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Short Communication

Bone Marrow Protection with Amifostine in the Treatment of High-risk Malignant Lymphoma

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Based on preclinical and clinical studies which suggested that amifostine can protect against haematological toxicity of cyclophosphamide, we conducted a clinical trial of amifostine and intermediate doses of cyclophosphamide in patients with high-risk malignant lymphoma. 40 patients were enrolled to receive amifostine (910 mg/m^2) before cyclophosphamide (1500 mg/m^2) for two cycles (10 patients); 20 patients were allocated to receive amifostine/cyclophosphamide only on one cycle (patients were their own control) and 10 patients received cyclophosphamide alone without amifostine protecion. Patients who received amifostine had fewer days of severe granulocytopenia (grade III or IV) and infectious episodes, and delay on treatment was minimal. Amifostine was well tolerated; only 2 patients developed transient and mild hypotension. The complete response rate was 72% (29/40). We conclude that amifostine is a good protector against haematological toxicity of cyclophosphamide and did not interfere with tumour response. Clinical trials with increasing doses of cytotoxic drugs or combination chemotherapy are needed to define the role of this myeloprotector agent in the treatment of patients with malignant lymphoma. © 1997 Published by Elsevier Science Ltd.

Key words: malignant lymphoma, non-Hodgkin's lymphoma, chemotherapy, cyclophosphamide, amifostine, granulocytopenia

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INTRODUCTION

IN THE last few years, treatment of aggressive malignant lymphoma has changed because long-term follow-up of patients treated with conventional chemotherapy has shown that only 30–37% of patients have a prolonged disease-free survival (DFS) [1]. The introduction of haematopoietic growth factors to the therapy has resulted in an increase in dose intensity with improvement in the complete response (CR) rate [2]. Although haematopoietic growth factors can shorten the period of severe granulocytopenia, some patients remain at risk of developing severe haematological toxicity, with infections secondary to granulocytopenia and, in extreme cases, death. Amifostine (WR-2721) is a sulphhydril compound that was developed as an agent to protect against ionising radiation in the event of a nuclear war. Clinical applications in oncology were derived from studies of tumour-bearing animals, which showed that amifostine can protect normal tissues from toxicity associated with radiation, alkylating agents and cisplatin without protecting neoplasms [3–5]. Initial studies in human tumours confirmed that amifostine can protect different normal tissues [6, 7].

Clinical studies in patients with malignant lymphoma are scarce [8]. We conducted a randomised clinical trial to assess the efficacy and toxicity of amifostine administered to patients who received cyclophosphamide for treatment of diffuse large cell lymphoma.

PATIENTS AND METHODS

40 patients with previously untreated high-risk diffuse large cell lymphoma were entered into this clinical trial. Patients had to have a diagnosis of diffuse large cell lymphoma (intermediate and immunoblastic subtypes of the Working Formulation Classification), clinical high-risk according to the International Prognostic Study Group [9], no bone marrow infiltration with adequate renal, hepatic

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and cardiac function, and be previously untreated. Exclusion criteria were: pregnant women, previous history of malignancy, acquired immunodeficiency syndrome, previous history of congestive heart failure or uncontrolled high blood pressure. Consecutive patients were enrolled. Informed consent was obtained for all patients and the study was approved by our Ethical Committee.

Patients were randomly assigned to one of the four groups, according to the following schedule:

	No. of patients	Arms	
Group 1	10	A	A
Group 2	10	A	B
Group 3	10	B	A
Group 4	10	B	B

Patients assigned to arm A received amifostine, 910 mg/m^2, as a 15 min intravenous (i.v.) infusion completed 5 min before cyclophosphamide.

Cyclophosphamide, 1500 mg/m^2, was administered as a 30 min i.v. infusion. Patients in arm B received cyclophosphamide alone without amifostine protection. Cycles were planned to be administered every 14 days. The treatment given after cyclophosphamide included a high-dose (1 g/m^2) of etoposide, 180 mg/m^2 epirubicin and 5 g/m^2 ifosfamide, as previously described [2].

No dose modification was considered. If at day 14 patients had granulocytopenia ($<1.8 \times 10^9$/l) or thrombocytopenia ($<100 \times 10^9$/l), treatment was delayed. If at day 21, haematological recovery was not observed, patients were considered toxic failures and were withdrawn from the study.

Blood pressure was monitored every 5 min during the amifostine infusion. If systolic blood pressure decreased 20 mmHg over the baseline level, amifostine infusion was interrupted for 15 min. If blood pressure did not return to the baseline level, treatment was stopped.

All patients underwent serum chemistry and complete blood counts on days 5, 10 and 14. Toxicity was assessed weekly on days 5, 10 and 14 using the common toxicity criteria.

Complete response (CR) was defined as a total resolution of all tumour mass at the time of re-evaluation, maintained for at least 3 months.

Because, in our experience, patients with a partial response have a poor outcome, we considered partial responses together with failure, when a reduction in the tumour mass was less than 50% or development of new tumour masses occurred.

Because the aim of the study was to assess the efficacy and toxicity of amifostine to prevent severe granulocytopenia and/or thrombocytopenia, the results were analysed on this basis. Responses were analysed according to the total chemotherapeutic programme, taking into consideration the administration or exclusion of amifostine. Disease-free survival was calculated from the date of response until the date of relapse.

RESULTS

From January 1994 to February 1995, 40 patients were entered into the study. The patients' characteristics are shown in Table 1. All patients had clinical high-risk disease and features of poor prognosis such as bulky disease (65%), high levels of lactic dehydrogenase (95%) and beta 2 microglobulin (85%) and extranodal disease (68%). However, no statistical differences were observed between those patients who were randomised to receive amifostine and those who were not ($P = 0.5$). All patients were considered assessable for response and toxicity.

Table 1. Patients' characteristics

	Groups			
	1	2	3	4
Number	10	10	10	10
Sex: male/female	5/5	4/6	3/7	5/5
Age (years) median	50	48	48	49
Bulky disease	8	5	7	6
Lactic dehydrogenase (>2 normal levels)*	9	10	10	9
Beta 2 microglobulin (>3500 μg/ml)	7	9	9	9
Extranodal disease	9	8	4	6

*Between January 1994 and October 1994, normal lactic dehydrogenase level was 275 UI/l. Between November 1994 and February 1995, the normal value was 110 UI/l, because two different kits were used over these periods.

Table 2 shows haematological toxicity. Patients who received amifostine had fewer days of severe granulocytopenia (grade III or IV). For 2/40 cycles in patients treated with amifostine and cyclophosphamide, a mean delay to treatment of 0.8 days was observed, whereas in patients who were treated with cyclophosphamide alone in 11/40 cycles a mean delay of 6.3 days was seen. No infections related to granulocytopenia were observed in patients who received amifostine compared with four (two septicaemia and two pneumonia) in patients without amifostine infusion. Nevertheless, no treatment-related death was recorded in either arm.

The CR rate was 72% (29 out of 40 patients), similar to previous reported results with intensive brief chemotherapy [2]. 25 patients (83%) who received amifostine in any of the cycles (groups 1–3) were alive and disease-free at 18 months compared to only 4 (40%) who did not receive amifostine.

Toxicity

2 patients developed a transient decrease in systolic blood pressure. Amifostine was interrupted by 15 min, following

Table 2. Haematological toxicity

	Amifostine + cyclophosphamide	Cyclophosphamide alone
Number of cycles	40*	40†
Granulocytes (days, mean)		
$<0.5 \times 10^9$/l	3.6	8.5
$<1.0 \times 10^9$/l	5.1	11.4
$>1.8 \times 10^9$/l	11.7	16.9
Delay on treatment (days)	0.8	6.3
Infection episodes	0	4
Treatment-related deaths	0	0

*Twenty cycles in group 1, 10 cycles in group 2 and 10 cycles in group 3.

†Ten cycles in group 2, 10 cycles in group 3 and 20 cycles in group 4.

which blood pressure returned to normal values. No saline infusion was necessary to increase blood pressure. Amifostine was restarted without further decrease in blood pressure.

No other side-effects secondary to amifostine administration were observed, including hypomagnesaemia.

DISCUSSION

Amifostine has been shown to protect normal tissues against the toxicity of alkylating agents in animal models. Theoretically, combining amifostine with high doses of antineoplastic chemotherapy should permit higher doses of the cytotoxic drugs to be administered without increasing bone marrow damage, leading to greater tumour cell kill. Clinical studies have been performed and it has been demonstrated that amifostine can protect different organs from the side-effects of some chemotherapeutic agents, including cyclophosphamide [6–8].

The results of our study showed that patients who received amifostine had less myelosuppression with fewer days of severe granulocytopenia and fewer infections. The CR rate is difficult to evaluate because cyclophosphamide therapy is only a part of the total chemotherapeutic regimen and the groups of patients were too small to achieve any difference. However, patients who received amifostine in one or both cycles of cyclophosphamide therapy had longer DFS. However, controlled trials need to be conducted to confirm whether amifostine can be useful in the treatment of patients with malignant lymphoma.

We feel that amifostine is a useful agent, and can protect bone marrow from damage from different agents in patients with poor prognostic factors and who need more intensive chemotherapy. The use of amifostine should be considered in combination with aggressive chemotherapy for the treatment of poor prognosis malignant lymphoma.

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