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Phase II Study of Nimustine in Metastatic Soft Tissue Sarcoma

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The EORTC Soft Tissue and Bone Sarcoma Group has conducted a phase II trial in 33 eligible patients with metastatic soft tissue sarcoma with nimustine 100 mg/m^2 every 6 weeks. In 31 evaluable patients there were 3 (10%) partial responses lasting 4.5,6 and 7.5 months, and 5 cases of stable disease. 12 patients had progressive disease and 11 patients early progressive disease. Toxicity consisted mainly of leukopenia and thrombocytopenia and nausea and vomiting. It is concluded that nimustine has only minor activity in soft tissue sarcoma.
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INTRODUCTION

NIMUSTINE (ACNU) is a water-soluble nitrosurea [1]. Previous clinical studies with nimustine have mainly been performed in Japan. Responses have been observed in small cell lung cancer, non-small cell lung cancer, head and neck cancer, gastric cancer, uterine cancer, chronic myelocytic leukaemia, Hodgkin's and non-Hodgkin lymphoma and brain tumours [2, 3]. The experience with nimustine in sarcoma is very limited. In a collected series, two responses in 8 evaluable patients were reported [3]. Because of these interesting results and the great lack of effective drugs for soft tissue sarcomas a phase II study was initiated.

PATIENTS AND METHODS

Patients could enter the study if they fulfilled the following eligibility criteria: histologically proven advanced and/or metastatic soft tissue sarcoma, age 15–75 years, and performance status 0–2 (WHO). Patients were required to have measurable progressive disease. Recurrent tumour in irradiated areas was not permitted as the sole evaluable lesion, and pleural effusions or bony metastases were not considered to be measurable. Other criteria for exclusion were prior treatment with nitrosureas, chemotherapy in previous 4 weeks or previous treatment with more than four cytotoxic agents, a previous or concomitant different malignant tumour, serious concurrent disease, and central nervous system metastases. Prior to entry patients were required to have adequate hepatic excretory (serum bilirubin < 25 μmol/l) and kidney function (serum creatinine < 150 μmol/l) and bone marrow reserve (leucocytes $> 4 \times 10.9/l$, platelets $> 125 \times 10.9/l$).

Nimustine was given by slow intravenous injection at a dose of 100 mg/m^2 every 6 weeks. In pretreated patients the dose was

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Table 1. Patients' characteristics

Age	
Median (years)	53
Range	22–69
Sex	
Male	14
Female	19
Performance WHO median	1
Range	0–2
Site of metastatic disease	
Lung	20
Liver	11
Soft tissue	19
Other visceral localisation	3
Total number of lesions at entry	
Not known	3
< 5	13
5–9	6
> 10	11
Prior surgery	
Curative	19
Palliative	7
Both	3
None	4
Prior radiotherapy	12
Prior chemotherapy	28
With no response	19
With response	9

reduced in the first cycle to 75 mg/m^2. If this dose was well tolerated (nadir leucocytes $> 2 \times 10.9/1$, platelets $> 50 \times 10.9/1$) and the blood counts were recovered completely, then the dose was increased to the full dose of 100 mg/m^2 in the following cycles.

Response was evaluated after every two cycles. Definition of response was according to WHO criteria [4].

RESULTS

From April 1988 until March 1989 36 patients from 14 institutions were registered. 2 patients are ineligible because they had no measurable lesions at entry. 1 patient was excluded because the data were not available. These patients are not included in the analysis. The patients' characteristics are shown in Table 1 and the cell types in Table 2. All diagnosis were confirmed by a central histopathological review committee.

Table 2. Histological subtypes

	No. of patients
Leiomyosarcoma	13
Synovial sarcoma	4
Malignant fibrous histiocytoma	3
Fibrosarcoma	3
Liposarcoma	2
Rhabdomyosarcoma	1
Angiosarcoma	1
Neurogenic sarcoma	1
Unclassified sarcoma	1
Miscellaneous sarcoma	4

Table 3. Toxicity (no. of observations)

	WHO grade					
	0	1	2	3	4	no data
Nadir leucocytes	18	8	3	3	0	3
Nadir platelets	15	6	4	2	3	3
Nausea/vomiting	10	6	9	7	0	1
Diarrhoea	28	2	0	0	0	2
Phlebitis	30	1	0	0	0	1
Cutaneous	28	1	1	0	0	1
Hair	25	0	0	1	0	1
Oral	27	3	1	0	0	3
Liver	27	1	0	0	0	5

There were 3 partial remissions (PR); 1 of soft tissue lesions, 1 of lung lesions, 1 of soft tissue and lung lesions. 2 of the remissions were achieved after two cycles, one lasting 4.5 and the other 6 months from the start of treatment. 1 patient achieved the PR after four cycles which lasted 7.5 months. 5 patients had stable disease, 12 progressive disease and 11 patients early progressive disease.

The toxicities are given in Table 3. They are as could be expected by the use of nitrosureas and consisted mainly of leucocytopenia, thrombocytopenia and nausea and vomiting. 2 patients had no good documentation of toxicity.

DISCUSSION

Unfortunately, we could not confirm the preliminary good results of nimustine in the collected series of Saijo and Niitani [3] and we have to conclude that the drug has only minor activity in soft tissue sarcoma. This is in agreement with the results obtained with other nitrosureas in metastatic soft tissue sarcomas when used as a single agent. The response rate to carmustine, lomustine and methyl-lomustine used as a single agent in metastatic sarcoma is less than 13% [5]. However, we have to realise that most patients were treated in phase II protocols and had received previous therapy as our patients, whereas the majority of them had also progressive disease during the previous cytotoxic treatment.

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