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

well-tolerated and effective cytarabine schedule for leukaemia patients as employed by the EORTC in the LAM-5 trial. The courses were repeated every 3 weeks. After two courses a first evaluation took place, and the treatment was only continued in case of responses (complete or partial remission).

Dose modification

For WBC between 2 and 3 × 10^9/l or platelets between 75 and 100 × 10^9/l 50%, if below 2 × 10^9/l WBC or 75 × 10^9/l platelets the next cycle was postponed for one week. There were no dose adjustments for nadir counts.

Evaluation of response

All patients had an examination after the second course. This evaluation included at least repetition of all techniques which had shown abnormal findings. Complete remission (CR) was complete disappearance of all involved nodes or lesions and symptoms with normalisation of blood values and X-rays examination. If the nodes on the lymphogram had become normal in size but the configuration remained abnormal, the patient was considered as a complete remission if they fulfilled the other criteria. Partial remission (PR) showed a decrease of 50% or more of the largest diameter of all measurable and evaluable lesions with disappearance of symptoms and no lesions increasing in size.

Both CR and PR had to be documented by two series of measurements within a period of 4 weeks. CR and PR had to last at least 4 weeks. All other patients were considered as failures (no change or progressive disease).

RESULTS

Patients were included from September 1985 till May 1987. A total of 26 were entered. 17 are evaluable for response and 24 for toxicity. 7 had rapidly and 17 slowly relapsing disease. The reasons for not being evaluable are listed in Table 1. 1 patient was entered but no further data became available and 1 patient was ineligible as he had not been pretreated. Of the 24 eligible patients 7 could not be evaluated for response as they completed only one cycle due to early progressive disease (4), haematological intolerance (2) and refusal for further therapy (1). Thus 17 patients were fully evaluable for response and are the basis of this report. A median of three cycles was given [1–6].

Table 1. Characteristics of 26 patients

Total number entered	26	
Age: 23–64, med. 38.5 years		
Sex: 9 females—17 males		
Pathology: LP: 0		
NS: 17		
MC: 5		
LD: 1		
NOS: 3		
Rapidly progressive disease:	7	
Slowly progressive disease:	17	
Not evaluable	2	1 entered—no follow-up, 1 ineligible
Eligible	24	
Not evaluable for response (only 1 cycle)	7	4 early progression 1 persistent leukopenia 1 pancytopenia 1 refused therapy
Evaluable for response	17	CR 1 PR 2 17.6% NC 5 PD 9

CR = complete remission, PR = partial remission, NC = no change, PD = progressive disease.

Table 2. Toxicity of cytarabine (WHO criteria) [6]

	Grade						
Toxicity level	I	II	III	IV	Total	No eval.	%
Leukopenia	2	6	4	5	17	23	74
Thrombocytopenia	1	5	2	3	11	23	48
Anaemia	5	9	2	1	17	23	74
Nausea/vomiting	4	6	1	0	11	23	48
Diarrhoea	0	1	0	0	1	23	4
Stomatitis	2	2	0	0	4	23	17
Fever	1	2	1	0	4	21	19
Skin eruption	2	0	1	0	3	22	14
Dizziness	1	1	0	0	2	22	9
Alopecia	0	1	0	0	1	22	5
Other*	3	1	3	0	7	23	30

* 1 vasculitis with itching and burning sensation (generalised), 2 asthenia (feeling of extreme exhaustion), 1 cystitis with hematuria, 2 short period of impaired hearing, 1 pyrosis (mild) (gastric reflux).

The responses are shown in Table 1. 1 CR and 2 PR were observed with a total response rate of 3 out of 17 evaluable patients (17.6%). All responses occurred in patients with slowly progressive Hodgkin disease. The duration of the responses was short lived and lasted 6 months for the CR and 2 months for both PR. The patient who attained a CR had normalisation of all nodal localisations while skeletal abnormalities remained unchanged on radiographic examination. This patient developed a myelodysplastic syndrome afterwards.

Sixty-seven cycles were administered in the 24 patients evaluable for toxicity for an average of 2.8 courses per patient. The toxicity of these courses is detailed in Table 2. The main side effect was haematological with severe leukopenia and thrombocytopenia. In 2 patients this was the reason for giving one cycle only.

Gastro-intestinal toxicity was moderate and consisted of nausea, vomiting, diarrhoea and stomatitis. 3 patients developed skin eruption and 1 patient had a severe vasculitis with itching and a burning sensation.

DISCUSSION

The results of this phase II study of cytarabine in patients with relapsing Hodgkin's disease indicate that cytarabine has very little activity when given alone to heavily pretreated patients with limited bone marrow capacity at a dose of 80 mg/m^2 twice a day on 5 consecutive days every 3 weeks. The response rate is 17.6% while a response rate of 30–50% is needed to warrant further study [5]. The duration of the responses was short. Moreover, the toxicity observed required termination of the study.

So far there are no data proving that cytarabine is an active agent in Hodgkin's disease. We therefore recommend that,

before incorporating cytarabine in combination chemotherapy for Hodgkin's disease, the drug should be further investigated, exploring different dose-schedules in patients with slowly progressive disease and a reasonable bone marrow tolerance. Cytarabine has been incorporated in high dose schemes and claims a high response rate in previously treated Hodgkin patients [7] but there is no indication that the use of cytarabine in those schemes adds to the efficiency of these treatments.

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Lymphocyte Infiltrates as a Prognostic Variable in Female Breast Cancer

S. Aaltomaa, P. Lipponen, M. Eskelinen, V.-M. Kosma, S. Marin, E. Alhava and K. Syrjänen

The predictive value of lymphocyte infiltrates (LI) was studied in 489 patients with breast cancer followed-up for over 10 years. LI were positively correlated to axillary lymph-node status, tumour diameter and histological and morphometric variables ($P < 0.001$). In a multivariate analysis LI were independently related to axillary lymph-node status. LI predicted recurrence-free survival (RFS) in rapidly proliferating tumours ($P = 0.0269$). LI predicted RFS ($P = 0.08$) and breast cancer related survival (BS) ($P = 0.0164$) in rapidly proliferating, axillary lymph-node negative tumours. In a multivariate analysis LI independently predicted BS ($P = 0.08$) in rapidly proliferating tumours. LI independently predicted BS in rapidly ($P = 0.025$) and slowly ($P = 0.09$) proliferating, axillary lymph-node negative tumours. If the tumours were not categorised according to proliferation rate, LI and outcome were not significantly related. The results clearly confirm the presence of efficient immunological antitumour defence mechanisms in human breast cancer. Consequently tumour–host interactions are subject to further studies particularly in axillary lymph-node negative breast cancer.
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INTRODUCTION

BREAST TUMOURS are often surrounded by inflammatory cell infiltrates as a sign of tumour–host interactions [1–6] and the presence of lymphocyte infiltrates (LI) is considered to reflect hosts effort to resist tumour growth [3]. Although there is evidence in experimental conditions for an immunological antitumour activity against breast tumour cells [6, 7] the effectiveness of these mechanisms in clinical oncology of breast tumours is a matter of debate [8–10]. Some authors have related the presence of LI to favourable prognosis [11, 12] whereas others have found no positive correlation between prognosis and the LI [13, 14]. The presence of dense LI has also been related to high recurrence rate [15]. Previous studies have shown that LI are significantly related to malignant histological features [3, 5, 12, 15]. Therefore, the assessment of the independent role of LI is impossible without multivariate statistics and fractioning of breast tumours into comparable groups in relation to other prognostic factors. Thus, the present study was carried out to evaluate the predictive value of LI in relation to clinical, morphomerical and histological variables in 489 breast cancer patients followed up for over 10 years in one Finnish institution.

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