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Short Communication

Results of a Phase II Trial with Second-line Cystemustine at 60 mg/m^2 in Advanced Soft Tissue Sarcoma: A Trial of the EORTC Early Clinical Studies Group

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The aim of this phase II trial was to examine the efficacy of a new nitrosourea, cystemustine, in soft tissue sarcoma. Between January 1990 and March 1991, 32 pretreated patients with advanced soft tissue sarcoma were enrolled. Cystemustine was given every 2 weeks at 60 mg/m^2 via a 15-min i.v. infusion. All eligible patients were considered evaluable for response and toxicity (WHO criteria). Of the 32 enrolled patients, 4 were ineligible, leaving 28 evaluable patients. All but 1 had been pretreated: 6 with adjuvant chemotherapy, 18 patients with first-line palliative chemotherapy without nitrosourea, 3 with both treatments, and 18 had received radiotherapy. Median age was 54 years (range 20–73) and median performance status was 1 (0–2). One partial response (PR, duration 12 weeks), 2 stable disease and 25 progressions were observed, giving an overall response rate of 3.57% (confidence interval: 0.1–18.4%). Toxicity was mild, and was mainly neutropenia (no grade 3 or 4), thrombocytopenia (3.57% grade 3 and grade 4) and nausea–vomiting (no grade 3 or 4). It should be noted that the treatment for the patient who obtained a PR was third line with no previous response. Cystemustine with this schedule appears to have a low clinical activity and toxicity in advanced soft tissue sarcoma.

Key words: cystemustine, soft tissue sarcoma, new nitrosourea
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INTRODUCTION

SOFT TISSUE sarcoma has an incidence of 2 per 100 000 [1] and is relatively resistant to chemotherapy. The principal effective drugs are doxorubicin and its analogue epirubicin, and to a lesser degree dacarbazine (DTIC), cyclophosphamide and ifosfamide [2]. Nitrosoureas are not considered to be particularly efficacious in this tumour. When metastatic disease appears, patient survival expectancy is reduced dramatically to a few months [3]. At this stage of the disease, surgery is rarely curative unless there are only a few lung metastases [4], and radiotherapy is only palliative [5]. The best combination chemotherapy regimes are (cyclophosphamide, vincristine, doxorubicin, dacarbazine) and MAID (mesna, doxorubicin, ifosfamide, dacarbazine), but complete responses are rare; furthermore, studies conducted by EORTC Soft Tissue and Bone Sarcoma Group (STBSG) have shown that combination chemotherapy as well as high-dose treatments have not yet achieved better activity than single-agent doxorubicin at its optimal dosage (75 mg/m^2) [3, 5, 6]. Therefore, clinical

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screening for new drugs is still necessary in phase II trials. Taxanes are now under evaluation and may be active agents [7].

We report here the results of a phase II study conducted by the EORTC Early Clinical Studies Group (ECSG) in soft tissue sarcoma with a new nitrosourea, cystemustine, at a dose of 60 mg/m^2 every 2 weeks. This drug has shown clinical activity in malignant recurrent glioma [8].

PATIENTS AND METHODS

Patients

Eligibility criteria included at least one measurable metastatic non-previously irradiated target, a WHO performance status of 0–2, normal white blood cell and platelet count and normal renal and liver function. In addition, one previous adjuvant regimen and two previous lines of palliative chemotherapy without nitrosourea were accepted before patient inclusion.

All patients provided written consent.

Treatment

Cystemustine was given intravenously at a dose of 60 mg/m^2 infused for 15 min in 100 ml% 5% dextrose. The treatment plan consisted of one dose every 2 weeks, with a minimum of four injections. The target measurement was assessed before the 3rd and 5th infusions, then every two months. In responding or stable patients, the treatment was continued until progression or excessive toxicity, for a maximum of 12 months.

Dose modification

The injection was postponed for 1 week, if at day 14 the granulocyte count fell below 1500/µl or the platelet count below 100 000/µl. A WHO grade III or IV thrombocytopenia resulted in a dose reduction to 45 mg/m^2 for subsequent courses. If the treatment had to be delayed for more than 3 weeks, the patient was withdrawn from the study.

RESULTS

32 patients were included, but 4 were ineligible because of previous treatment limitations, or because of previously irradiated targets.

28 heavily pretreated patients (pts) were evaluable for response and toxicity. There were 11 males and 17 females with a median age of 54 years (range 20–73) and a good WHO performance status (0 = 10 pts; 1 = 14 pts; 2 = 4 pts). Among them, only one patient had not been pretreated with cytostatics; 6 had received adjuvant treatment (none with nitrosoureas), 18 at least one palliative chemotherapy, and 3 had received both treatments. 10 patients had not been previously irradiated, whilst 18 had received radiotherapy (5 to haematopoietic sites).

The median number of cycles of cystemustine given was 3. One partial response (duration 12 weeks), 2 stable diseases, and 25 progressions were observed, giving an overall response rate of 3.57% (confidence interval 0.1–18.4%). The patient that presented with a partial response had been previously treated with two palliative lines of chemotherapy, without response.

Haematotoxicity was mild at this dose, in spite of previous treatments; no patient experienced WHO grade 3 or 4 toxicity for leucocytes or neutrophils; 1 patient (3.57%) had a grade 3 thrombocytopenia and the other had a grade 4 thrombocytopenia, both reversible; and no grade 3 or 4 non-haematological toxicity was found.

Overall tolerance was good in spite of previous treatments. No late toxicity was found in 22 patients, but 1 patient had persistent thrombocytopenia at 83 000/ml 3 weeks after the last course. 26 patients were withdrawn from the study due to progressive disease, one at the end of protocol, and one died on the tenth day of the first course, probably of disease. It is suggested that the drug should be tested at a higher dose in this situation.

DISCUSSION

Cystemustine has limited clinical activity on advanced pretreated soft tissue sarcoma at the dose tested. The response rate was low. Due to the low toxicity observed, a new phase II trial with an increased dose could evaluate any possible antitumour activity.

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