treated in this geographical region and to further characterise the pattern of neuroendocrine differentiation in these tumours, in order that the group which may be eligible for chemotherapy be correctly identified.

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Phase II Study of Mitozolomide in Advanced Soft Tissue Sarcoma of Adults: the EORTC Soft Tissue and Bone Sarcoma Group

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INTRODUCTION

TREATMENT OF advanced inoperable and metastatic soft tissue sarcoma remains disappointing with the chemotherapeutic drugs available. Doxorubicin, ifosfamide and dacarbazine are the only active drugs available. Phase II studies therefore remain mandatory.

In the EORTC Soft Tissue and Bone Sarcoma Group we investigated mitozolomide, an imidazoltetrazine. Mitozolomide, with a general formula of $C_7H_7C_1N_6O_2$, showed activity by intraperitoneal route, in experimental tumour in mice such as the L_{1210}, P_{388} leukemia. Noteworthy is that there is also activity to solid tumours such as Lewis lung carcinoma and B_{16} melanoma [1, 2]. The mechanism of action has not been fully elucidated, but seems related to mechanism of action of nitrosureas, via DNA interstrand cross-link formation.

Clinical studies were done with a single dose regimen and a 5 times daily [3]: dose limiting toxicity was thrombopenia. The duration of the leukopenia and thrombopenia followed a pattern of nitrosurea derivatives, the nadirs occured with a median of 26 and 22 days, with a range of recovery up to 6 weeks. As a result of the phase I studies a dose of 100 mg/m^2 was advocated for previously untreated patients and a dose of 90 mg/m^2 for previously treated patients.

PATIENTS AND METHODS

Patients in the age range of 15–75 years were eligible, with a histologically proven, measurable locally advanced and/or

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metastatic soft tissue sarcoma. Further entry criteria were: WHO performance status 0–1, no treatment with chemotherapy in the previous 4 weeks (or 6 for nitrosurea). Initial leucocyte count should be $> 4 \times 10^9$/l, the platelet count $> 125 \times 10^9$/l. Patients were excluded if serum creatinine was above 150 μmol/l or the serum bilirubin > 25 μmol/l. Prior treatment with more than 4 drugs, central nervous system localisations, concomittant disease or second primary malignancy were also considered as exclusion criteria.

Mitozolomide was administered in a dose of 90 mg/m^2 in a 1 h infusion every 6 weeks. The solution was prepared by adding 5 ml of dimethylsulphoxide into the vial containing 200 mg of the drug. The desired quantity was than added to 500 ml saline in a polyethylene infusion bag. The solution is incompatible with polyvinyl bags.

Subsequent doses were administered if haematological recovery had occurred at day 42 [white blood cells (WBC) $> 4 \times 10^9$/l, platelets $> 100 \times 10^9$/l]. In case of insufficient recovery the administration was delayed for one week or a second week if necessary. If at day 56 the above mentioned values were not reached a 50% dose was given in case of WBC level of 2.5–3.5 $\times 10^9$/l and platelets above 100×10^9/l. If the nadir of the WBC remained above 4×10^9/l and the platelet nadir above 100×10^9/l, 110% of the initial dose was given at the day of the next course. In case of a WBC nadir of $< 2 \times 10^9$/l or a platelet nadir $< 50 \times 10^9$/l the dose at the next courses was reduced to 50%.

The intention was to administer at least two cycles of mitozolomide prior to reassessment. In case of stable disease or regression treatment was continued until progression or unacceptable toxicity. Response was evaluated according the WHO criteria and was assessed 5 weeks after the second course. In case of clear progression after one course ($> 50\%$ increase in volume or appearance of new lesions) treatment was considered as a failure and was discontinued. Such a case was classified as progressive in the study analysis.

RESULTS

29 patients were registered from 9 centres in Europe. 3 patients were considered ineligible (performance status > 1, more than four previous drugs, and primary malignant fibrous histiocytoma (MFH) of the bone). Of the remaining 26 patients one was inevaluable for response and toxicity because she was lost to follow-up after one course. Patient characteristics are given in Table 1, the histological subtypes in Table 2.

Response was evaluated after one course in 15 cases, after two or more courses in the other 10. Of the 15 cases evaluated after one course 13 showed progression, there was one early death due to malignant disease and 1 patient died from complications of treatment. Three weeks after the first injection of 150 mg mitozolomide bleeding started from the digestive tract, leucocytes being 9×10^9/l, platelets 100×10^9/l. Later the platelets dropped to 30×10^9/l and the WBC to 2.5×10^9. During this period the patient developed fever and died from septic shock. Evaluation after two courses showed 8 progressions and 2 cases with no-change, progressing after three and seven courses, respectively.

The non-haematological toxicity was generally mild. Nausea (grade 1–2: 15 patients, grade 3: 2 patients), diarrhoea (grade 1–2: 4 patients), haematuria (grade 2: 1 patient), hair loss (grade 1–2: 2 patients, grade 3: 4 patients), were the main toxicities encountered (Table 2).

The haematological toxicity is given in Table 3. The nadir of

Table 1. Patients' characteristics

Patients registered	29
Not eligible	3
Evaluable for response/toxicity	25
Median age (range)	47 (28–72 years)
Male/female	12/13
Performance status (0/1)	9/16
Prior chemotherapy	
Advanced disease, no resp.	17
Advanced disease, resp.	7
Adjuvant only	1
Prior radiotherapy (yes/no)	11/14
Site of disease	
Local	3
Metastatic	11
Lung only	8
Liver only	1
Lung + other	2
Primary + metastatic	11
Soft tissue only	1
Lung only	1
Liver only	2
Lung + other	7

Table 2. Histological subtype (25 patients)

	No. of patients
Leiomyosarcoma	6
Synovial sarcoma	5
Angiosarcoma	4
MFH	3
Liposarcoma	2
Fibrosarcoma	1
Rhabdomyosarcoma	1
Neurogenic sarcoma	1
Miscellaneous	1
Unclassifiable	1

Table 3. Toxicity

	No. observed				
Toxicity	WHO grade: 0	1	2	3	4
Nausea/vomiting	8	7	8	2	0
Diarrhoea	21	2	2	0	0
Haematuria	23	1	1	0	0
Haemorrhage	21	1	1	1	1
Alopecia	11	1	1	4	0
Phlebitis	25	0	0	0	0
Liver	22	0	0	0	0
Kidney	24	0	0	0	0
Nadir WBC	5	3	8	1	1
Nadir granulocytes	0	1	4	6	1
Nadir platelets	9	4	1	4	1

WBC after the first or first two courses was available for 18 patients: 2 patients experienced grade 3–4 toxicity (WBC < 2–1 × 10^9/l), 7 out of 12 patients of whom data were available experienced grade 3–4 toxicity for granulocytes. The nadir of the granulocytes was reached with a median of 29 days (range 1–49 days). Platelet nadirs were available for 19 patients, 5 of whom had grade 3–4 toxicity.

DISCUSSION

From this study it can be concluded that mitozolomide is an inactive drug in the treatment of patients with inoperable or metastatic soft tissue sarcoma. All patients had prior chemotherapy with known active drugs. The majority (17 out of 24) did not respond to their first line chemotherapy. No responses were obtained with mitozolomide in 25 evaluable patients, 2 patients were evaluated as no-change. Thrombocytopenia was the main toxicity, contributing to the death of 1 patient. The question remains if phase II studies are to be undertaken in second line in patients with metastatic soft tissue sarcoma. The response rate of the first line regimens varies from 30 to 50%. So at least 50% is resistant to first line chemotherapy and therefore possibly other drugs. It may be a more useful approach to perform phase II studies in first line before standard palliative chemotherapy is started. Such a strategy, however, may be reevaluated if new regimens with high doses chemotherapy in combination with growth factors may have curative potential.

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Phase II Study of Cytarabine in Hodgkin's Disease

José Thomas, Ben de Pauw, Anton Hagenbeek, Reinier Somers, Patrice Carde, Umberto Tirelli, Nicole Duez, on behalf of the EORTC Lymphoma Cooperative Group

Cytarabine was administered to 24 patients with previously treated Hodgkin's disease in the EORTC Lymphoma Cooperative Group. The drug was administered at the dose of 80 mg/m² subcutaneously twice a day on 5 consecutive days every 3 weeks. The overall response rate was 17.6% (3 responses among 17 evaluable patients) with a short duration (2–6 months). The main toxicity was myelosuppression. Our experience in the EORTC Lymphoma Cooperative Group could not demonstrate a significant activity at this dose and schedule in Hodgkin's disease.
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INTRODUCTION

CYTARABINE IS an arabinoside nucleoside isolated from the sponge *Cryptothethya crypta*. As a single agent, cytarabine is very active in acute myeloblastic leukaemia and in other leukaemias. Its selective activity against rapidly growing tumours and its pharmacokinetic features have rendered this agent less useful in most solid malignancies [1].

However, cytarabine has been incorporated in several combinations prior to autologous bone marrow transplantation in Hodgkin's disease [2] and in combinations for relapsing Hodgkin's disease [3, 4]. An extensive literature search, including consulting computer data and data from the manufacturer, could not give any phase II data of ARA-C in Hodgkin's disease. Therefore, the EORTC Lymphoma Cooperative Group decided to perform a phase II study on cytarabine in Hodgkin's disease, after taking in consideration the absence of data on phase-specific drugs in Hodgkin's disease.

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PATIENTS AND METHODS

Selection of patients

The study was confined to patients with histologically proven Hodgkin's disease refractory to standard first and second line chemotherapy with or without radiotherapy. They needed to have measurable lesions and a good haematological profile (leucocytes above 3 × 10^9/l and platelets above 100 × 10^9/l). The activity index had to be WHO grade 2 or better.

Treatment

Cytarabine was given at the dose of 80 mg/m² subcutaneously twice a day on 5 consecutive days. The dose was based on the