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Treatment of Ifosfamide-induced Urothelial Toxicity by Oral Administration of Sodium 2-Mercaptoethane Sulphonate (MESNA) to Patients with Inoperable Lung Cancer

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Abstract—*The protective effect of oral administration of the thiol compound sodium 2-mercaptoethane sulphonate (MESNA) against urothelial toxicity induced by ifosfamide (IF) was tested in a group of 45 patients with inoperable lung cancer under treatment with IF (2250 mg/m² on days 2–5) as part of a polychemotherapy regimen repeated in a 4-week cycle. MESNA was given orally on the days of treatment with IF in 3 doses of 840 mg/m², each administered at 0 hr (= injection of IF), 4 hr and 8 hr p.i. Out of a total of 88 courses of this treatment we observed 10 episodes of asymptomatic microscopic haematuria and no episodes of gross haematuria. In this group of 45 patients under protection with MESNA there were 5 complete remissions and 9 partial remissions (total 31%). A further group of 25 patients under polychemotherapy with IF were treated by conventional prophylactic measures (raised fluid intake and forced diuresis). In this group there were 1 complete and 5 partial remissions (total 24%), but nearly all patients developed either gross haematuria and/or symptoms of bladder irritation (cystitis and pollakisuria). There were no appreciable differences between the MESNA series and the conventional prophylaxis series with respect to either haematological or systemic toxicity of the cytostatic treatment. Our results support the view that MESNA, given orally in conjunction with combined cytostatic regimens which include IF, simplifies the treatment and provides optimum protection for the urinary epithelium. Protection with oral MESNA is particularly suitable for outpatients.*

INTRODUCTION

IFOSFAMIDE (IF, Holoxan®, Asta-Werke Bielefeld, Federal Republic of Germany) is an analogue of cyclophosphamide. It belongs to the *N*-2-chloroethyl-amino-oxazaphosphorines and it has a wide range of antitumoral activity both in animal experiments and clinically. Both drugs are activated in the liver to antitumorally effective metabolites [1]. A further metabolite is acrolein, which has no antitumoral activity but which is highly irritating to the urinary epithelium and causes severe and dose-limiting dysuria, pollakisuria and haematuria [2, 3]. IF causes less myelosuppression than cyclophosphamide, but its urotoxic side effects are more severe. Various measures such as alkalization of the urine, raised fluid intake and forced diuresis, and irrigation of the bladder with isotonic saline or with solutions of sulphhydryl-containing compounds, collectively referred to as 'standard prophylaxis', have been used in the past in an attempt to reduce the incidence and the severity of these side effects, but have been only partially successful.

Sodium 2-mercaptoethane sulphonate (MESNA, Uromitexan®, Asta-Werke Bielefeld), administered intravenously, forms non-toxic addition compounds with the reactive IF metabolites in the urine of patients under therapy with IF, and allows regional detoxification in the kidneys and the urinary tract, and thus clinical prevention of the urotoxic side effects of the above cytostatics [4–7]. Experiments on animals suggested that the

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toxicity of MESNA is extremely low. The LD_{50} in the mouse and the rat ranges from 1.2 to 2 g/kg with i.v. administration, whilst the doses required to successfully prevent experimental bladder lesions induced by oxazaphosphorines are of the order of 1% of the LD_{50} [8]. In a first study we were able to confirm that MESNA does reliably prevent the urotoxicity of IF and that there is no difference in this respect between the intravenous and the oral modes of administration of MESNA [9]. Based on these findings we started a new trial to study the efficacy of orally administered MESNA in preventing IF-induced urothelial toxicity of combined cytostatic regimens which include IF.

MATERIALS AND METHODS

Patients

Seventy evaluable male patients who had histologically confirmed non-resectable lung cancer, a Karnofsky score ≥ 50 and a life expectancy of more than 8 weeks from starting therapy were entered in this study. The clinical characteristics of these 70 patients, assessed at the time of first presentation, are shown in Table 1. The patients were assigned to two different polychemotherapy groups (I and II) depending on the histological type of the cancer, each including IF, for squamous cell and non-squamous cell lung cancer. In group I, 37 patients with squamous cell carcinoma were treated with adriamycin (ADM) 40 mg/m^2 i.v. given on day 1 followed by four times IF 2250 mg/m^2 i.v. given on days 2–5 (Table 2).

Table 1. Clinical data on the patients

	Group A	Group B
No. of patients	25	45
Histological type of the tumour:		
Sq	12	25
Ad	8	13
Sc	4	5
Lc	1	2
Age:		
mean	58.7	55.5
range	(38–72)	(40–70)
Extended disease	19	33
Limited disease	6	12
Performance status (range)	50–80	50–90

Group A: conventional prophylaxtic measures; group B: MESNA per os. Histological type of the tumour: Sq: sqamous cell carcinoma; Ad: adenocarcinoma; Sc: small-cell carcinoma; Lc: large-cell carcioma.

In group II, 33 patients with non-squamous cell carcinoma (adenocarcinoma 21, small-cell carcinoma 9, large-cell carcinoma 3) were treated with dicarbazine (DTIC) 800 mg/m^2 i.v. given on day 1, methotrexate (MTX) 30 mg/m^2 i.v. given on day 2, and IF 2250 mg/m^2 daily i.v. given on days 2–5 (Table 3).

The patients in the groups I and II were assigned to the two types of prophylaxis at random. Standard prophylaxis (raised fluid intake and forced diuresis) was given to 25 patients (12 of group I and 13 of group II), whilst prophylaxis with MESNA was given to 45 patients (25 of group I and 20 of group II). This proportion of about 1:2 between the sizes of both groups was chosen for ethical reasons in view of previously reported effectiveness of MESNA [9]. All the patients were hydrated during the treatment with IF on days 2–5 of each treatment cycle. IF was administered by i.v. infusion in 500 ml isotonic saline over 3 hr. A first oral dose of 840 mg/m^2 MESNA was administered at the start of the IF infusion. A second and then a third dose, each of 840 mg/m^2, were given 4 hr and 8 hr later. The unpleasant taste of the MESNA solution was masked by giving it in a cola-type drink [7].

All the patients admitted to the study were scheduled to receive at least 2 courses of chemotherapy. Thereafter, chemotherapy was continued if the patients showed stable disease or evidence of tumour regression. All chemotherapy was stopped if tumour progression was observed or when a cumulative limit dose of 550 mg/m^2 ADM was reached.

Excluded from the study were patients with WBC counts $<4000/\mu$l, platelet counts $<$ 150,000/μl, a serum creatinine level $>$ 1.5 mg/100 ml, a BUN level >35 mg/100 ml and/or hepatic failure characterized by a bilirubin level >2.0 mg/100 ml. No chemotherapy or radiation therapy were given during the 8 weeks preceding the start of the study, and all toxic side effects of previous treatments had subsided.

The treatment courses were repeated at 4-week intervals, with dose modifications based on the nadir WBC and platelet counts. If the nadir WBC count remained above 2000/μl and the nadir platelet count remained above 50,000/μl, the dose was kept constant. Below these limits the resumption of chemotherapy was postponed by one week. WBC toxicity was defined as moderate (2000–2999/μl), severe (1000–1999/μl) and life-threatening ($<$ 1000/μl). Platelet toxicity was defined as moderate (50,000–99,999/μl), severe (25,000–49,999/μl) and life-threatening ($<25,000/\mu$l).

Table 2. Therapeutic regimen for squamous cell carcinomas

Drugs (mg/m^2)	Administration on days: 1	2	3	4	5	28	29
ADM (40)	×					×	
IF (2250)		×	×	×	×		×
MESNA (3 × 840)		×	×	×	×		×

Each infusion of IF (500 ml) was followed by infusion of isotonic saline 1500 ml/m^2. Each infusion of IF was started at 0800 hours. MESNA 840 mg/m^2 p.o. was administered at 0800, 1200 and 1600 hours.

Table 3. Therapeutic regimen for non-squamous cell carcinomas

Drugs (mg/m^2)	Administration on days: 1	2	3	4	5	28	29
DTIC (800)	×					×	
MTX (30)		×					×
IF (2250)		×	×	×	×	×	
MESNA (3 × 840)		×	×	×	×		×

Each infusion of IF (500 ml) was followed by infusion of isotonic saline 1500 ml/m^2. Each infusion of IF was started at 0800 hours. MESNA 840 mg/m^2 p.o. was administered at 0800, 1200 and 1600 hours.

The results of the therapy were evaluated by serial chest radiography, physical examinations and hepatic and renal functions tests. The radiographic findings were rated as follows: complete remission (CR) was defined as the complete disappearance of all measurable tumour masses (and of the relevant symptoms). Partial remission (PR) was defined as a $>50\%$ reduction in the radiographic area (product of the two largest diameters at right angles to each other of all the measurable lessions for at least 4 weeks. Improvement (IMP) was defined as 25–50% reduction in the radiographic area of all the measurable lesions. Stable disease (SD) was defined as a $<25\%$ change in the area of all the measurable lesions. Progressive disease (PD) was defined as a $>25\%$ increase in the area of any one measurable lesion or the appearance of a new lesion.

The duration of remission was calculated from the time of first improvement to the time of the first relapse. Survival times were calculated from the start of treatment. During treatment with IF, the urine sediment was examined for erythrocytes and casts on days 2, 4 and 5. Haemoglobin, WBC and platelet counts, and the serum creatinine levels were checked on days 1 and 12 of the treatment-free interval.

Statistical analyses were carried out using the chi square test with partition of degrees of freedom, the chi square test with Yates' correction and Fisher's two-tailed exact probability test for 2×2 tables.

RESULTS

There were no cases of drug-related death.

Toxicity

This was evaluated according to Miller *et al.* [10], as shown in Table 4. The haematological toxicity is summarized in Table 5. Severe bone-marrow toxicity (WBC $< 1000/\mu l$) was recorded in only one case. It occurred in the group under standard prophylaxis. Anaemia was generally severe, with 35% of the patients developing haemoglobin levels of less than 9.5 g/100 ml and requiring blood transfusions.

Urological symptoms

The incidence of urological symptoms in the patients treated with IF is shown in Table 6, separately for the two prophylaxis groups. Evidence of haemorrhagic cystitis, when it did develop, was generally observed on days 3–5. In such cases, further treatment with IF was postponed until all evidence of cystitis subsided completely. The differences between the two prophylaxis groups (with and without MESNA)

Table 4. Grading of toxicity

	0	1	2	3	4
Haematological					
Haemoglobin (g/100 ml)	≥ 11.0	9.5–10.9	8.0–9.4	6.5–7.9	< 6.5
Leucocytes (1000/μl)	≥ 4.0	3.0–3.9	2.0–2.9	1.0–1.9	< 1.0
Platelets (1000/μl)	≥ 100	75–99	50–74	25–49	< 25
Gastrointestinal					
Nausea/vomiting	none	nausea	transient vomiting	vomiting, requiring therapy	intractable vomiting
Diarrhoea	none	transient, 2 days	tolerable, 2 days	intolerable, requiring therapy	haemorrhagic with dehydration
Renal					
Creatinine	≤ 1.25 × N*	1.26–2.5 × N	2.6–5 × N	5–10 × N	> 10 × N
Haematuria	none	microscopic	gross	gross + clots	obstructive uropathy
Hair	none	minimal hair loss	moderate patchy alopecia	complete alopecia but reversible	irreversible alopecia
Neurotoxicity					
State of consciousness	alert	transient lethargy	somnolence < 50% of waking hours	somnolence > 50% of waking hours	coma

*N = upper limit of normal range [10].

Table 5. Haematological toxicity

	Group A	Group B	χ^2	p
Courses (patients)	18(9)	27(14)		
Haemoglobin (g/100 ml)				
> 11	4(2)	8(4)		
9.5–10.9	4(2)	6(3)	0.204	N.S.
< 9.5 (requiring transfusion)	10(5)	12(7)		
Leucopenia				
2000–3600	3(2)	1(1)		
1999–1000	2(1)	3(2)		
< 1000	1(1)			
Thrombocytopenia				
50000–74000	1(1)	1(1)		

Group A: conventional prophylactic measures; Group B: MESNA per os. N.S.: no significance. WBC and haemoglobin level nadirs on day 10.

in the incidence of cystitis, casts and haematuria were statistically highly significant. The serum creatinine levels ranged between 0.80 and 1.68 mg/100 ml.

Other toxic symptoms (Table 7)

The incidence and severity of nausea, vomiting, anorexia and alopecia was about the same in both prophylaxis groups. This also applies to CNS symptoms in three patients induced by the IF therapy appearing on days 2–3 of treatment. A side effect observed only in the patients under prophylaxis with MESNA was a moderate diarrhoea.

Response

The response rates with the two regimens are shown in Table 8. The overall response rate (CR + PR) was 28.5%. Complete remission (CR) was observed in 11% of the patients in the

Table 6. Urological symptoms and haematuria in patients treated with IF 2250 mg/m² with and without MESNA

	Group A	Group B	χ^2	*P*
Patients	25	45		
Courses	50	88		
Cystitis	38	4	73.6*	$< 10^{-17}$
Casts	8	0	12.16*	< 0.0004
Haematuria:				
no haematuria	14	78		
microscopic	10	10		
gross	26	0	52.8†	$< 10^{-12}$
Ratio yes/no	36/14	10/78	12.1†	< 0.0005

Group A: conventional prophylactic measures; Group B: MESNA per os.
*χ^2 for 2 × 2 tables with Yate's correction.
†χ^2 for 2 × 3 tables with partition of degrees of freedom.

Table 7. Other toxic effects

	Group A	Group B	Difference A vs B χ^2	*P*
Patients	25	45		
Courses	50	88		
Nausea and vomiting*	46	52	15.2	< 0.0001
Diarrhoea*	0	6		< 0.02
Fever*	2	1		
Hallucinations*	1	3		1.00
Alopecia†	12	30	1.62	< 0.25

Group A: conventional prophylactic measures; Group B: MESNA per os. The data on alopecia relate to the number of patients. All the other data relate to the number of treatment courses.
*Number of courses.
†Number of patients.

Table 8. Response rates depending on the histological type of tumor

Response	Group A					Group B				
	ADM + IF	DTIC + IF + MTX			Total	ADM + IF	DTIC + IF + MTX			Total
	Sq	Ad	Sc	Lc	*n*	Sq	Ad	Sc	Lc	*n*
CR	1	0	0	0	1	2	1	2	0	5
PR	3	1	1	0	5	5	2	2	0	9
CR + PR	4	1	1	0	6	7	3	4	0	14
No response	8	7	3	1	19	18	10	1	2	31
Total	12	8	4	1	25	25	13	5	2	45

Group A: conventional prophylactic measures; Group B: MESNA per os. Group A vs Group B: $\chi^2 = 0.126$: N.S. Sq: Squamous cell carcinoma; Ad: adenocarcinoma; Sc: small-cell carcinoma; Lc: large-cell carcinoma.

MESNA group and in 4% of the patients in the conventional prophylaxis group. Partial remission (PR) was observed in 20% of the patients in both groups. The overall differences are not significant.

Survival

The median survival time under both regimens was 6 months (Table 9). The survival time of responders was longer than that of non-responders in all the groups, but the difference in the median survival time between responders and non-responders was significant only for adenocarcinoma (10 months vs 5 months).

DISCUSSION

MESNA has been proved to be a reliable prophylactic agent against the urotoxicity of oxazaphosphorines. In a controlled study, Scheef *et al.* [11] showed the superiority of MESNA over standard prophylaxis. The efficacy of MESNA has been confirmed in a field study on 242 patients [12] and in a single blind cross-over trial [13]. Scheulen *et al.* [14] observed the same response rate in 27 patients with testicular tumours treated with IF + standard prophylaxis as in 33 patients with testicular tumours treated with IF + MESNA.

Pharmacodynamic studies have shown that MESNA does not interfere either with the metabolism of IF or with the chemotherapeutic action of its metabolites [13]. When MESNA is administered intravenously, high sulphhydryl levels are rapidly achieved in the urine, and the urotoxic metabolites of IF are rapidly detoxified. The total dosage of MESNA, administered intravenously, required to ensure reliable protection against urotoxic side effects amounts to about 3 × 20% of the daily dose of IF, given in 3 separate doses. For oral administration of MESNA we suggest about 3 × 40% of the daily dose of IF. With i.v. administration of MESNA the first dose should be given at the same time as IF, the second dose at 4 hr p.i. and the third dose at 8 hr p.i. [1]. We adopted the same time schedule with oral administration.

MESNA is physiologically inert and its permeation into the tissues is minimal. It is rapidly and completely eliminated via the kidneys. Its half-life of elimination after i.v. administration is about 1.5 hr. The major metabolite found in the blood after oral and after intravenous administration is MESNA disulphide. About 50% of the administered dose appears in the urine as free MESNA [8].

Extensive studies have been carried out to determine whether MESNA interacts with oxazaphosphorine derivatives and other cytostatic agents, and with other drugs. MESNA does not lower the acute or the subacute toxicity of oxazaphosphorines and it does not attenuate their haematological or immunosuppressive effects. We have evaluated the actual doses of IF administered to the patients in our study. We found that there were no significant differences on the amounts of drugs administered in the two groups of patients. The total dose of IF was 9000 mg/m^2, administered over 4 days. In all cases, we gave 2250 mg/m^2/day on 4 consecutive days. Single daily doses of IF ranged between 3000 and 4500 mg per patient. The mean single doses per patient were 3.77 ± 0.05 g in the standard prophylaxis group and 3.78 ± 0.04 g in the MESNA group, with a median of 4 g/patient in both groups.

We observed no appreciable differences in the haematological or the systemic toxicity of IF between the conventional prophylaxis group and the MESNA group.

The use of MESNA in conjunction with

Table 9. Survival times in months

	Histotype			
	Squamous cell (ADM + IF)	Non-squamous cell (DTIC + IF + MTX)		
		Ad	Sc	Lc
Patients	37	21	9	3
Median	6	6	6	5
Range	2–17	3–20	4–17	4–5
Responders median	7	10	6	—
Non-responders median	5	5	5	5

Ad: Adenocarcinoma; Sc: small-cell carcinoma; Lc: large-cell carcinoma.

combined cytostatic regimens which include IF simplifies the treatment and ensures optimal protection of the urinary epithelium. This, then, would suggest including new therapeutic regimens increasing the IF doses, according to the improvement of toxicity, for treatment of resistant neoplastic disease.

As the pharmacokinetics of MESNA after oral administration are not yet fully known, there might be scope for further optimization of the time and dosage schedule of oral MESNA administration.

Conclusions

In cytostatic polychemotherapy regimens which include IF, uroprophylaxis with MESNA eliminates the need for alkalization of the urine and for other conventional prophylactic measures, and is associated with significantly lower urotoxicity rates. This opens possibilities for developing new therapeutic regimens with higher doses of IF. Administration of MESNA by the oral route is simpler than the conventional prophylactic measures and is indicated particularly for outpatients.

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