Amifostine before Chemotherapy: Improved Tolerance Profile of the Subcutaneous Over the Intravenous Route

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ABSTRACT

Introduction: **The i.v. administration of the cytoprotective agent amifostine is associated with reversible clinical hypotention, protracted emesis, and malaise in a various percentage of patients. We evaluated, prospectively, whether the s.c. route is a better tolerated alternative to the i.v. route in patients receiving chemotherapy.**

Patients and Methods: **Fifty-nine patients treated with "once every 2 weeks" regimens received 1000 mg of amifostine i.v. before chemotherapy. Patients who developed protracted vomiting and malaise and/or clinical hypotension for two consecutive i.v. administrations received the same dose of amifostine s.c. for the subsequent cycles (i.v./s.c. study). In an additional cohort of 12 patients (s.c. study), 1000 mg of amifostine were given s.c. since the first chemotherapy cycle.**

Results: **In the i.v./s.c. study, 8 (13.5%) patients showed protracted emesis/malaise and/or clinical hypotension during the first two cycles. An additional 4 (6.6%) patients developed similar side effects during the subsequent cycles. Switching to the s.c. route, an improved tolerance was noted. In the s.c. study, a total of 76 injections was administered. Protracted vomiting or clinical hypotension was absent, and this tolerance profile was significantly better than the i.v. one ($P = 0.001$). There were no other systemic side effects related to the s.c. administration.**

Conclusions: **Amifostine, at a dose of 1000 mg, is better tolerated when administered s.c. Switching to the s.c. route in patients with poor tolerance using the i.v. administration allows the continuation of cytoprotection with minor side effects. Although preliminary, 1000 mg of amifostine effectively protected against the lower, still more frequently administered doses of chemotherapy given once every 2 weeks.**

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INTRODUCTION

Amifostine (Ethyol) is a selective broad spectrum cytoprotector of normal tissues. The United States Food and Drug Administration has approved the use of amifostine as a cytoprotector for radiation-induced xerostomia and platinum-based chemotherapy after randomized studies that confirmed the efficacy and cost benefit effectiveness (1, 2). The recommended dose of amifostine before chemotherapy is 740–900 mg/m^2 given by the i.v. route, whereas a lower dose of 200–350 mg/m^2 before each radiotherapy fraction is recommended for radioprotection.

Amifostine fulfills two main prerequisites for cytoprotective agents to be of value in clinical oncology: (*a*) it does not interfere with the cytotoxic efficacy of radiotherapy and drugs; and (*b*) it is deprived of severe side effects (reviewed in Ref. 3). The i.v. administration of amifostine, however, is associated with reversible clinical hypotension and protracted nausea vomiting in a various percentage of patients. It is, therefore, strongly recommended that the amifostine is administered i.v. with patients in a supine position, under continuous monitoring of blood pressure for ≥15 min and, overall, with an excess alert of the medical staff and nurses. The increased workload and discomfort of patients receiving amifostine discourage the broad use of the drug, and, especially in busy departments, only a fraction of patients receives cytoprotection.

In an attempt to reduce the workload from i.v. amifostine administration in radiotherapy departments, we evaluated the s.c. route (4). Indeed, the administration of 500 mg of amifostine s.c. before radiotherapy was never linked with hypotension, and the incidence of protracted vomiting was reduced, whereas the cytoptrotective efficacy was maintained. An increased incidence of fever rash symptomatology, however, was noted. These results were confirmed in a recent study by Anne *et al.* (5). In the present prospective study, we evaluated whether the s.c. route may be a better tolerated alternative to the i.v. in patients receiving chemotherapy on a "once every 2-week" basis.

PATIENTS AND METHODS

Study Design. From October 2001 to September 2002, 59 patients with various malignancies treated with different chemotherapeutic regimens delivered once every 2 weeks entered a prospective study to evaluate the incidence of protracted vomiting and clinical hypotension after the administration of 1000 mg of amifostine (flat dose) i.v. before chemotherapy and examine how the tolerance profile changes by switching to the s.c. route in the same patients (i.v./s.c. study).

All patients had a good performance status (WHO 0/1) and no history of severe cardiovascular, lung, renal, or hepatic disease. All patients were hematologically fit to receive full dose chemotherapy (neutrophils > 2,500/μl and platelets > 150,000/μl). Pregnant women or patients with neurological/psychiatric disease or hematological malignancies were excluded. Patients with history of cardiac infarction that occurred ≥6 months

Table 1 Patient's characteristics[a]

	i.v./s.c.	s.c.
No pts	59	12
Age		
(median, range)	62, 34–76	64, 37–78
Sex		
(M/F)	41/31	6/6
PS		
0/1	59	12

[a] IV/SC study, initial i.v. administration followed by switch to s.c. in case of poor tolerance; SC study, SC administration since the first amifostine injection.

before recruitment were eligible. Patients with hypertension controlled with medication were also eligible for inclusion in the protocol. No modification of the antihypertensive regimen was performed. Patients with serum creatinine or liver enzyme serum levels $>$ 1.5 and 2.5 of the normal values, respectively, were excluded.

Patients who would develop protracted vomiting or clinical hypotension for two consecutive i.v. amifostine administrations were scheduled to receive the same dose of amifostine s.c. for the subsequent cycles of chemotherapy, if better tolerated.

In an additional cohort of 12 patients (s.c. study; recruitment criteria as reported above), 1000 mg of amifostine were given s.c. starting with the first cycle of chemotherapy to obtain further data on the safety/tolerance profile of the schedule.

Table 1 shows the patients' characteristics. Table 2 describes the disease and chemotherapeutic regimens used. The study was approved by the Institutional Oncology Board.

Administration of Amifostine. Patients were instructed to consume high amounts of liquids the days before and during the morning of chemotherapy. As a prechemotherapy medication, patients received i.v. 3 mg of granisetron (Kytril), 16 mg of dexamethasone (Decadron), or 250 mg of methylprednisolone (Solu-Medrol) and 50 mg of ranitidine (Zantac). Subsequently, 1000 mg of amifostine (Ethyol), diluted in 50 ml of normal saline, were given as a 5-min infusion, the patient being in a supine position and under a continuous monitoring of the blood pressure.

For the s.c. administration, the same prechemotherapy procedure was maintained. Two vials of 500 mg were dissolved in 2.5 ml of normal saline each, and the drug was injected s.c. into the right and left shoulders (total dose of 1000 mg), respectively.

Chemotherapy administration began 20 min after the amifostine injection (whether i.v. or s.c.) to allow assessment of amifostine-related side effects without biases from chemotherapy-related reactions.

Scoring of Side Effects. The scoring of nausea vomiting was performed according to a three grade system: (*a*) nausea but no vomiting; (*b*) transient nausea and vomiting lasting for $<$15 min; and (*c*) protracted nausea and vomiting with intense feeling of malaise that lasted for $>$15 min. Vomiting grade 3 that persisted for $>$1 h after amifostine infusion and during/after chemotherapy infusion was characterized as "protracted grade 3 emesis."

Hypotension was graded as: (*a*) no hypotension or transient drop without clinical signs; and (*b*) clinical hypotension that required interruption of infusion or medical care (rapid infusion of normal saline and hemodynamic manipulations). Scoring of skin reactions, local pain, and other toxicities was based on the WHO toxicity evaluation scale (6).

Treatment and Results Evaluation. Baseline studies included physical examination, chest X-rays, blood counts with differential and platelet counts, complete biochemical profile, and electrocardiogram. Chest or upper/lower abdomen computerized tomography scans (computed tomography scan) were performed according to the tumor location. Complete blood cell count, serum urea and creatinine, and liver enzymes were assessed once every 2 weeks during the chemotherapy period and for 4 weeks thereafter.

Response to treatment was assessed with computed tomography scan of the chest or abdomen/pelvis lesion, as appropriate, after the completion of four and eight cycles of chemotherapy, at 2 months after treatment completion and 3 monthly thereafter. Complete response was defined as 95–100% reduction of the measurable lesions. Partial and minimal response refers to 50–95% and 25–49% reduction of tumor dimensions, respectively. Small reduction of tumor dimensions between 0 and 24% that lasted $\geq$2 months after response documentation was considered as stable disease. All other cases were considered as PgD.[2] Any response that lasted $<$2 months was considered as PgD.

Statistical Analysis. Statistical analysis was performed using the GraphPad Prism 2.01 package (GraphPad, San Diego, CA).[3] Fisher's exact test was used for testing relationships between categorical variables. A $P \leq 0.05$ was considered significant.

RESULTS

Systemic Side Effects from i.v. Administration. Of 59 patients treated, 8 (13.5%) showed grade 3 emesis and/or grade 2 hypotension (7 patients, emesis and 5 patients, hypotension) during the first two cycles. An additional 3 (5%) patients developed grade 3 emesis and 1 (1.6%) grade 2 hypotension during the subsequent cycles (Fig. 1). All patients with grade 3 emesis presented with malaise and vomiting that lasted from 20 up to 60 min, starting at 5–20 min after injection of amifostine. Hypotension was rapidly resolved in all cases. Chemotherapy infusion was delayed by 30–60 min in all patients who developed severe vomiting and/or hypotension. No other side effects were observed. Emesis or hypotension was independent of the patients' age, sex, and weight (data not shown).

In 3 of 10 patients (2 receiving irinotecan and 1 platinum-based regimen) with grade 3 emesis, vomiting started before the beginning of chemotherapy infusion and was protracted, although to a lesser intensity, to 8–12 h thereafter. In these cases, it was unclear whether amifostine or chemotherapy was the principal cause of this protracted grade 3 emesis. Table 3 shows the distribution of severe emesis/hypotension side effects according to the chemotherapy regimen.

Systemic Side Effects from the s.c. Administration. For 12 patients who presented with grade 3 emesis and/or grade 2 hypotension, the i.v. amifostine administration was switched

[2] The abbreviations used are: PgD, progressive disease; G-CSF, granulocyte colony-stimulating factor.
[3] Internet address: http://www.graphpad.com.

Table 2 Disease characteristics of patients treated in the i.v./s.c. and s.c. studies

Disease	No pts		Chemotherapy	
	i.v./s.c.	s.c.	Drugs/Dose	Schedule
NSCLC			Taxotere 40 mg/m^2 (day 1)	
Stage IIIb	5	3	Gemzar 1000 mg/m^2 (day 1)	Every 2 weeks
Stage IV	4	2	Caelyx 25 mg/m^2 (day 1)	
			G-CSF 300 μg (days 6, 7, and 8)	
SCLC				
Limited stage	1	0	Taxotere 40 mg/m^2 (day 1)	Every 2 weeks
Extensive stage	4	0	Carboplatin AUC4 (day 1)	
			G-CSF 300 μg (days 3, 4, and 5)	
Colorectal Ca				
Dukes' Stage C	7	1	5FU 600 mg/m^2 (days 1 and 2)	Every 2 weeks
Dukes' Stage D	9	2	Campto 180 mg/m^2 (day 1)	
			G-CSF 300 μg (days 4, 5, and 6)	
Gastric Ca				
Stage III	7	1	Taxotere 40 mg/m^2 (day 1)	Every 2 weeks
Stage IV	4	1	Cisplatin 40 mg/m^2 (day 1)	
			5FU 600 mg/m^2 (days 1 and 2)	
			G-CSF 300 μg (days 4, 5, and 6)	
Breast Ca				
Stage II/III	9	0	Taxotere 50 mg/m^2 (day 1)	Every 2 weeks
Stage IV	4	1	Caelyx 25 mg/m^2 (day 1)	
			+/− Herceptin 4 mg/kg	
			G-CSF 300 μg (days 6, 7, and 8)	
Ovarian Ca				
Stage III	5	1	Taxotere 50 mg/m^2 (day 1)	Every 2 weeks
			Caelyx 25 mg/m^2 (day 1)	
			G-CSF 300 μg (days 6, 7, and 8)	

[a] NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

to the s.c. route. An improved tolerance was noted, because none of the patients developed clinical hypotension or protracted vomiting (Fig. 1). In all 3 patients with grade 3 emesis who had protracted vomiting during/after chemotherapy infusion, the tolerance profile was clearly improved by replacing the i.v. with the s.c. route of administration. In 2 patients, no protracted emesis or malaise $>$ 2 h was reported, and in 1 patient, malaise and nausea persisted without vomiting.

In a cohort of 12 patients treated with amifostine since the beginning of therapy, a total of 76 s.c. injections was administered. None of these administrations was linked with grade 3 vomiting or grade 2 hypotension. In 4 of 12 patients, grade 2 vomiting was noted. This tolerance profile was significantly better than the one recorded in patients receiving amifostine through the i.v. route (Table 4).

In a total of 24 patients treated with s.c. administered amifostine, there were no other systemic side effects recorded.

Local Side Effects from the s.c. Administration. Regarding the local effects of the s.c. injection, mild local pain grade 1 was reported in 5 of 24 patients (lasting for some minutes), and local erythema grade 1 was noted in 4 of 24 patients. This local skin reaction resolved within 1–3 days without any local steroid or antihistamine therapy.

Chemotherapy Toxicities. All of the chemotherapy schedules used for the treatment of the patients were "nonconventional" (one every 2 weeks), and we continue to recruit patients in these Phase II studies. The treatment protocols comprised low dose G-CSF administration (300 μg) for three consecutive days after chemotherapy as shown in Table 2. Briefly, of 590 (i.v./s.c. study) and 76 (s.c. study) cycles of chemotherapy administered, 4 (0.6%) were linked with grade 3 or 4 neutropenia, 3 of which with neutropenic sepsis. In all these patients, normal white cell count was restored within 2–4 days after administration of G-CSF, and fever regressed within 3–5 days with i.v. antibiotics. Of 19 patients treated with the combination of irinotecan and 5-fluorouracil (high intestinal toxicity expected), none developed more than grade I diarrhea. None of the patients treated with docetaxel or platinum showed any signs of drug-related neurotoxicity (clinical assessment) or nephrotoxicity (stable creatinine clearance). None of the patients receiving liposomal doxorubicin developed more than grade 2 palmar-plantar erythrodysesthesia or more than grade 2 p.o. mucositis.

Response to Chemotherapy. In Table 5, the responses observed in patients with measurable lesions 4 months after the beginning of chemotherapy are shown.

DISCUSSION

Amifostine is a wide spectrum cytoprotective agent with proved efficacy against radiation xerostomia and platinum-related hematological, renal, and neurological toxicity (1, 2). Continuously accumulating data have already provided evidence that amifostine protects against radiotherapy and chemotherapy-induced mucositis (4, 7–9), radiation pneumonitis (10, 11), and taxane-related hematological and neurological toxicity (12).

The significant benefit obtained with the i.v. administration of amifostine is, however, accompanied by the quite common undesirable side effects of emesis and hypotension. These side effects, although never severe, produce lots of discomfort to the

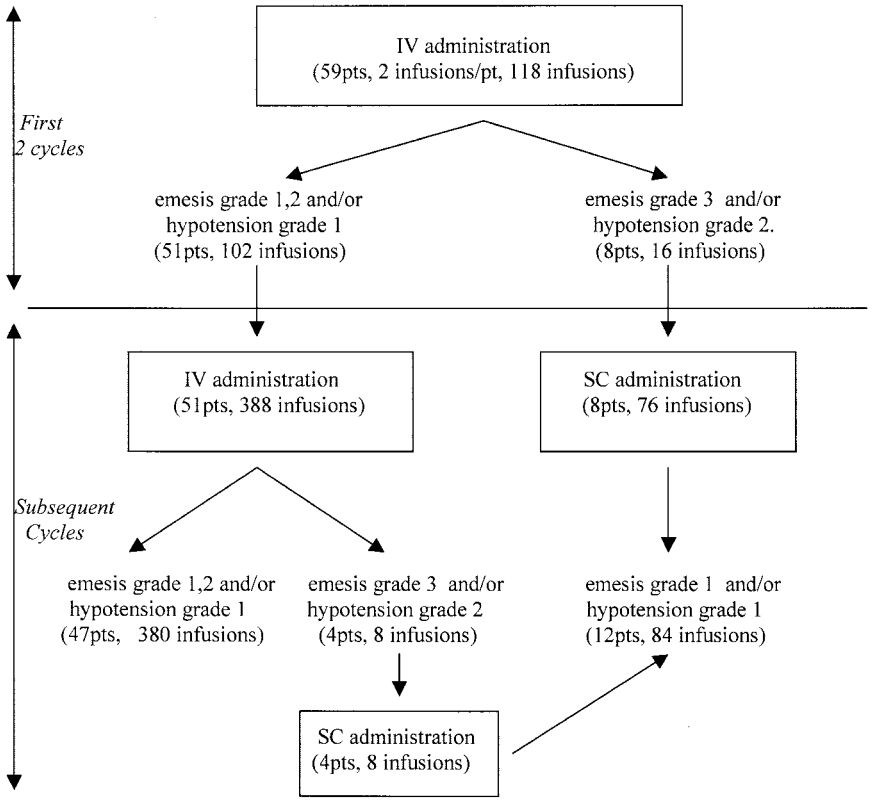

Fig. 1 Diagrammatic representation of the i.v./s.c. study and side effects noted after i.v. and subsequent s.c. administration of 1000 mg of amifostine.

Table 3 Distribution of severe vomiting and hypotension in different chemotherapy regimens

i.v. administration (i.v./s.c. study)	Regimen[a]			
	A	B	C	D
Vomiting grade 3	4	4	1	1
Protracted vomiting grade 3	0	2	0	1
Hypotension grade 2	3	2	1	0

[a] A, Docetaxel/Gemcitabin/Liposomal Doxorubicin; B, Irinotecan/5FU/Leucovorin; C, Docetaxel/Liposomal Doxorubicin +− Herceptin; D, Docetaxel/Cisplatin/5FU.

patients and are disruptive to the nurses and medical staff in chemotherapy or radiotherapy units. Elimination of these side effects would lift reservations raised by physicians and nurses and contribute to the wider use of the drug for the benefit of patients.

The first study reporting on the s.c. use of amifostine in patients with myelodysplastic syndrome showed good tolerance, and the plasma levels of the drugs achieved were estimated to 70% of the ones obtained with i.v. administration of the same dose (13). As amifostine is rapidly hydrolyzed to WR1065 and distributed intracellularly within 5 min after i.v. injection (14), assessment of the plasma levels of the drug and metabolites is not the best way to compare the i.v. with the s.c. route. Comparative studies on the intracellular concentration of the active forms of amifostine (WR1065 and WR33278) are required. Indeed, in a recent study by Cassat *et al.* (15), tissue levels of WR1065 were strongly related to radioprotection, whereas plasma levels were not.

In a study presented at the 2001 annual meeting of the American Society of Clinical Oncology, the concentration of WR-1065 in the salivary glands of rats was similar whether the drug (200 mg/kg) was given i.v. or s.c. (16). Furthermore, it was shown that s.c. administration of amifostine protected against radiation-induced mucositis for $\leq$8 h after administration, whereas the duration of cytoprotection conferred by the i.v. route was $<$4 h (16). In a subsequent study from the same group, the s.c. route provided overlapping tissue pharmacokinetics with the i.v. administration (15). Bonner *et al.* recently showed in a Phase I study that the protein bound form of WR1065 plays an important role in the bioavailability of amifostine and that the s.c. route of administration is convenient to obtain a reasonable area under the concentration time curve of the protein bounded drug, which is associated with a better tolerance (17).

Indeed, in a large randomized Phase II study, we confirmed that the s.c. route of amifostine administration has a different toxicity profile than the i.v., which renders the s.c. use convenient for busy radiotherapy departments (4). As hypotension never occurs, 500 mg of amifostine flat dose could be given in a sitting position without the need of blood pressure monitoring, and the patients could go directly to the radiotherapy unit without unpredictable delays that can jeopardize the treatment program of the department. We estimated that the average time required for the i.v. administration and monitoring of the patient was 20 *versus* 1 min for the s.c. Nausea and emesis were far less frequent than the observed from the i.v. route, the only side effects being the cumulative asthenia and a "fever rash" symp-

Table 4 Tolerance of 1000 mg of amifostine delivered through the i.v. *vs.* s.c. route (i.v./s.c. study, initial i.v. administration followed by switch to s.c. in case of poor tolerance; s.c. study, s.c. administration since the first amifostine injection)

	Emesis[a] (Grade)				Hypotension[b] (Grade)			Emesis/hypotension		
	1	2	3	*P*	1	2	*P*	1-2/1	3/2	*P*
No pts										
i.v./s.c. study (i.v. administrations)										
(59)[c]	38	14	7	0.40	54	5	0.29	51	8	0.33[e]
(59)[d]	38	11	10	0.21	53	6	0.24	47	12	0.19[e]
i.v./s.c. study (s.c. administration)										
(12)[d]	6	6	0		12	0		12	0	
s.c. study										
(12)	8	4	0		12	0		12	0	
No cycles										
i.v./s.c. study (i.v. administrations)										
(118)[c]	76	28	14		108	10		104	14	
i.v./s.c. study (SC administration)										
(84)[d]	58	26	0		84	0		84	0	
s.c. study										
(24)[c]	16	8	0	0.16	24	0	0.13	24	0	0.12[f]
(76)[d]	58	18	0	0.006	76	0	0.009	76	0	0.001[f]

[a] Emesis Grading System: 1, nausea but no vomiting; 2, transient nausea and vomiting lasting for <15 min, and 3, protracted nausea and vomiting with intense feeling of malaise that lasted for >15 min.
[b] Hypotension Grading System: 1, no hypotension or transient drop without clinical signs and 2, clinical hypotension that required interruption of infusion or medical care (rapid infusion of normal saline and hemodynamic manipulations).
[c] First two administrations.
[d] All administrations.
[e] Compared with the s.c. study.
[f] Compared with the i.v. administration of the i.v./s.c. study.

Table 5 Response to chemotherapy supported with amifostine (i.v. and s.c.)

			Response (%)[a]			
Disease	No pts	Stage	CR	PR	MR/SD	PgD
NSCLC[b]	14	IIIb/IV	1 (7)	7 (50)	2 (14)	4 (29)
SCLC[c]	5	All	0 (0)	3 (60)	1 (20)	1 (20)
Colorectal	11	D	2 (19)	3 (27)	3 (27)	3 (27)
Gastric	9	III/IV	2 (22)	3 (34)	2 (22)	2 (22)
Breast	5	III/IV	0 (0)	3 (60)	2 (40)	0 (0)
Ovarian	4	III	0 (0)	2 (50)	1 (25)	1 (25)

[a] CR, complete response, PR, partial response, MR/SD, minimal response or stable disease.
[b] NSCLC, non-small cell lung cancer.
[c] SCLC, small cell lung cancer.

tomatology that enforced amifostine interruption in 15% of patients. The cytoprotective efficacy of s.c. amifostine was also confirmed, because oropharyngeal, esophageal, and intestinal mucositis were significantly reduced compared with radiotherapy alone. Similarly, in a more recent study, we confirmed that s.c. amifostine protects normal mucosa against aggressive chemo-radiotherapy (18).

In the present study, we evaluated comparatively the tolerance of 1000 mg of amifostine given i.v. *versus* s.c. A majority (80%) of patients receiving this dose i.v. tolerated well the drug, whereas 13.5% developed prolonged nausea and emesis and/or clinical hypotension from the first administration. An additional 6.5% of patients developed similar symptoms during the subsequent injections of amifostine. We concluded that in 20% of patients, the tolerance of 1000 mg of amifostine given i.v. is not good, and patients suffer from emesis, malaise, and/or hypotension. Switching the route of administration to s.c., we noted an impressive amelioration of the tolerance because none of these patients developed protracted vomiting or clinical hypotension.

We recruited a cohort of 12 patients in a pilot study to investigate better the tolerance of the s.c. route. A total of 76 administrations was evaluated. Mild nausea and transient vomiting were noted in 18 of 76 injections, whereas clinical hypotension never occurred. This tolerance profile was significantly better than the one recorded after i.v. administration.

Concerning the cytoprotective efficacy of the s.c. administration, this should be sought in prospective randomized trials. Neurotoxicity and nephrotoxicity were negligible in patients recruited in docetaxel and platinum cohorts, but the cytoprotective benefit conferred by amifostine regarding these toxicities is impossible to compare because of the nonconventional schedules used. All chemotherapy regimens used in the present studies were biweekly and, therefore, nonconventional. The only

comparison of our results with previous experience is allowed in the group of colorectal cancer patients receiving irinotecan and 5-fluooruracil. Neutropenia grade 3–4 was very rare, and intestinal toxicity in patients receiving irinotecan was negligible, not exceeding grade I. Using a similar regimen with a slightly higher 5-fluorouracil dose without amifostine, Vamvakas *et al.* (19) reported a 13% incidence of grade 4 diarrhea and neutropenia grade 3–4 in 36% of patients. In a study by Ohtsu *et al.* (20), where an irinotecan dose of 150 mg/m^2 together with a 72-h infusion of 600 mg/m^2/day 5-fluorouracil was administered, the incidence of grade 3–4 diarrhea was 18%. Although premature, it seems that 1000 mg of amifostine protects normal tissues against chemotherapy regimens based on weekly or biweekly cycles. In these regimens, a lower dose of amifostine is delivered per cycle (1000 mg of flat instead of 750 mg/m^2 recommended), whereas the frequency of amifostine delivery is increased. Such regimens offer the advantage of using a good cytoprotective dose of amifostine (*i.e.*, 1000 mg) before lower doses of chemotherapy, so that the ratio "total dose of amifostine" to the "total chemotherapy dose" rises.

Despite the extensive experimental and clinical data on amifostine selective cytoprotection of normal compared with tumoral tissues (reviewed in Ref. 3), worries still exist on an eventual interference of amifostine with chemotherapy efficacy. In the trials herein reported, the 57, 45, and 56% response rates noted in non-small cell lung cancer, colorectal cancer, and gastric cancer, respectively, are high enough to exclude any tumor protection effect from amifostine.

It is concluded that the tolerance of s.c. amifostine administration at doses of 1000 mg is better than expected from the i.v. injection. A portion (20%) of patients receiving i.v. 1000 mg of amifostine before chemotherapy shows poor tolerance, and by switching to the s.c. route, cytoprotection can continue with minor side effects. Although randomized trials are necessary, it seems that 1000 mg of amifostine protect against the lower, still more frequently administered doses of chemotherapy prescribed in various regimens given once every 1 or 2 weeks.

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