacerbation of pleural or abdominal effusions, nausea and vomiting.

Imatinib produced no objective response in this group of patients. The median survival was 398 days (range 88—840). There was no regression of the tumor observed in any of the patients. All of the 15 patients that continued treatment for a prolonged period eventually experienced progression of their disease. For three patients, there was a stabilization of disease for over 6 months during treatment. Patients stopping protocol treatment

Table 1 Patient characteristics

Characteristics	Number of patients (%)
Total	25
Male/female	20/5 (80/20)
Median age (years)	58 (range 48—74)
Pleural/peritoneal	23/2 (92/8)
Histological subtype	
Epithelial	20 (80)
Mesenchymal	1 (4)
Mixed	3 (12)
Unknown	1 (4)
Prior chemotherapy	2 (8)

Table 2 Toxicity due to imatinib

Type of toxicity	CTC grade (number of patients)				Dose at which symptom appears	Number of patients stopping treatment due to symptom
	G1	G2	G3	G4		
Edema/increase in pleural effusion	3	2	2		400 mg, $N = 6$; 600 mg, $N = 1$	5
Nausea and/or vomiting	7	3			400 mg, $N = 9$; 600 mg, $N = 1$	2
Constipation		2			400 mg, $N = 2$	2
Diarrhea	3				400 mg, $N = 2$; 600 mg, $N = 1$	1
Rash	1				400 mg, $N = 1$	1
Lymphopenia		1			400 mg, $N = 1$	
Hemoglobin		1			400 mg, $N = 1$	

because of side effects were treated as censored at the time of dismissal, because they were subsequently recruited for further trials using other investigational agents.

4. Discussion

Despite there being sound biochemical grounds for hoping that imatinib could act on mesothelioma as it does on GIST and CML, the results of this study are negative. While the doses administered were sufficient to elicit side effects, no regression could be observed. The results of this study are broadly in agreement with a comparable study conducted in Australia by Millward et al. [10], where the best overall response was stable disease for over 3 months in 4 out of 25 patients with initial doses of 600 mg of imatinib. We conclude that further study of imatinib as a single agent therapy in mesothelioma is not justified.

This highlights the pressing need for better understanding of the precise biological pathways involved in mesothelioma pathogenesis. In GIST, imatinib's inhibiting effect on the c-Kit receptor is the crux of the therapy. However, the role and importance of c-Kit expression in mesothelioma are still disputed [11,12]. Furthermore, there is evidence pointing towards VEGF as an important factor [13], confirming the prominent role of angiogenesis in the pathology. Early clinical experience with VEGF inhibitors (such as thalidomide and bevacizimab) suggests that this may be a fruitful pursuit. While imatinib also affects angiogenesis via PDGF, this does not seem to be as effective as in CML. It is possible that combination therapies with imatinib as a component could reveal that synergistically targeting the angiogenesis pathways will increase the response to treatment. More research in the mechanisms of the disease should hold the key to developing effective therapies.

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