treatment for HCC should be concluded only after prolonged follow-up studies are completed in more patients.

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Mitoxantrone in Malignant Pleural Mesothelioma: A Study by the EORTC Lung Cancer Cooperative Group

Frans J.M. van Breukelen, Karin Mattson, Giuseppe Giaccone, Nico van Zandwijk, Hans T. Planteydt, Anne Kirkpatrick and Otilia Dalesio

46 patients with malignant pleural mesothelioma were entered in a phase II study of mitoxantrone 14 mg/m² every 3 weeks. Histology was confirmed by a pathology panel. None of the patients had received previous chemotherapy. Toxicity was mainly mild gastrointestinal and haematological side-effects. Out of 34 patients evaluated for response, only 1 partial response was recorded. Mitoxantrone at this dose and schedule has marginal activity in malignant mesothelioma.
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INTRODUCTION

CHEMOTHERAPY OF malignant mesothelioma is disappointing. Doxorubicin has been reported to be one of the most active agents, with a cumulative response rate of 18% in 164 evaluable patients [1]. Combinations including doxorubicin or other drugs do not significantly improve response rates over doxorubicin alone [1]. Mitoxantrone is a synthetic anthracenedione [2]; its antitumour activity is related to DNA intercalation [3] and topoisomerase II inhibition [4]. Mitoxantrone is less cardiotoxic than doxorubicin [5, 6] and is an active drug in breast cancer and leukaemia [2, 7]. The EORTC Lung Cancer Cooperative Group has completed a phase II of mitoxantrone in malignant mesothelioma.

PATIENTS AND METHODS

To be eligible, patients had to have histologically confirmed diagnosis of malignant mesothelioma with measurable or evaluable lesions, Karnofsky performance status 60% or higher, no other malignancies, normal bone marrow reserve, normal liver, kidney and cardiac functions and be aged 75 or under. Previous chemotherapy, radiotherapy or intracavitary therapy with anticancer drugs were exclusion criteria. Informed consent was obtained in all patients. Pathology was reassessed by a central pathology panel and diagnosis of mesothelioma was classified as definite, probable, possible, improbable, or excluded. Only cases classified as definite or probable were considered eligible for this study.

Mitoxantrone was diluted into 100 ml 5% dextrose, and given by a 20 min intravenous infusion at 14 mg/m^2 every 3 weeks. Dose reduction was planned for severe haematological toxicity, but dose escalation was not allowed. Response was evaluated after three courses. Treatment was discontinued earlier if clear progression was observed. In cases of stable disease, treatment was continued to tolerance or until progression. Prestudy computed tomography (CT) and chest X-ray were performed in all patients. Chest X-ray was repeated before every course, and CT was repeated after three cycles and as frequently as required thereafter. Palpable lesions were measured at each cycle. Response and toxicity criteria used were those recommended by WHO [8].

RESULTS

46 patients entered the study. 5 were not eligible: in three cases the histological diagnosis was not confirmed by the pathology panel, 1 patient had received prior radiotherapy, and another had received intrapleural ^{32}P. Details of the 41 eligible patients are given in Table 1. All patients had pleural mesotheliomas. Response could be adequately evaluated after three cycles of chemotherapy in 34 patients, who received a total of 191 cycles (mean six per patient, range 3–10). However, 6 patients died of tumour progression before the evaluation date (treatment failure). In 1 patient there was no follow-up information; therefore, 40 patients were evaluable for treatment outcome. There were no complete remissions, 1 partial remission, 21 no change, and 12 progressive disease in the 34 evaluable patients (1/40 including treatment failures = 2.5%; 95% confidence interval 0–13%). The partial remission lasted 16 weeks. 1 patient showed disappearance of tumour in the thoracoscopy scar while intrapleural tumour progressed (considered as a progressive disease patient). Median survival time was 135 days (range 13–532).

Toxicity was evaluable in 38 patients who received an average of five courses (range 1–14). Main side-effects were myelotoxicity, nausea and vomiting. Leucocyte nadir was 2.7 × 10^9/l with 6 patients having grade 3 or 4 leukopenia. Platelet nadir was 235 × 10^9/l, with no patient having grade 3 or 4 thrombocytopenia. Nausea and vomiting was observed in 75% of patients, but was severe in 4 only; hair loss was seen in 21%, but was total in only one patient. Mild mucositis, diarrhoea, drug fever, infection and cardiac, hepatic and neurological toxicities were occasionally observed.

Table 1. Patients' characteristics

Eligible patients	41
Age (years)	
Median	57
Range	41–74
Sex	
Male	38
Female	3
Performance status (Karnofsky, %)	
Median	90
Range	60–100
Staging*	
I	11
IIA	15
IIB	2
III	10
IV	1
Unspecified	2
Histological type	
Epithelial	25
Connective tissue	3
Mixed	13

* Modified from Butchart *et al.* [10]: I tumour confined to homolateral pleura, lung, and pericardium; IIA tumour invading chest wall or involving mediastinum (oesophagus, heart) and lymph nodes within the chest; IIB involvement of contralateral pleura; III tumour penetrating diaphragm to involve peritoneum directly, lymph nodes outside the chest; and IV distant blood-borne metastases.

DISCUSSION

Mitoxantrone given at 14 mg/m^2 every 3 weeks, a schedule generally employed in untreated patients, was inactive in mesothelioma patients. Our study confirms the previous findings of Eisenhauer *et al.* who observed only 2 responses out of 28 patients with malignant pleural mesothelioma when mitoxantrone was given at a starting dose of 12 mg/m^2 with escalation of the dose performed in 17 patients [9]. Further investigation of mitoxantrone in malignant mesothelioma is not warranted.

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Parathyroid Hormone-related Protein$^{(50–69)}$ and Response to Pamidronate Therapy for Tumour-induced Hypercalcaemia

D.J. Dodwell, S.K. Abbas, A.R. Morton and A. Howell

A region-specific radioimmunoassay has been employed to measure levels of immunoreactive parathyroid hormone-related protein$^{(50–69)}$ (iPTHrP$^{(50–69)}$) in patients with tumour-induced hypercalcaemia (TIH). This assay is based on an antiserum raised against synthetic human PTHrP$^{(50–69)}$. The assay showed no cross-reactivity with human or bovine parathyroid hormone$^{(1–84)}$. The effect of a single dose (60 mg) of pamidronate was studied in 25 consecutive patients with TIH. All were rehydrated prior to treatment. All but 2 patients (8%) became normocalcaemic after treatment; both of these had very high levels of iPTHrP$^{(50–69)}$. Time to achieve normocalcaemia, as an index of relative resistance to pamidronate, correlated positively with pretreatment level of iPTHrP$^{(50–69)}$. Absence of radiological evidence of bone metastases also predicted relative resistance to pamidronate. In this study, iPTHrP$^{(50–69)}$-induced osteoclastic bone resorption was a more important mechanism in the causation of TIH than PTHrP-induced renal reabsorption of calcium as assessed by the renal thresholds for calcium and phosphate.
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INTRODUCTION

ALBRIGHT RAISED the possibility, in 1941, that tumour-induced hypercalcaemia (TIH) may be due to production of a parathyroid hormone (PTH)-like substance by the cancer [1]. Following this, the term "ectopic PTH secretion" came into common usage to describe the syndrome of patients with cancer who had a high plasma calcium, and it was only with recent developments in radioimmunoassay (RIA) and gene probing techniques, that doubt began to emerge about the involvement of PTH in this syndrome [2, 3].

Since that time cell culture and immunohistochemical studies have demonstrated that many malignant tumours produce a parathyroid hormone-related protein (PTHrP) which has sequence homology to, but is distinct from, PTH [4–8]. PTHrP is present in a wide variety of fetal tissues and is found in high concentrations in breast tissue and milk [9]. It has been suggested that it is important in the control of mammalian fetal plasma calcium levels [10]. Others have suggested that it may control tissue calcium levels in adults by an autocrine mechanism [11].

Although its physiological role is incompletely understood, much recent evidence implicates PTHrP in the causation of TIH [8, 9, 12]. The recent recognition of such a circulating 'humoral' factor in TIH has meant that two forms of this syndrome are now commonly described. One results from the local resorption of bone by skeletal deposits (occurring most frequently in breast cancer and myeloma) and the other from the release by the tumour of a circulating factor (commonly occurring in squamous cell lung cancer and hypernephroma) which causes distant effects on the skeleton (to promote osteoclastic bone resorption) and the kidney (to promote the renal tubular reabsorption of calcium). However, it is unlikely that these two forms of TIH are distinct clinical entities and both mechanisms may operate in some patients [12–14].

Bisphosphonates, and in particular pamidronate, are the treatment of choice for TIH and restore normocalcaemia in over 85% of unselected patients with this complication of malignancy [15–17]. Bisphosphonates inhibit osteoclastic bone resorption with little or no effect on the renal reabsorption of calcium and would therefore be of limited value in situations where excessive renal reabsorption of calcium was the predominant pathophysiological mechanism.

In this regard, Gurney *et al.* [18] found that renal tubular phosphate threshold (RPT), as an indicator of renal PTH receptor stimulation, was the best predictor of response to

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