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Phase II Study of Fotemustine in Advanced Soft Tissue Sarcomas

A trial of the EORTC Soft Tissue and Bone Sarcoma Group

P. Kerbrat, R. Somers, J. Verweij, D. Crowther, T. Tursz, A. Santoro, W. P. Steward, M. A. Lentz, M. van Glabbeke and H. T. Mouridsen
On behalf of the EORTC Soft Tissue and Bone Sarcoma Group

INTRODUCTION

ONLY A few drugs have some activity in soft tissue sarcomas (STS). Doxorubicin, ifosfamide and dacarbazine induce an objective response rate of approximately 20%, but there are very few long-term survivors after chemotherapy for metastatic disease. New compounds with significant activity are therefore urgently needed for these tumors.

Fotemustine has a high lipophilicity and a chemical structure including a phosphonoalanine carrier group grafted onto the nitrosourea radical to achieve better penetration through the cell membrane. A phase I trial and other phase II studies with 3-weekly administration showed cumulative and dose-related leucopenia and thrombocytopenia [1, 2]. The recommended dose for further phase II studies was 100 mg/m^2. A phase II trial was initiated to assess the activity and to further characterise the toxic effects of this drug in metastatic or advanced progressive STS.

PATIENTS AND METHODS

Patients were eligible if they had a confirmed diagnosis of soft tissue sarcoma, measurable disease with documented progression within 2 months prior to protocol therapy, no more than one previous regimen and no previous chemotherapy with a nitrosourea, performance status under 2 (WHO), normal white blood cell and platelet counts and normal renal and liver function. Informed consent was obtained. Fotemustine was given intravenously at 100 mg/m^2, infused over 1 h in 250 ml 5% dextrose, protected from light. The treatment plan consisted of one administration per week for 3 consecutive weeks. Disease response was assessed after a 5-week rest. In patients with non-progressive disease, fotemustine was then given at the same dose every 3 weeks, until emergence of toxic effects or progressive disease. The initial dose was then reduced to 50 or 75% according to haematological toxicity. Response and toxicity were scored according to the WHO criteria.

RESULTS AND DISCUSSION

From March to December 1989, 31 patients entered the study: 2 were ineligible, 1 was found not to have a soft tissue sarcoma at central pathology review and another did not have a measurable lesion. There were 18 males and 11 females, median age 43 (range 22–67). Performance status was 0 in 7, 1 in 15 and 2 in 7 patients. 5 patients had received previous adjuvant chemotherapy, and 26 had received previous chemotherapy for advanced disease (15 had had an objective response). Histological diagnosis was leiomyosarcoma (8), synovial sarcoma (7), malignant fibrohistiocytoma (5), neurogenic sarcoma (4) and miscellaneous (5).

Table 1. Toxicity non-haematological after the three induction cycles

WHO grade	0	1	2	3
Nausea and/or vomiting	7 (24.1%)	9 (31%)	5 (17.2%)	6 (20.6%)
Drug fever	28 (96.5%)	1 (3.45%)		
Diarrhoea	27 (93.1%)	2 (6.9%)		
Alopecia (6 pre-existing)	22 (75.7%)			1 (3.45%)

Antitumour activity

2 patients were lost to follow-up and 2 were excluded for protocol violation; 25 patients were therefore analysed. There was progressive disease in 18 patients and 1 early death due to malignant disease. 6 patients showed no change and received maintenance therapy (2–5 cycles) without late objective response.

Toxicity

Haematological indices were assessed in 29 patients, and liver and renal function tests in all patients. Non-haematological toxicity was mild (Table 1). The most common-side effect was delayed reversible myelosuppression (Table 2).

Table 2. Hematological toxicity after the three induction cycles

WHO grade	0	1	2	3	4
Haemoglobin	17 (58.5%)	5 (17.4%)	5 (17.4%)	2 (6.9%)	
Leukopenia	16 (55.1%)	2 (6.9%)	4 (13.7%)	2 (6.9%)	5 (17.4%)
Thrombocytopenia	12 (41.3%)	2 (6.9%)	4 (13.7%)	7 (24.1%)	4 (13.7%)

Correspondence to P. Kerbrat.
P. Kerbrat is at the Centre Eugène Marquis, CHU Pontchaillou, 35033, Rennes, Cedex, France; R. Somers is at the Antoni Van Leeuwenhoek Hospital, Amsterdam, the Netherlands; J. Verweij is at the Rotterdam Cancer Institute, the Netherlands; D. Crowther is at the Christie Hospital, Manchester, U.K.; T. Tursz is at the Institut Gustav Roussy, Villejuif, France; A. Santoro is at the Instituto dei Tumori, Milan, Italy; M.A. Lentz is at the General Hospital, Glasgow, U.K.; M. van Glabbeke is at the EORTC Data Center Brussels, Belgium; and H.T. Mouridsen is at the Finsen Institute, Copenhagen, Denmark.
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After the three induction cycles, thrombocytopenia and leucopenia were observed in 58.7 and 44.9% of cases, respectively, with 37.8 and 24.3% at grade III–IV. Neutrophil nadir occurred at a median of 43 days and platelet nadir at a median of 37 days. In 2 patients, treatment was interrupted because of grade IV thrombocytopenia.

Comments

Fotemustine, administered according to our schedule, had no activity in patients with advanced or recurrent soft tissue sarcomas. In contrast, the only drugs with known activity in this disease were also found to have activity in second-line chemotherapy [3]. This underlines the justification of further drug testing as second-line. Of the other nitrosourea derivatives, lomustine has no activity [4] and recently we found nimustine to have minor activity. Our study also confirmed the mainly haematological toxicity of fotemustine.

The lack of responses added to the haematological toxicity mean that fotemustine must not be used for further studies in soft tissue sarcomas.

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CA 15.3 Determination in Patients with Breast Cancer: Clinical Utility for the Detection of Distant Metastases

Emilio Bombardieri, Maria Pizzichetta, Paolo Veronesi, Ettore Seregni, Anna Bogni, Lorenzo Maffioli, Gloria Saccani Jotti, Maria Antonietta Bassetto, Stefano Zurrida and Alberto Costa

In 81 healthy women, 26 pregnant women, 25 patients with fibrocystic disease and 144 breast cancer patients, the overall diagnostic sensitivity and specificity of the CA 15.3 test was 27 and 97%, respectively. The positive and negative predictive values were 93 and 43%. In 150 node-negative patients taking part in a chemoprevention trial CA 15.3 was assayed at baseline and every 4 months for a median follow-up of 24 months (range 4–48). In these patients, 5 had local recurrences, 1 had a regional recurrence, 9 had distant metastases and 3 developed cancer in the contralateral breast. Among the patients with recurrences, those with distant metastases showed the highest ratio of CA 15.3 increase (8/9); in local and regional recurrences, this ratio was lower (2/6). The patients with contralateral breast cancer had no significant increase in CA 15.3. Patients in whom metastases were detected showed an increase in CA 15.3 4–48 months before clinical or instrumental detection of the metastases.
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INTRODUCTION

SEVERAL CIRCULATING tumour markers for breast cancer have been discovered [1]. However, despite extensive research in this field, no specific markers for breast cancer are available as yet. Nevertheless, many clinical oncologists still use various tumour markers, especially carcinoembryonic antigen (CEA) [2–6] and tissue polypeptide antigen (TPA) [7–9]. Unfortunately, these tumour markers do not have sufficient specificity. The development of monoclonal antibodies (Mabs) against human mammary carcinomas has improved the specificity of the reaction with breast cancer-associated antigens and has stimulated the search for new tumour markers for breast cancer [10]. One of these markers is CA 15.3; it can be measured by an immunoradiometric method (IRMA) based on Mab DF 3 raised against a membrane fraction of liver metastases from breast cancer, and Mab 115 D8 raised against milk fat globule membranes [11, 12]. Although the diagnostic sensitivity of CA 15.3 seems to be superior to that of CEA, CA 15.3 determination does not have much validity in the early detection of primary tumours [13, 14]. Its main clinical indication is in the monitoring of response to treatment and in the follow-up of tumour-free patients. In some studies, CA 15.3 serum elevations appeared to anticipate