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Letter to the Editor: Lack of Protection of Proximal Tubular Cells by Amifostine (Ethyol) in Ifosfamide-containing Regimens

To the Editor: Ifosfamide (IF) is an effective drug in paediatric oncology [1]. However, there is great need for agents that can deal with the dose-limiting tubular toxicity of IF.

Amifostine (Ethyol) is a prodrug that forms an activated free thiol when dephosphorylated by alkaline phosphatase. The metabolite appears to be selective in its entry into nonmalignant cells. In this way, it can protect against toxicity associated with alkylating agents and platinum-containing regimens. Preclinical studies suggested that nephrotoxicity caused by alkylating agents and organoplatinums could be prevented. Hence amifostine seemed to be a suitable drug for clinical testing in IF tubulotoxicity in the paediatric age group.

We performed a pilot study to investigate the safety of amifostine in children and to judge the efficacy of amifostine in decreasing acute tubular toxicity in patients receiving a cumulative dose of 12–18 g/m^2 of IF. Eight patients were included in this study. After having obtained informed consent, four consecutive patients (group A) were treated with amifostine and the next four were not (control group C). The two groups were comparable concerning age, underlying disease, total dose of ifosfamide, regimen of how the IF was administered, and protection of tubular toxicity by mesna. Amifostine was given in a dose of 740 mg/m^2 i.v. in 15 minutes just before the start of the IF infusion and a second dose after 2 hours. Tubular function was documented before treatment and after a cumulative dose of 12–18 g of IF. Four parameters were used, namely, tubular phosphate reabsorbtion, β_2 microglobulin excretion in a fresh-voided urine specimen, DMSA uptake [2], and the ratio of α-amino nitrogen versus total nitrogen excretion in a 24-hour urine collection [3]. Serum creatinine and creatinine clearances were measured and calculated. It was decided to study the data after four patients in each group were entered and completed the study period.

The aim was to assess outcomes in these patients to determine whether a randomised study should be mounted. Since we knew the possibility of orthostatic

TABLE I. Results of Four Parameters for Tubular Function Before and After Therapy in Amifostine-treated Patients (group A) and Controls (group C)

Controls (group C)				Amifostine (group A)			
Patient no.	Before	After	Difference	Patient no.	Before	After	Difference
			TRP in %				
1	91	78	13	5	91	91	0
2	99	90	9	6	95	92.5	2.5
3	N.D.	90	N.D.	7	88	95	−7
4	93	88	5	8	95	92	3
			β_2 microglobulin mg/l				
1	0.1	4.7	4.6	5	0.1	13.2	13.1
2	0.1	N.D.	N.D.	6	0.1	29.6	29.5
3	0.9	5.8	4.9	7	0.1	12.7	12.6
4	0.1	2.6	2.5	8	0.2	45.6	45.4
			DMSA-uptake in %				
1	33	25	8	5	48	19	29
2	42	28	14	6	27	23	4
3	40	14.5	25.5	7	50	0.8	49.2
4	41	32	9	8	48	50	2
			Ratio α-amino N/total N				
1	2.0	N.D.	N.D.	5	2.1	1.8	−0.3
2	1.0	2.0	1.0	6	1.3	4.8	3.5
3	N.D.	2.7	N.D.	7	0.8	2.6	2.8
4	6.4	3.7	−2.7	8	1.3	4.3	3.0

N.D. = not determined.

hypotension in adult patients, we kept these patients in bed during the reinfusion of amifostine. We did not observe any decrease in systolic blood pressure of more than 10 mm Hg. Concerning the tubular toxicity parameters, the following values were observed (Table I): for phosphate reabsorption, all posttherapy values in the control group were lower than the posttherapy values in the amifostine group. In β_2 microglobulin excretion, we observed a higher excretion in all the amifostine-treated patients, both in absolute values and as in differences between pre- and posttherapy. Also, in DMSA-uptake studies we could not find any indication of a difference. The ratio of α-amino N/total nitrogen in 24-hour urine collection was also not different in the two groups.

It is extremely difficult to test a new drug for its effectivity and toxicity in a paediatric setting, especially when it concerns agents used in malignant diseases. The number of children with cancer is small, the requirements for inclusion into a study are very strict, and ethical dilemmas are difficult to overcome. It is for these reasons that we evaluated the results after only four patients were included in each group. Not only was there no indication of a protective effect, but some patients showed more signs of deterioration in tubular function than the control patients.

Since the test groups were quite comparable, the counterproductive findings in the admittedly small number of children treated with these doses of IF and amifostine caused us to stop the study. Sometimes, preliminary results suffice, as we believe they do here, and thus save everyone time and effort while at the same time, protecting from potential harm the larger number of subjects who would need to be enrolled in order to achieve statistical significance.

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