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Phase I study of cyclohexylamine and lysine salt of mafosfamide

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Summary. Mafosfamide is a new oxazaphosphorine that breaks down spontaneously into 4-hydroxy-cyclophosphamide. A phase I trial with cyclohexylamine and lysine salts of mafosfamide was carried out in 16 patients, using weekly IV perfusion. Dose-limiting toxicities were not hematological, but consisted in the development of severe pain along the vein during administration. A particular mucosal syndrome with sneezing and conjunctivitis was seen only after administration of the lysine salt. The dose of 700 mg/m^2 per week represents the maximum tolerated dose with this weekly schedule.

Introduction

Mafosfamide is a chemically stable thioethane sulfonic acid salt of cyclophosphamide, which spontaneously breaks down into 4-hydroxy-cyclophosphamide. This compound is directly active in vitro and does not require enzymatic activation. Mafosfamide has been found to have similar or better antitumor activity than cyclophosphamide in several mouse models and also in a cyclophosphamide-resistant P 388 subline [1]. Animal toxicological studies have revealed that mafosfamide induced reversible myelosuppression much lower than that induced by equimolar doses of cyclophosphamide. A minimal increase in bladder weight has been produced at high doses, in contrast to severe urotoxicity of other oxazaphosphorines given at low doses. The LD_{50} is between 500 and 625 mg/kg in mice and between 250 and 310 mg/kg in rats after IV administration [4]. These values are much higher than the corresponding ones for 4-OH-cyclophosphamide [2].

Because of these marked differences between mafosfamide and the other known oxazaphosphorines, we felt that a phase I trial with this compound was warranted.

Material and methods

Patients with advanced malignancies not amenable to standard treatments were eligible for the trial. Cyclohexylamine salt of mafosfamide (Asta Z 7557) was initially tested. The lysine salt (Asta Z 7654) was tested later, in an attempt to reduce the drug-induced local toxicity. Performance status 0–3, leukocytes $\geqslant 4000/mm^3$, platelets $\geqslant 100000/mm^3$, and normal biochemical profiles were required at entry. No prior chemotherapy was allowed within 4 weeks before the study. Mafosfamide was administered weekly as an IV infusion over at least 5 min. The initial dose, extrapolated from toxicological studies, was 200 mg/m^2, and the dose was escalated to 400 m^2 and 700 mg/m^2 in at least three patients at each dose level.

Mesna was given along with mafosfamide salts in an attempt to reduce drug toxicity, since this substance binds to common degradation products of the oxazaphosphorines.

Results

Forty-two evaluable courses of cyclohexylamine salt and 15 of lysine salt were administered in 16 patients (Table 1). The results are shown in Table 2. After administration of cyclohexylamine salt of mafosfamide, moderate (W.H.O. grade 2–3) [5] anemia was seen at all dose levels tested. At 700 mg/m^2 grade 3 leukopenia was seen in 1 patient and grade 1–2 thrombocytopenia 2 patients. Hematological toxicity was not encountered with the lysine salt at the dose levels tested.

Table 1. Patient characteristics

Characteristic	No. of patients	
	Cyclohexylamine salt	Lysine salt
No. entered	11	5
Median age in years (range)	51 (37 – 72)	57 (46 – 76)
Sex		
Male	9	5
Female	2	0
Median performance status (range)	2 (0 – 3)	1 (0 – 2)
Primary tumors		
Lung	3	1
Lymphoma + myeloma	3	1
Various	5	3
Previous therapy		
Radiotherapy + chemotherapy	6	0
Chemotherapy	3	3
Radiotherapy	0	1
None	2	1

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Table 2. Toxicities related to drug administration

Toxicity	Dose level (mg/m²)				
	Cyclohexylamine salt			Lysine salt	
	200	400	700	400	700
No. evaluable	3	3	4	3	2
Median hemoglobin nadir[a]	8.7	9.2	11.7	11.9	13.3
Range	8.0 – 11.5	9.2 – 11.2	7.2 – 13.4	10.3 – 12.1	12.1 – 14.4
Median Wbc count nadir[b]	6.8	4.8	3.2	5.7	7.7
Range	3.9 – 7.2	3.2 – 10.8	1.6 – 5.2	5.2 – 8.9	7.6 – 7.8
Median platelet count nadir[b]	255	159	94	208	217
Range	207 – 343	157 – 236	50 – 240	176 – 429	149 – 285
Local pain	2	3	4	2	2
Nausea and vomiting	0	2	3	1	1
Temperature elevation above 38.5°C	0	0	1	0	0
Phlebitis	0	0	1	0	0
Mucosal syndrome	0	0	0	3	2

[a] g/dl
[b] Cells/mm³

The most frequently encountered side effect with both salts was the development of severe pain along the vein, starting soon after the beginning of the infusion. We attempted to circumvent this phenomenon by increasing the infusion volume up to 1000 ml, changing the vehicle to buffered solutions, slowing the infusion time up to 120 min or administering mesna. None of these procedures diminished the intensity of the local pain. Only IV 2% xylocaine perfusion during the mafosfamide administration seemed to alleviate the local symptoms somewhat. In 1 patient only, pain was associated with the development of phlebitis of more than 1 months's duration without tissue necrosis.

The lysine salt of mafosfamide induced an unique side effect, consisting in severe and intractable sneezing with a watery nasal discharge, conjunctivitis, and lacrymation during administration in all patients.

Discussion

Cyclohexylamine and lysine salts of mafosfamide were administered weekly in 16 patients in increasing doses. Up to 700 mg/m², no severe myelosuppression was seen. At this level, dose-limiting factors consisted in the development of severe local pain, exceptionally phlebitis, and in a particular mucosal syndrome with nasal and conjunctival irritation. We were not able to prevent or diminish the intensity of these drug-related toxicities. The mechanisms of these side effects are not yet understood. However, it has been reported that mafosfamide salts induce local irritation 24 h after intracutaneous injection in animals [3].

We conclude that further clinical use of cyclohexylamine and lysine salt of mafosfamide as given in this schedule does not seem possible.

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