Malignant pleural mesothelioma: a phase II trial with docetaxel

D. A. Vorobiof1*, B. L. Rapoport2, M. R. Chasen1, R. P. Abratt3, N. Cronje4, L. Fourie5, G. McMichael1 & D. Hacking6

*Correspondence to: Dr D. A. Vorobiof, Sandton Oncology Centre, PO Box 2059, Parklands 2121, Johannesburg, South Africa. Tel: +27-11-883-0900; Fax: +27-11-883-0905; E-mail: voro@global.co.za

Current cytotoxic therapy has been of limited benefit to patients with malignant pleural mesothelioma. Single agent chemotherapy has been extensively evaluated in small series of phase II clinical trials, with disappointing responses. Docetaxel, an effective taxane in the treatment of advanced breast cancer and non-small-cell lung cancer, was administered intravenously at a dose of 100 mg/m2 every 3 weeks to 30 chemotherapy naive patients with malignant pleural mesothelioma in a prospective multi-institutional phase II clinical trial. An objective response rate (partial responses) of 10% was documented. Additionally, 21% of the patients had minor responses (intention-to-treat analysis). Three patients died within 2 weeks post-first cycle of therapy, although only one patient’s death was directly attributed to the investigational drug, whilst in the majority of the patients, manageable and treatable toxicities were encountered. In this phase II clinical trial, docetaxel proved to be mildly effective in the treatment of patients with malignant pleural mesothelioma.

Key words: docetaxel, malignant pleural mesothelioma, phase II

Introduction

During the past few years, reviews of malignant pleural mesothelioma epidemiology, pathology, diagnosis, prognostic signs and therapies have been published in the medical literature [1, 2].

As a result of its increased incidence during the past 30–40 years in the industrialised countries, and its relationship with previous asbestos contact, malignant pleural mesothelioma has become not only a medical but also a socioeconomical problem.

South Africa has mined, milled, transported and used the three major commercial varieties of asbestos for decades [3]. During the early 1990s, the South African National Cancer Registry recorded an annual average of 166 new cases (male to female ratio 3:1) [4].

Many different chemotherapeutic drugs, doses, schedules and combinations have been reported during the last two decades. Few randomised trials have been performed, and in those, moderate antitumour activity has been documented. Newer agents, including the taxanes may improve the dismal outcome for these patients [5–7].

Given the known activity of taxanes in other tumour types such as breast and lung cancers, docetaxel was chosen for a multi-institutional national phase II study in the treatment of chemotherapy naive patients with malignant pleural mesothelioma.

Patients and methods

Patients aged 18–70 years with histologically confirmed malignant pleural mesothelioma (epithelial, sarcomatoid or mixed cell types), who had not received prior chemotherapy and/or immunotherapy, were prospectively accrued into this phase II study.

Patients were required to have measurable disease (uni- and/or bidimensionally), no prior radiotherapy to the measurable area, adequate hematological, hepatic and renal functions, with an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0–2, be geographically accessible to follow-up and with a life expectancy of ≥12 weeks.

Prior chemical pleurodesis was allowed provided ≥4 weeks elapsed since its administration and the patient had recovered from possible side effects.

Patients were ineligible if they had abdominal mesothelioma, were pregnant, had symptomatic peripheral neuropathy and/or other serious medical illnesses (ischaemic heart disease/failure, neurological and/or psychiatric disorders, active infection, unstable diabetes mellitus, brain or leptomeningeal involvement), had history of prior malignancies or had undergone total pleurectomy as initial treatment. All patients signed an informed consent and the trial was approved by the corresponding ethics committees of the various participating institutions. The trial was conducted according to the Helsinki declaration.
**Patient characteristics**

Between September 1997 and November 1999, 31 patients were accrued into this multi-institutional national study. One patient was unevaluable (review of the histology showed an adenocarcinoma of the lung). Patient characteristics are summarised in Table 1.

**Treatment**

The docetaxel dose was 100 mg/m², intravenously administered by a 1 h infusion, every 3 weeks. Premedication with oral dexamethasone 8 mg was administered at 13, 7 and 1 h before docetaxel infusion, and at 12, 24 and 36 h post-infusion.

Dose modifications were made according to the systems showing the greatest degree of toxicity and using National Cancer Institute common toxicity criteria guidelines. No dose escalation was permitted once the dose was reduced as a result of toxicity. Treatment continued until tumour progression, death or unacceptable toxicities were reported.

Patients were enrolled to receive six cycles of docetaxel, but in patients with disease stabilisation or response, an extra three cycles of the trial drug were allowed.

All patients entered into study underwent a baseline physical examination, haematology and biochemistry as well as radiological assessment with chest X-ray and computed tomography (CT) scan of the chest. The radiology was performed after every two cycles, and the rest of the evaluations were carried out on day 1 of every treatment cycle.

**Assessment of response and toxicity**

All X-rays and CT scans were assessed and measured for response by two independent radiologists. A target area was measured at baseline and follow-up according to protocol requirement.

Complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks. Partial response (PR) was defined as a ≥50% decrease in the sum of the products of the tumours’ longest dimension and its widest perpendicular measurement for at least 4 weeks, without the appearance of new lesions or progression of any one lesion. Minor response was defined as a ≥25% (but <50%) decrease in the size of the measurable disease without the appearance or progression of any new lesion, for at least 4 weeks. Stable disease or no change was defined as a <25% decrease or <25% increase in the size of the measurable disease, without the appearance of new lesions or progression of any lesion >25%, for a minimum of 4 weeks. Progressive disease was defined as a >25% increase in one or more of the measurable lesions or the appearance of new lesions. Response duration and survival were calculated from the date of first treatment using the standard life-table method of Kaplan and Meier [8].

**Results**

Two of the 31 patients entered were not assessable for response (see Table 2) Of the remaining 29 patients, three obtained a PR (10%) and six achieved minor responses (21%). In eleven patients, disease stabilisation was documented.

The median duration of response, measured in days, was 126 days (range 44 to >473). The median duration of time to progression was 107 days (range 15–746) and the median duration of survival was 371 days (range 6 to >820) (Figure 1)

**Toxicity**

Twenty-nine patients (of 30 evaluable) were assessable for toxicity. One patient was lost to follow-up after the first cycle of therapy. A median of four cycles was administered (range one to nine cycles).

In 13 patients, no side effects were documented. Three patients died whilst receiving treatment, all within the first 2 weeks and their characteristics are as follows.

**Patient 1.** Patient 1 was a 72-year-old male with PS2 without any other known concomitant diseases or therapies when entered on study. Six days after the first cycle of therapy he died at home. According to the family there was no evidence of infection or diarrhoea. No autopsy was performed. The association between his demise and the investigational agent was unclear.

**Patient 2.** Patient 2 was a 58-year-old male, PS1, who also died 6 days after the first cycle. He had no concomitant diseases. A day before his demise, neutropenia (grade II), diarrhoea (grade III) and nausea and vomiting (grade II) were documented. He received symptomatic therapy from the attending doctor. The patient also received enemas performed by a ‘traditional healer’. An autopsy was performed and necrotic and haemorrhagic ischaemic changes of the colon.
mucosa were present. Although this patient received other (alternative) concomitant medication, his symptoms and findings were possibly attributable to the trial drug, and his death was considered to be chemotherapy related.

Patient 3. A third patient, a 56-year-old male, had a PS2 when entered onto our study. Fifteen days after the first cycle he died at home. The patient was also receiving oral morphine as well as other medications. He had hallucinations, which started a few days before his demise (neurocortical toxicity grade III). No autopsy was performed. As in the first described patient, there was no clear relationship between this patient’s death and the administered chemotherapy.

See Table 3 for a description of toxicities.

Figure 1. Survival of mesothelioma patients.

Table 3. Toxicities

<table>
<thead>
<tr>
<th>Grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tr>
<td>Haematological</td>
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<td>Anaemia</td>
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<tr>
<td>Neutropenia</td>
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<td>Mucositis</td>
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<td>Nausea/vomiting</td>
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<td>Alopecia</td>
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<td>Nail disorders</td>
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<tr>
<td>Infection</td>
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<td>Weight loss</td>
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<td>Hallucinations</td>
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Discussion

Malignant pleural mesothelioma is a disease unaffected by current therapeutic approaches and there is no standard single chemotherapeutic drug or combinations for its treatment.

The limited number of patients with malignant pleural mesothelioma, and with different tumour loads, cell types, stages and performance status, seen in the clinic hampers objective evaluation of the various chemotherapy drugs currently available.

Docetaxel, a taxane with proven activity in terms of improved response rates and survival in patients with metastatic breast cancer and second-line therapy of non-small-cell lung cancer, was used in our phase II trial, administered at a dose of 100 mg/m² every 3 weeks. This dose has been widely investigated as a single, first-line agent in a variety of frequent malignant conditions, such as lung and breast cancers. Although previous studies have been performed with taxanes in malignant pleural mesothelioma, the reported results have been disappointing. An ECOG study using the same dose and schedule, reported a limited benefit with an overall response rate of 5% (one partial response out of 20 treated patients) [9]. This study was terminated early because of insufficient responses.

In a Finnish study [10] using a combination of docetaxel (at a dose of 60 mg/m²) and irinotecan, two minor responses out of 13 patients (overall response rate 15%) were documented. An European Organisation for Research and Treatment of Cancer (EORTC) phase II study with paclitaxel showed no documented objective responses [5].

There are no uniform criteria to measure and evaluate response in malignant pleural mesothelioma. Cancer and Leukaemia Group B (CALGB) criteria for response have been used for the past 10 years [11, 12].
Measurement of responses using RECIST criteria in a disease such as malignant pleural mesothelioma is practically impossible to implement. Imaging techniques are crucial to the management of this disease at diagnosis and during its clinical course. The diffuse growth pattern of malignant pleural mesothelioma is often difficult to assess and measure on CT scans, because of the partial volume effects when imaging curved structures at the axial planes. The presence of concomitant pleural effusions also contribute to the imaging difficulties [13].

In the present study, specific target lesions were identified, measured and followed during the course of treatment.

In our phase II trial, docetaxel induced response rates and survival similar to other well documented anti-cancer agents, with manageable toxicities, and it can be safely administered in an outpatient facility. Although the deaths occurred during the first administered cycle of docetaxel, only one death can probably be attributed to the investigational agent.

Future studies of its use in combination with a number of potentially active compounds, such as platinum derivatives, gemcitabine, vinorelbine and mitomycin C, should be considered.

Phase II clinical trials involving new agents in co-operative or multi-institutional groups will hopefully lead to beneficial and sustained responses in this otherwise dismal disease.

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References