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ORIGINAL ARTICLE

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Phase I-II study of escalating doses of amifostine combined with high-dose cyclophosphamide

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Abstract *Purpose*: To evaluate the feasibility and clinical effects of increasing doses of amifostine administered four times in 1 day with high-dose (HD) cyclophosphamide (CTX). *Methods*: A group of 16 patients with a diagnosis of lymphoma were treated with HD-CTX given at a total dose of 7 g/m^2 subdivided into four doses, each preceded by increasing doses of amifostine. A group of 12 lymphoma patients previously treated with the same HD-CTX regimen was used as historical controls. *Results*: The dose of amifostine was escalated in cohorts of three patients each from 4×570 mg/m^2 to 4×910 mg/m^2 without severe toxic effects. Further patients were treated at the highest dose level. Side effects included a fall in blood pressure (always less than 20% of baseline value), asymptomatic hypocalcemia (from a median value of 2.4 to 1.7 mmol/l) and a decrease in creatinine clearance (from a median value of 102 to 85 ml/min). The parameters of hematotoxicity for patients treated in the study were not significantly different from those of the historical control patients. *Conclusions*: Amifostine can be given safely at a dose of 910 mg/m^2 four times in 1 day in combination with HD-CTX. With this schedule amifostine did not show a myeloprotective effect.

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Introduction

Amifostine (WR-2721, Ethyol) is a phosphorylated aminothiol prodrug, which becomes dephosphorylated in tissues to the free thiol active metabolite, WR-1065 [1, 2]. Amifostine has been shown to confer cytoprotection on many organ systems against the side effects of radiation and many chemotherapeutic agents. This protective effect seems to be selective for normal tissues, while tumor cells are not protected [3, 4, 5, 6].

The compound has several mechanisms of action, which also explains its selectivity. The activation of the prodrug is minimal in serum, and occurs primarily by dephosphorylation through a membrane-bound alkaline phosphatase, an enzyme with high specific activity in the endothelium of normal capillaries and membranes of normal cells, but which is present only in small amounts in neovascular endothelium and membranes of cancer cells [1]. WR-1065 can upregulate p53 expression, resulting in more efficient DNA repair. The thiol is an oxygen free-radical scavenger, and also binds directly to the active species of alkylating and platinum agents, preventing them from forming adducts with DNA [2]. When used in autologous bone marrow purging, the drug protects hematopoietic stem cells, allowing a faster hematological recovery of the transplanted patient without reducing the efficacy of tumor cell kill [7, 8, 9].

A myeloprotective effect of amifostine has been demonstrated in a number of clinical studies. In ovarian cancer patients treated with cisplatin and cyclophosphamide (CTX), amifostine reduced the incidence of neutropenic fever and the number of days on antibiotics [10]. In patients with colorectal cancer treated with mitomycin, amifostine has been shown to reduce the severity of thrombocytopenia [11], while in patients with non-small-cell lung cancer and other solid tumors it

reduces the incidence and severity of thrombocytopenia [12, 13]. In patients with solid tumors treated with CTX, amifostine reduces the severity of neutropenia and leucopenia [14, 15]. Initial reports suggested that amifostine could also have a role in enhancing the number of circulating hemopoietic precursors (peripheral blood progenitor cells, PBPC) when given with a mobilizing regimen of chemotherapy with G-CSF [16].

Based on these preliminary data, we undertook this study to determine whether high-dose (HD) amifostine could reduce the myelotoxicity of HD-CTX/G-CSF in patients with lymphoma. We administered HD-CTX subdivided into four doses, each 3 h apart to reduce the risk of cardiotoxicity [17]. Since amifostine has a very short half-life of 12 min, we decided that, if a protective effect was to be seen, we should administer it immediately before each CTX dose, i.e. four times a day. At the time the study was initiated, the optimal dose of amifostine was considered to be 910 mg/m^2, higher than the presently recommended dose of 740 mg/m^2 for which the best therapeutic index has been reported [2]. Since the administration of 910 mg/m^2 of amifostine repeated four times over 1 day had not been tested before, we had to first perform a phase I evaluation of this regimen. The decision to use 570 mg/m^2 four times over 1 day as the first dose level was based on data from previous trials with carboplatin, in which doses of 680–740 mg/m^2 had been given safely three times a day [12, 18].

Materials and methods

Patients

Relapsed, resistant or high-risk lymphoma (Hodgkin's or non-Hodgkin's) patients, for whom an autologous peripheral stem cell transplantation (PBSCT) was planned, were eligible for the trial. Eligibility criteria included age 16–65 years, adequate bone marrow, renal (normal creatinine) and liver function (normal bilirubin, transaminases less than twice the upper limit of normal), no clinical or radiological (chest radiography) signs of infection, LVEF ≥50% by echocardiography, and no prior history of cardiac disease. Written informed consent and approval of the local ethics committee were requested. A control group of 12 consecutive patients conforming to the same selection criteria and treated with the same HD-CTX + G-CSF regimen in the period immediately preceding the activation of this trial was defined.

Treatment

On day 1, CTX at a total dose of 7 g/m^2 was administered i.v. subdivided into four doses to be infused each over 1 h every 3 h. Hydration and alkalinization were performed by i.v. administration of 2000 ml fluids the day before, 5000 ml on the day of treatment (of which 1500 ml were sodium bicarbonate), and 3000 ml on the following day. Acetazolamide 250 mg i.v. was also given every 8 h on day 1. KCl (80 mmol/24 h) and Mg (32 mmol/24 h) were added to the fluids. To prevent hemorrhagic cystitis, 1 g mesna was given just before each CTX infusion, and 500 mg every 8 h was given after the last dose of CTX for 24 h. Antiemetic prophylaxis consisted of granisetron 3 mg i.v. and methylprednisolone 125 mg i.v. before the first and the fourth CTX infusions, repeated on the morning of day 2. G-CSF was started on day 6, and was self-administered daily by the patient up to a WBC of $>4000\times10^9$/l and the leukaphereses were terminated. The G-CSF dose was 12 μg/kg divided into two daily s.c. injections at 12-h intervals. The dose was approximated to one vial of 30 or 48 MU filgrastim. Chemotherapy, growth factor administration and ancillary treatments were similar in the control group.

Amifostine

In the phase I part of the study, the maximal tolerable dose (MTD) of amifostine in combination with HD-CTX was defined. Cohorts of three patients, six in the case of dose-limiting toxicities (DLT), received escalating doses of amifostine (570, 740, 910 mg/m^2) before each CTX infusion. The MTD was defined as the dose preceding the one producing DLT in at least two patients and its toxicity had to be evaluated in seven additional patients.

Amifostine was diluted in 50 ml normal saline and administered over 15 min immediately before the CTX. Patients in the amifostine trial received an additional 20 mg dexamethasone orally 12 h and 4 h before the first dose of amifostine, and 6.5 mg triethylperazine orally 4 h and 1 h before.

Patient monitoring and follow-up

Blood pressure and pulse were measured before the amifostine was given, every 5 min during its administration, then every 5 min until normalization of any blood pressure drop which may have occurred. Chemistry values (Na, K, Ca, phosphates, parathormone, glucose, creatinine and creatinine clearance) were assessed before chemotherapy and on day 2. Total and ionized Ca, phosphates and Mg were also measured on day 1, 7 and 14 h after the first infusion of amifostine. The 24-h urinary excretion of Na, K, Mg, phosphates and Ca were measured before and after CTX therapy.

Patients were seen every other day in the outpatient clinic for hematological evaluations and transfusions when necessary. Packed red cells were given in the presence of an hemoglobin value <10 g/dl (outpatients) or ≤ 8 g/dl (inpatients); platelet units were transfused in the presence of a platelet count of $\leq 10\times10^9$/l (outpatients) or $\leq 5\times10^9$/l (inpatients). Creatinine clearance was repeated before the subsequent chemotherapy cycle, scheduled for 3 to 4 weeks later.

Statistical analysis

All patients receiving amifostine were analyzed as a single group, independently of the dose received, due to the small size of the dose-level cohorts. Hematological toxicity in the study group was compared to that of the historical control cohort by means of a stepwise regression analysis accounting for prognostic factors found to be relevant in previous studies on similar patients [19].

Results

Patients and treatment

The characteristics of the 16 patients entered in the study are summarized in Table 1.

Dose escalation

No DLTs were observed at any dose level, so that three patients were treated at each dose of amifostine evaluated (570, 740, 910 mg/m^2 four times over 1 day). Seven additional patients were then entered at the dose of 910 mg/m^2 four times over 1 day. During or immediately after amifostine infusion, the blood pressures (systolic

Table 1 Patient characteristics (medians and range, n = 16)

	Number of patients	Median	Range
Age (years)		49.5	16–66
Male/female	10/6		
Diagnosis			
Hodgkin's disease	3		
High-grade NHL	11		
Low-grade NHL	2		
Time from diagnosis (months)		11.5	1–120
Duration of prior chemotherapy (months)		4.5	0–34
Time from last chemotherapy (days)		24	12–180
Baseline hematological values			
Hemoglobin (g/dl)		11.2	9.8–15
Platelets ($\times 10^9$/l)		263	114–522
WBC ($\times 10^9$/l)		5.4	2.5–13.1
CD34 ($\times 10^3$/l)		6.4	0–65.5
GM-CFC (/l)		133	6.5–610
Bone marrow function			
CD34 (/10^5 MNC)		1400	70–3600
GM-CFC (/10^5 MNC)		61	8–143

and diastolic) dropped by a maximum of 20%, without significant difference among the four subsequent administrations, or among the three dose levels evaluated. The other parameters studied (heart rate, creatinine clearance, liver function tests, electrolytes and glucose) also did not vary significantly among dose levels. Gastrointestinal toxicity was as expected in patients receiving high doses of CTX.

Effects on renal function and electrolytes

The serum and urinary electrolyte values before and after treatment with CTX and amifostine are shown in (Table 2). Amifostine-treated patients, 24 h after treatment, showed a significant reduction of blood concentrations of Na, K, Ca and ionized Ca, with a concomitant increase in phosphates and Mg. Serum creatinine also significantly increased, while the median parathormone levels remained constant. During treatment with amifostine/CTX even lower ionized Ca levels (0.89 mmol/l), and a transient reduction in the blood phosphate levels were observed. In the 24-h urine collection of day 1, a significant increase in urinary excretion of Na, Ca and Mg was seen, while the urinary excretion of phosphates remained constant. Serum creatinine significantly increased from 76 to 82 μmol/l. Creatinine clearance decreased from a median of 102 to 85 ml/min ($P < 0.001$); a significantly decreased value ($P < 0.001$ from baseline) of 84 ml/min was still present after 3–4 weeks. This decrease in creatinine clearance had not been seen in the control group, in which unchanged values were found before and after treatment for both creatinine clearance (median 88 ml/min before vs 95 ml/min after treatment) and blood creatinine (median 94 μmol/l before vs 90 μmol/l after).

Hematological toxicity

Some of the main hematological toxicities observed are presented in Table 3 together with the same values for the historical control group. None of the differences between the two groups was significant in the multivariate analysis.

Progenitor cell mobilization

The first day WBCs were $>4\times10^9$/l (corresponding to the day of first leukapheresis) the median concentration of $CD34^+$ in the blood was 16,150/ml for the amifostine group and 48,500/ml for the controls. GM-CFC were 483/ml and 2414/ml for study patients and controls, respectively. These differences were not significant. The

Table 2 Median serum and urinary electrolyte values before and after treatment with HD-CTX and amifostine. Values are medians (range) ($n = 16$)

	Before treatment (time 0)	During treatment (7–14 h after first CTX)	After treatment (24 h after first CTX)
Serum			
Na (mmol/l)	138 (136–143)		131 (128–143)*
K (mmol/l)	4.45 (3.9–5.0)		3.50 (2.8–4.2)*
Total Ca (mmol/l)	2.4 (2.3–2.6)	1.7 (1.5–1.9)*	1.7 (1.5–2.1)*
Ionized Ca (mmol/l)	1.23 (1.16–1.38)	0.89 (0.81–1.04)*	0.93 (0.83–1.06)*
Phosphate (mmol/l)	0.81 (0.55–1.33)	0.69 (0.51–1.33)*	1.13 (0.78–1.52)*
Mg (mmol/l)	0.78 (0.62–0.9)	0.78 (0.62–0.9)	0.97 (0.8–1.22)*
Parathormone (pmol/l)	4.2 (2.7–13.0)		5.1 (1.5–10.7)
Creatinine (μmol/l)	76 (47–93)		82 (48–107)*
Urine			
Na (mmol/24 h)	220 (92–366)		558 (221–836)*
Ca (mmol/24 h)	4.6 (0.1–14)		13.9 (6.9–19.9)*
Mg (mmol/24 h)	2.9 (0.7–10.5)		14.3 (1.0–476)*
Phosphates (mmol/24 h)	20.7 (9.2–31.6)		23.5 (13–48.4)
Creatinine (mmol/24 h)	9.8 (3.4–17)		9.7 (4.3–14.6)
Creatinine clearance (ml/min)	101 (60–153)		84 (58–111)*

*$P < 0.05$ compared to baseline

Table 3 Hematological toxicity and stem cell mobilization of HD-CTX with or without amifostine. Values are medians (range)

	Control group ($n=12$)	Amifostine group ($n=16$)
Time in hospital (days)	8.5 (5–19)	12.5 (5–29)
Red cells transfused (units)	2.5 (0–10)	4 (0–8)
Platelets transfused (units)	0 (0–4)	1.5 (0–6)
Platelet nadir ($\times 10^9$/l)	18 (6–134)	10.5 (4–66)
Time with platelets $<20\times10^9$/l (days)	2 (0–10)	5 (2–13)
Time with ANC $<0.5\times10^9$/l (days)	5 (0–11)	6 (3–11)
Time to WBC $>4\times10^9$/l (days)	12 (0–19)	13 (10–26)
Mobilization of $CD34^+$ (/ml)	48,500 (0–180,000)	16,150 (0–128,000)
Mobilization of GM-CFC (/ml)	2,414 (0–28,662)	483 (0–7359)

median number of leukaphereses performed per patient was two in both groups.

Discussion

In the phase I part of the study, despite the small number of observations, there appeared to be no difference in the side effects of the drug among the three dose levels, so that a total of ten patients could be treated at the highest dose of 910 mg/m^2 four times daily. This is the first study demonstrating the feasibility of administering amifostine at a dose of 910 mg/m^2 four times in one day, and the feasibility of combining this schedule with HD-CTX.

Other investigators have failed in escalating the daily dose to this level [12, 18], mainly because of symptomatic blood pressure falls. It is possible that we succeeded in escalating the dose up to 910 mg/m^2 four times over 1 day because of the very short half-life of the drug ($t_{1/2\alpha}$ 0.19 h), and the 3-h time interval between administrations which allowed complete clearance of the drug. In addition, the intensive hydration and premedication with steroids and antiemetics given for the HD-CTX probably helped to decrease the incidence of blood pressure fall below that seen in previous trials [12, 18]. We did observe drops in systolic and diastolic blood pressure, but these were independent of the dose and timing of administration and never exceeded 20% of baseline.

The main objective of this trial was to verify whether escalated doses of amifostine could have a myeloprotective effect against HD-CTX. The results show that such was not the case, nor did we observe an improvement in PBSC mobilization in comparison to controls. Since this was a comparison with historical controls, no definitive conclusions can be drawn as to which of the two HD-CTX regimens, i.e. with or without amifostine, is the more myelotoxic. Nevertheless, if amifostine were to have some myeloprotective effect in this schedule, we should at least have observed a trend in this direction, which was not the case. This observation is in contrast to data from other studies in which amifostine was given with CTX in different doses and schedules [1, 14, 15], and which showed a higher ANC nadir, a reduction in the duration of neutropenia and in time spent in the hospital as well as a lower incidence of infections. On the other hand, several other studies have failed to demonstrate a myeloprotective effect of amifostine from substances such as taxanes [20], possibly because of their mechanisms of action.

A first possible reason for the lack of myeloprotection seen in our study may be the observed acute reduction in renal function. A lower creatinine clearance may result in a higher AUC of CTX and its metabolites (which are at least partially cleared by the kidneys), and consequently a higher exposure of the bone marrow to the alkylators and thus a higher toxicity. Alterations in the drug's pharmacokinetics associated with a reduction in creatinine clearance by amifostine have been observed before with substances such as carboplatin [18, 21] and taxanes [22]. Another hypothesis concerning the lack of cytoprotection by amifostine is its possible interaction with mesna. Very little information about such a possibility is available, since in previous studies with CTX [10, 14] mesna was not administered. In a more recent study, however, it was shown that mesna does not interfere with the pharmacokinetics of amifostine [23].

An unexpected effect, particularly since amifostine has been accepted by the FDA as a nephroprotector, was a constant, statistically significant and permanent drop in the value of creatinine clearance, paralleled by a significant increase in serum creatinine which was not seen in the group of patients not receiving amifostine. This worsening of renal function may even have been underestimated due to the fact that the 24-h urine collection on the day of treatment included urine collected before treatment with amifostine was started. The persistence of this reduction after 3–4 weeks suggests that it might not be due to a functional phenomenon such as the inhibition of the tubular excretion of creatinine or a contraction of the circulating volume. A significant increase in serum creatinine after amifostine has also been observed in another trial in patients receiving carboplatin [18].

Other phenomena related to an effect on renal function were a severe hypocalcemia and a relative hypoparathyroidism, as already described for amifostine [24]. In contrast to that study, we failed to find any absolute variation of parathormone levels, suggesting that hypocalcemia is not a consequence of hypoparathyroidism. The observation of a persistent phosphaturia makes the hypothesis of a tubular resistance to parathormone or of

drug-induced tubular damage unlikely. Hypomagnesemia, another possible cause of low parathormone levels and hypercalciuria, was prevented by i.v. Mg supplementation, leaving the massive increase in urinary Ca loss, corresponding to a threefold baseline value, as the only possible explanation for the observed hypocalcemia. Even though it has been reported that increased natriuria induces more calciuria [25], the extent of this phenomenon in our study was much higher than expected, and therefore not explainable only by Na supplementation or treatment with acetazolamide. We therefore conclude that hypocalcemia was mainly due to an increased calciuria, the cause of which is still unexplained.

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