Individualization of the Subcutaneous Amifostine Dose During Hypofractionated / Accelerated Radiotherapy

MICHAEL I. KOUKOURAKIS, IOANNIS ABATZOGLOU, LEONIDAS SIVRIDIS, MARIA TSARKATSI and HELEN DELIDOU

Department of Radiotherapy / Oncology, Democritus University of Thrace, University Hospital of Alexandroupolis, Alexandroupolis, Greece

Abstract. *Background: Individualization of the daily dose of amifostine may prove of value in achieving maximum cytoprotection during radiotherapy. Patients and Methods: Using an algorithm based on: i) the gradual increase of the amifostine dose, ii) an amifostine tolerance-recording scale and iii) the intermittent administration of dexamethasone, the individualization of the subcutaneous amifostine dose was prospectively attempted in a large cohort of 132 cancer patients, treated with 12-15 consecutive fractions of 3.4-3.5 Gy (hypofractionated accelerated radiotherapy with cytoprotection, HypoARC). Results: Using the above algorithm, a daily dose of 1000 mg of amifostine was successfully delivered in 62% of patients. An additional 20% of patients tolerated well a mean daily dose of 750-975 mg. Nausea and fatigue were minimal, while fever/rash enforced amifostine interruption in 7% of cases. Conclusion: Individualization of the amifostine dose allowed an up to two-fold increased daily-dose administration of amifostine and can be tested as a support to aggressive radio-chemotherapy schemes aiming at improving the cure rates of cancer patients, while avoiding excess toxicity.*

Amifostine is a broad spectrum cytoprotective agent that entered clinical practice after decades of experimental research. Randomized studies allowed the FDA approval of amifostine as a cytoprotector against cisplatin chemotherapy and radiation-induced xerostomia (1, 2). There is continually growing evidence that amifostine can protect normal head-neck, esophageal and intestinal mucosa against chemotherapy and radiotherapy (3-7), while an important role as a protector against radiation pneumonitis opens new directions in the radio-chemotherapy of locally advanced lung cancer (7-9). Fears that amifostine may interfere with the efficacy of cytotoxic therapy (10) are subsiding under the strong evidence provided by experiment data and, most importantly, by accumulating data from randomized clinical studies (reviewed in 11, 12). Amifostine may, in fact, enhance the strength of anticancer regimens, probably by preventing unnecessary reductions of the dose-intensity of therapy. Immunological protection or even stimulation may also contribute to this effect (13-15).

It should, however, be recognized that the 2.5 radioprotection factor promised by experimental studies has not been confirmed in clinical studies. One of the possible reasons accounting for this failure is the fact that the optimal dose of amifostine required to obtain strong cytoprotection during fractionated radiotherapy is elusive. Such a dose optimization is a difficult task as it depends on the tissue target, the individual metabolism of amifostine and, above all, the individual tolerance to amifostine. Some patients can receive high amifostine doses without any side-effects, while others cannot tolerate doses as low as 250 mg. In our experience, this tolerance variation is independent of age, gender, body weight or tumor type, while poor performance status is certainly linked with poor amifostine tolerance.

Pharmacokinetics studies suggest that the non-linear kinetic behavior of amifostine results in the accumulation in the plasma and renal excretion of the unmetabolized form of amifostine for doses higher than 750 mg/m^2 (16). It seems that doses of amifostine at least as high as 1200 mg can be well metabolized and distributed to tissues, resulting in intracellular amifostine levels proportional to the dose administered. The increasing amifostine accumulation in tissues by increasing the dose administered has been suggested in experimental studies, showing that the cytoprotective efficacy against radiation mucositis is dose-dependent and reaches a maximum at doses near the maximum tolerated dose of amifostine (200 mg/kg in rats) (17). The dose of 250-500 mg, used in clinical radiotherapy,

Correspondence to: Michael I. Koukourakis, MD, Department of Radiotherapy / Oncology, D.U.Th, P.O. Box 12, Alexandroupolis 68100, Greece. Tel: -30-6932480808, Fax: -30-25510-30349, e-mail: targ@her.forthnet.gr

Key Words: Amifostine dose, subcutaneous, radiotherapy, acceleration, hypofractionation.

0250-7005/2006 $2.00+.40

is certainly not the optimal dose for humans and clinical investigations to resolve this question are warranted.

The establishment of safety and confirmation of a high efficacy aggressive schedule would bring forward a new clinical role for amifostine. A paradigm of such an aggressive scheme is the HypoAR (hypofractionated accelerated radiotherapy) regimen, where large fractions of radiotherapy (3.5 Gy) are given daily to accomplish therapy within 3 weeks (18, 19).

In the present study, the feasibility of HypoAR with cytoprotection (HypoARC), using daily amifostine delivered subcutaneously, was investigated. An algorithm was used to obtain an optimum dosage of amifostine, higher than the standard of 500 mg, in an attempt to achieve optimal protection of organs against the substantial toxicity expected from the accelerated use of large radiotherapy fractions. The radiation toxicity and preliminary efficacy data in various tumor locations are reported.

Patients and Methods

One hundred and thirty-two patients, with tumors of various locations, were recruited in a prospective study to investigate the tolerance and efficacy of conformal HypoARC, using an individualized daily-dose administration of amifostine. The disease characteristics and radiotherapy intent are listed in Table I. Various chemotherapy schedules were delivered concurrently, depending upon the tumor location and stage (data not shown). All patients had a good performance status (0-1, median 0).

The use of HypoARC was approved by the Ethics and the Scientific Committee of our Hospital and all patients gave written informed consent. Radiotherapy was given using an 6/18MV linear accelerator (ELECTA) endowed with a multi-leaf collimator, after CT-simulation and conformal radiotherapy planning (Plato, Nucletron). Large daily fractions were used (3.4-3.5 Gy) for a total of 12-15 fractions to deliver the whole planned dose within 12-26 days. The specific fractionation and dosimetric analysis according to different tumor types are summarized in Table II. Details on the calculation of the normalized total dose (NTD) and time corrections were previously reported (20, 21).

Amifostine administration. Amifostine (1000 mg) was diluted in 5 ml water for injection (Winj) and was injected in two sites (usually in the right and left shoulder), with the patient in a sitting position. Blood pressure monitoring before and 30 and 60 min after administration was performed in the first 30 patients. As no changes were recorded, the blood pressure was not measured in the remaing patients.

The choice of Winj instead of normal saline (NS) for amfostine dilution was based on a pilot study on 30 patients, receiving 1000 mg subcutaneously of amifostine daily (unpublished data). Briefly, patients were injected with 500 mg diluted in 2.5 ml Winj to the right (day 1) and to the left (day 2) shoulder and 500 mg diluted in 2.5 ml NS to the left (day 1) and to the right (day 2) shoulder. Twelve out of the 30 patients stated that they preferred the Winj dilution because of less pain, while the remaining noted no difference. Thereafter, our standard practice for subcutaneous amifostine injection was to use Winj for amifostine dilution.

Table I. *Disease and radiotherapy intent in 132 patients recruited in the HypoARC trial. Stage refers to American Joint Committee's TNM classification or Dukes' stage in colorectal cancer.*

Area, disease and RT intent	Number of patients
Head-neck area	20
Laryngeal/pharyngeal/parotid cancer (stage: T3,4 and/or N2b,3)	
Radical RT	14
Postoperative RT	6
Thoracic area	14
Non-small cell lung cancer (stage: T3,4-N2)	
Radical RT	10
SCLC (limited stage)	
Radical RT	3
Esophageal cancer (inoperable)	
Radical RT	1
Breast	52
Postoperative RT (stage: T1-3, N0-1biv)	
After partial mastectomy	38
After mastectomy	9
Locally advanced inoperable disease	
Radical RT	5
Pelvic area	43
Bladder cancer (stage: T2,3 -N0,1)	
Radical RT	17
Prostate cancer (stage: T2,3-N0,1)	
Radical RT	7
Cervix/vulva/endometrium (stage: T3,4-N0,1,2)	
Radical RT	5
Colorectal cancer	
Preoperative RT (Dukes' stage C/D1)	5
Postoperative RT (Dukes' stage C)	4
Radical RT (Dukes' stage D1)	5
Other	3
Paraganglioma (inoperable)	1
Pheochromocytoma (inoperable)	1
Sarcoma (inoperable)	1
Total	132

The technique of amifostine subcutaneous injection is as follows: using a 24 G needle (insulin needle), the patient is injected slowly (10 seconds) with the 2.5 ml solution deep subcutaneously, while the needle is guided in a 45-60 degree direction to the surface of the underlying muscle. Superficial injection of the drug leads to skin swelling, excess pain and decelerated absorption, which is often followed by the development of local erythema. Deep injection seems to protect the skin from direct contact with amifostine and to substantially prevent pain and erythema. Local massage for 1 minute is performed to facilitate absorption.

Table II. *Radiotherapy schedules, physical dose, normalized total dose and normalized total dose with time correction delivered to normal tissues and cancer.*

	(Gy/fraction) x (No. fractions)	Physical dose (Gy)	NTD(n) (Gy)	NTD(c) (Gy)	Treatment (days)	Accel(n) (days)	Accel(c) (days)	NTD-T(n) (Gy)	NTD-T(c)
Head-neck cancer									
Radical	3.4 x 15	51.0	62.9	56.9-68.8	26[a]	18	13-21	66.5	62.1-85.6
Post-operative	3.4 x 12	40.8	50.3	45.5-55.0	16	12	10-17	52.7	49.5-68.6
Lung cancer	3.5 x 15	52.5	65.6	59.0-72.1	26[a]	19	14-24	69.4	64.6-91.3
Breast cancer									
Breast/thoracic wall	3.5 x 10	35.0	43.7	39.3-48.1	12	9	5-11	45.5	41.3-56.9
Tumor bed (adjuvant)	+ 4 x 2	43.0	54.3	48.3-59.0	16	16	11-19	57.5	52.7-74.2
Tumor (radical)	+ 4 x 4	51.0	65.0	57.3-70.1	18	24	18-26	69.8	64.5-90.9
Pelvic/abdominal tumours									
Radical									
Target (**)	3.4 x 15	51.0	62.9	56.9-68.8	19	23	18-25	67.5	64.1-88.8
Pelvis(***)	2.7 x 14	37.8	42.2	40.0-44.4	18	8	5-8	43.8	42.0-50.8
Pre-operative	3.5 x 9	31.5	39.3	35.4-43.3	11	5	3-9	40.3	36.6-50.5
Post-operative	3.5 x 10	35.0	43.7	39.3-48.1	12	9	5-11	45.5	41.3-56.9

NTD(n) : normalized total dose to normal tissues calculated for α/β=4 Gy ; NTD(c): normalized total dose to cancer calculated for α/β=2-10 Gy; NTD-T(n) : normalized total dose corrected for time delivered to normal tissues calculated for α/β=4 Gy and for λ=0.2 Gy); NTD-T(c) : normalized total dose corrected for time delivered to cancer calculated for α/β=2-10 Gy and for λ=0.4-0.8 Gy) ; Accel(n) : days of acceleration for normal tissues ; Accel(c) : days of acceleration for cancer ; (*) time reduction considering the 21st day as the point of onset of rapid tumor repopulation.; (**) cancer and adjacent normal tissues; (***) normal and cancer tissues outside the cancer target area. [a] one week split.

Amifostine-dose individualization and assessment of tolerance. The dose of 1000 mg was reached gradually as follows: day 1, 500 mg; day 2, 750 mg; and day 3, 1000 mg. The tolerance to amifostine was recorded daily using a scoring system reported in Table III. According to this scale, the tolerance to amifostine was scored as good/acceptable, poor or unacceptable for each dose level. According to our previous experience, the intramuscular injection of dexamethasone improved the tolerance of subcutaneously-injected amifostine; "dexamethasone" together with "tolerance" was used in an algorithm to establish the dose of amifostine for each patient, as shown in Figure 1.

Although complicated at first sight, this algorithm is easy to apply. Briefly, if at any point of therapy patients showed poor tolerance (grade 3/4 nausea/emesis or grade 3/4 fatigue), dexamethasone 8 mg was administered intramuscularly immediately before injection of amifostine and tolerance was re-assessed the day after. If good tolerance was confirmed, amifostine was continued as prescribed. If not, the dose was reduced to 750 mg and, if necessary, to 500 mg. If patients did not tolerate the dose of 500 mg well, amifostine was interrupted. No more than two dexamethasone injections were allowed per week of radiotherapy, otherwise the dose of amifostine was reduced. Generalized rash or amifostine-related fever or necrolytic syndrome attributed to amifostine (or to any other drug) was followed by immediate interruption of amifostine and oral administration of cortisone and antihistamines for 3 days (15). Local rash at the site of injection was treated with steroid cream application.

Results

Amifostine dose individualization. The mean daily dose given to patients (total dose delivered to a patient divided by the number of treatment days, starting calculation on the third day, the day of the final dose escalation of amifostine is shown in Table IV.

Using the algorithm in Figure 1, 101/132 (76.5%) patients reached a dose of 1000 mg. Eighty-two (62%) of these patients continued the 1000 mg daily dose until the end of therapy, while for 19 patients (14.4%) dose reduction for some of the treatment days was necessary (mean amifostine dose received 780-975 mg). Fever/rash symptomatology was the cause of amifostine discontinuation and, therefore, of the reduction of the mean dose in 7/19 patients, while nausea or asthenia grade 3 was the cause of transient or permanent dose reduction in 12/19 patients.

For 14/132 (10.6%) patients, the established dose was 750 mg. Eight (6%) of these patients continued the daily dose of 750 mg, while dose reduction was necessary in six (4.6%) patients (mean dose received 550-740 mg). Fever/rash was the cause of amifostine discontinuation in 2/6 patients.

Table III. *Amifostine toxicity-recording scale developed in our Institute.*

Nausea – Vomiting	
Grade 0 ( )	None
Grade 1 ( )	Transient nausea without vomiting
Grade 2 ( )	Transient nausea with vomiting
Grade 3 (*)	Protracted nausea with vomiting for less than 4 hours
Grade 4 (*)	Protracted nausea with vomiting for more than 4 hours
Headache	
Grade 0 ( )	None
Grade 1 ( )	Transient (less than 2 hours) or regressing with paracetamol
Grade 2 (*)	Prolonged and resistant to paracetamol
Grade 3 (*)	Intolerable
Fatigue	
Grade 0 ( )	None
Grade 1 ( )	Transient fatigue and/or sleepiness for less than 2 hours
Grade 2 ( )	Fatigue and/or sleepiness for less than 6 hours acceptable by the patient
Grade 3 (*)	Fatigue and/or sleepiness for less than 6 hours unacceptable by the patient
Grade 4 (*)	Fatigue and/or sleepiness for more than 6 hours
Hypotension	
Grade 0 ( )	None
Grade 1 ( )	Sub-clinical hypotension
Grade 2 (*)	Hypotension requiring medical care
Grade 3 (**)	Life-threatening hypotension
Erythema	
Grade 0 ( )	None
Grade 1 ( )	Limited erythema around the site of injection
Grade 2 ( )	Extended erythema (>10 cm) around the site of injection
Grade 3 (**)	Generalized rash and/or fever symptomatology
Grade 4 (**)	Necrolytic skin syndrome regressing within 10 days
Grade 5 (**)	Life-threatening necrolytic syndrome

( ) Good or acceptable tolerance.
(*) Poor tolerance – amifostine dose modification demanded if not improved by dexamethasone.
(**) Intolerable – immediate and permanent interruption of amifostine without any attempt to repeat injection with reduced dose or with dexamethasone support.

For the remaining 17 patients, 14 were recruited at the 500 mg dose level and three could not tolerate the 500 mg daily dose (amifostine interruption).

Sixty-five (49.2%) patients received no or just one dexamethasone injection, 38 (28.8%) received two injections and 29 (22%) received three to five injections during the radiotherapy course.

As shown in Table IV, the best amifostine tolerance was noted in rectal and breast cancer patients, while lung cancer patients had the worst.

Amifostine-related local toxicity. The subcutaneous injection of amifostine (diluted in Winj) was associated with an excellent local tolerance. Lcoal pain was reported by 10/132 (7.5%) patients. Occasionally, bruises around the site of injection were noted. Local erythema extending up to 5 cm around the site of injection appeared in 15/132 (11.3%) patients. In two patients (1.5%), local erythema reaching a 10-cm diameter was noted. The site of injection was changed and therapy was continued without interruption. Local erythema regressed within 2-4 days and was never a cause for amifostine discontinuation.

Amifostine related systemic side-effects. Using the algorithm reported in Figure 1, the dose level of amifostine was adjusted so that, for all treated patients, grades 3,4 nausea, grades 2,3 headache or grades 3-4 fatigue were prevented. Most injections given at the established dose level were followed by grades 0-1 nausea (99/132; 75%) or grades 0-1 fatigue (108/132; 82%). Occasionally, higher grades were reported by patients on one or more of treatment days and dexamethasone was given to improve tolerance (no more than two dexamethasone injections allowed per week). The toxicity grade had drastically improved by the next day. Enforced permanent amifostine dose reduction to the previous level was less common (7/101 at the 1000-mg and 4/14 at the 750-mg dose levels).

None of the patients developed clinical hypotension (grades 2-3) and subclinical hypotension was not confirmed in any of the initial 30 patients, whose blood pressure was monitored. In 2/101 patients, intolerable nausea accompanied by sweating and a fainting feeling were noted at some point of their 1000-mg treatment. However, no hypotention was confirmed in these patients. Patients recovered within 30-60 min, while dexamethasone was injected intramuscularly. Headache grade 2 was reported by 5/132 patients.

Fever/rash symptomatology was noted in 7/101 (6.9%) and 2/28 (7.1%) patients recruited in the 1000-mg and the 750/500-mg dose levels, respectively. Fever accompanied with rash was noted in 7/9 patients, while in 2/9 patients fever was not accompanied with rash. Amifostine was immediately interrupted and the patients received oral methylprednisolone and antihistaminse. Complete regression of the rash was noted within 1-3 days, while fever regressed rapidly within 1-2 hours. There was no case of necrolytic skin syndrome recorded.

Discussion

Using an algorithm based on: i) the gradual increase of the amifostine dose (from 500 mg to 750 mg and to 1000 mg), ii) the intermittent administration of dexamethasone and iii) a proposed amifostine toxicity recording scale, it was possible

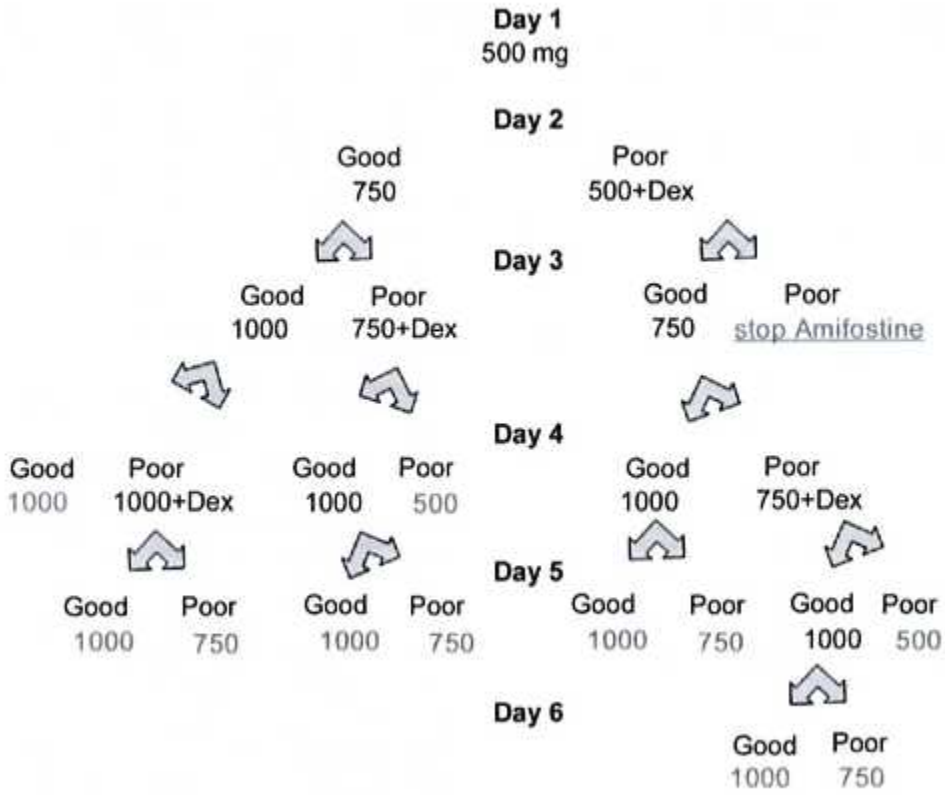

Figure 1. *Algorithm use to individualize the amifostine dose during accelerated radiotherapy. 'Good' or 'poor' refer to the tolerance score of the previous dose level and the number (500, 750, 1000) reported below the tolerance refers to the amifostine dose (mg) delivered following documentation of the tolerance score. Once the dose level had been established, transient or permanent reduction of the amifostine dose to the previous level was performed if, on any of the subsequent days, dexamethasone-resistant vomiting grades 3,4 or fatigue grades 3,4 were recorded.*

to individualize the dose of amifostine in a large cohort of 132 patients. The choice of the subcutaneous route of amifostine injection has been explained in previous studies (22-25). The absence of hypotension, the reduced incidence of acute emesis, the fast injection procedure, the avoidance of venous catheterization and the prompt transportation of the patients between the administration and the radiotherapy rooms are important advantages of the subcutaneous route. Experimental data suggest that the tissue kinetics of WR2721 after *i.v.* and *s.c.* administration practically overlapped, so that the active WR1065 thiol accumulates in tissues in a similar way, regardless of the route of administration (26, 27).

It is encouraging that, using the proposed algorithm, 62% of patients tolerated an amifostine daily dose of 1000 mg well and 14% of patients received a mean daily dose of 780-975 mg. An additional 6% of patients tolerated a daily dose of 750 mg well. During the 3 weeks of treatment (12-15 injections), the incidence of fever/rash was as low as 7%, which was not different from that observed in patients receiving a flat dose of 500 mg (22, 24, 25). Hypotension was never observed and nausea/vomiting was maintained at acceptable levels with the intermittent support of dexamethasone (not more than two injections of 8 mg allowed per week). It is quite probable that a fraction of patients could receive an even higher than 1000 mg daily dose, but this was not investigated in the present study. The finding that lung cancer patients showed the worse tolerance for the 1000-mg dose level can probably be attributed to the

Table IV. *Mean dose of amifostine received by patients according to the disease.*

	All cases (132)	Head/Neck (20)	Lung (14)	Urologic (24)	Rectal (14)	Breast (52)
Mean dose(mg)	No. pts (%)	No. pts (%)	No. pts (%)	No. pts (%)	No. pts (%)	No. pts (%)
0	3 (2.3)	1 (5)	0 (0)	0 (0)	1 (7.15)	0 (0)
<500	4 (3)	0 (0)	2 (14.3)	1 (4.2)	0 (0)	1 (1.9)
500	10 (7.6)	2 (10)	2 (14.3)	2 (8.4)	0 (0)	2 (3.9)
550-740	6 (4.6)	1 (5)	0 (0)	2 (8.4)	0 (0)	2 (3.9)
750	8 (6)	2 (10)	1 (7.1)	1 (4.2)	1 (7.15)	3 (5.7)
780-975	19 (14.4)	4 (20)	5 (35.7)	3 (12.5)	0 (0)	6 (11.5)
1000	82 (62.1)	10 (50)	4 (28.6)	15 (60.3)	12 (85.7)	38 (73.1)

fact that most of these patients had been pretreated with chemotherapy. Head and neck cancer patients, expected to have the worse tolerance due to malnutrition and dehydration, exhibited a very good tolerance, with half of them receiving the full 1000-mg amifostine dose. A multi-parametric analysis is on-going to better assess the factors that influence tolerance to amifostine.

Experimental data showed a dose-dependent cytoprotective effect (28). The high daily dose of amifostine achieved for up to 15 injections promises better results than the standard 350-500 mg dose used to date. Additional studies are necessary to investigate whether administration of such a high daily dose can continue for the 30 injections, required to cover standard radiotherapy schemes. The real benefit expected from cytoprotection will not emerge from the effective protection against standard radiotherapy but, rather, from the properties of amifostine to safely deliver aggressive radiotherapy and chemo-radiotherapy regimens. Low doses of amifostine produced a significant clinical benefit during accelerated radiotherapy (29) and hyperfractionated radiotherapy (7). For both schedules used by Bourhis *et al.* and by Komaki *et al.* in these two studies, 15 injections of amifostine covered the whole radiotherapy scheme and it would be of interest to examine whether the optimal amifostine dose (as herein defined) further improves results. For many aggressive radiotherapy schemes currently under evaluation (listed in Table V), 15 injections of amifostine adequately cover the whole therapeutic schedule and the support of these patients with the optimum amifostine dose is essential to maximize cytoprotection. Daily amifostine administration at optimal doses may also prove of value in specific chemotherapy schedules, such as continuous infusion chemotherapy (*i.e.*, 5-Fluorouracil and platinum chemotherapy), daily chemo-therapy (*i.e.*, topotecan administration) and liposomal chemo-therapy (*i.e.*, liposomal doxorubicin) (30).

The major conclusion from the present study is that optimization of the dose of amifostine can be achieved using the guidelines herein reported. Double the dose of amifostine used to date in fractionated radiotherapy can be safely administered in about 70% of patients to support accelerated chemo-radiotherapy schemes. Although it is unclear whether such high doses are better than the standard of 500 mg, the experimental data strongly suggest a dose-response effect (17, 27, 28). Carefully designed trials with aggressive chemo-radiotherapy regimens, adopting the dose individualization algorithm for amifostine administration, are required to clinically prove this hypothesis. The preliminary results regarding early and late toxicity, as well as tumor control rates, are encouraging (data not shown). The study is on-going to recruit large numbers of patients in the different disease groups in order to better define the long-term toxicity and the benefits in terms of cure-rates from HypoARC.

Table V. *Radiotherapy, chemo-radiotherapy and chemotherapy schedules where optimization of the daily dose of amifostine for 15 injections may become of clinical value.*

Continuous daily administration of amifostine during 2 to 4 weeks of:
1. hypofractionated accelerated radiotherapy
2. hyperfractionated accelerated or simple accelerated radiotherapy (suggested administration of amifostine before the morning daily fraction)
3. concomitant boost radiotherapy schedules delivering the total dose in 3 to 4 weeks.

'Less than daily' administration of amifostine during the 6 to 7 weeks of:
4. radio-chemotherapy using weekly administration of drugs (suggested administration during the first 2 to 3 days of each week, when maximum radiosensitization of normal tissues occurs).
5. split-course chemo-radiotherapy using once-every-3 to 4-week chemotherapy (administration during the first 5 to 10 days of each radio-chemotherapy cycle).
6. conventionally fractionated chemo-radiotherapy during 4 to 5-day continuous infusion chemotherapy (administration during the days of chemo-radiotherapy)

Administration of amifostine during specific radiotherapy techniques:
7. high (or medium) dose rate fractionated brachytherapy.
8. fractionated stereotactic radiotherapy.

Administration of amifostine during specific chemotherapy schedules:
9. 3 to 5-day continuous infusion chemotherapy (daily amifostine administration).
10. daily chemotherapy (before each drug injection)
11. liposomal chemotherapy (injection of amifostine for 4 to 5 days)

References

1 Brizel DM, Wasserman TH, Henke M *et al*: Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol *18*: 3339-3345, 2000.

2 Werner-Wasik M, Axelrod RS, Friedland DP *et al*: Preliminary report on reduction of esophagitis by amifostine in patients with non-small-cell lung cancer treated with chemoradiotherapy. Clin Lung Cancer *2*: 284-289, 2001.

3 Vacha P, Fehlauer F, Mahlmann B *et al*: Randomized phase III trial of postoperative radiochemotherapy +/- amifostine in head and neck cancer. Is there evidence for radioprotection? Strahlenther Onkol *179*: 385-389, 2003.

4 Antonadou D, Petridis A, Synodinou M *et al*: Amifostine reduces radiochemotherapy-induced toxicities in patients with locally advanced non-small cell lung cancer. Semin Oncol *30(Suppl)*: S2-9, 2003.

5 Athanassiou H, Antonadou D, Coliarakis N *et al*: Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: results of a randomized trial. Int J Radiat Oncol Biol Phys *56*: 1154-1160, 2003.

6 Antonadou D, Pepelassi M, Synodinou M *et al*: Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radiat Oncol Biol Phys *52*: 739-747, 2002.

7 Komaki R, Lee JS, Milas L *et al*: Effects of amifostine on acute toxicity from concurrent chemotherapy and radiotherapy for inoperable non-small-cell lung cancer: report of a randomized comparative trial. Int J Radiat Oncol Biol Phys *58*: 1369-1377, 2004.
8 Vujaskovic Z, Feng QF, Rabbani ZN *et al*: Assessment of the protective effect of amifostine on radiation-induced pulmonary toxicity. Exp Lung Res *28*: 577-590, 2002.
9 Brizel DM and Overgaard J: Does amifostine have a role in chemoradiation treatment? Lancet Oncol *4*: 378-381, 2003.
10 Lindegaard JC and Grau C: Has the outlook improved for amifostine as a clinical radioprotector? Radiother Oncol *57*: 113-118, 2000.
11 Koukourakis MI: Amifostine in clinical oncology: current use and future applications. Anticancer Drugs *13*: 181-209, 2002.
12 Koukourakis MI: Amifostine: is there evidence of tumour protection? Semin Oncol *30(Suppl)*: S18-30, 2003.
13 Mantovani G, Maccio A, Madeddu C *et al*: Antioxidant agents are effective in inducing lymphocyte progression through cell cycle in advanced cancer patients: assessment of the most important laboratory indexes of cachexia and oxidative stress. J Mol Med *81*: 664-673, 2003.
14 Provinciali M, Ciavattini A, Di Stefano G *et al*: *In vivo* amifostine (WR-2721) prevents chemotherapy-induced apoptosis of peripheral blood lymphocytes from cancer patients. Life Sci *64*: 1525-1532, 1999.
15 Koukourakis MI, Ktenidou-Kartali S, Bourikas G *et al*: Amifostine protects lymphocytes during radiotherapy and stimulates expansion of the CD95/Fas and CD31 expressing T-cells, in breast cancer patients. Cancer Immunol Immunother *52*: 127-131, 2003.
16 Shaw LM, Bonner HS, Schuchter L *et al*: Pharmacokinetics of amifostine: effects of dose and method of administration. Sem Oncol *26(suppl)*: S34-36, 1999.
17 Cassatt DR, Fazenbaker CA, Kifle G and Bachy CM: Preclinical studies on the radioprotective efficacy and pharmacokinetics of subcutaneously administered amifostine. Semin Oncol *29(Suppl)*: S2-8, 2002.
18 Koukourakis MI and Yannakakis D: High dose daily amifostine and hypofractionated intensively accelerated radiotherapy for locally advanced breast cancer. A phase I/II study and report on early and late sequellae. Anticancer Res *21*: 2973-2978, 2001.
19 Koukourakis MI, Giatromanolaki A, Kouroussis C *et al*: Hypofractionated and accelerated radiotherapy with cytoprotection (HypoARC): a short, safe, and effective postoperative regimen for high-risk breast cancer patients. Int J Radiat Oncol Biol Phys *52*: 144-155, 2002.
20 Macejewski B, Taylor JM and Wither HR: Alpha/beta and the importance of the size of dose per fraction for late complications in the supraglottic larynx. Radiother Oncol *7*: 323-326, 1986.
21 Koukourakis MI and Damilakis J: LQ-based model for biological radiotherapy planning. Med Dosim *19*: 269-277, 1994.
22 Koukourakis MI, Kyrias G, Kakolyris S *et al*: Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. J Clin Oncol *18*: 2226-2233, 2000.
23 Koukourakis MI, Simopoulos C, Minopoulos G *et al*: Amifostine before chemotherapy: improved tolerance profile of the subcutaneous over the intravenous route. Clin Cancer Res *9*: 3288-3293, 2003.
24 Anne PR: Phase II trial of subcutaneous amifostine in patients undergoing radiation therapy for head and neck cancer. Semin Oncol *29(Suppl)*: 80-83, 2002.
25 Bardet E, Martin L, Calais G *et al*: Preliminary data of the GORTEC 2000-02 phase III trial comparing intravenous and subcutaneous administration of amifostine for head and neck tumours treated by external radiotherapy. Semin Oncol *29(Suppl)*: 57-60, 2002.
26 Bachy CM, Fazenbaker CA, Kifle G *et al*: Tissue levels of WR-1065, the active metabolite of amifostine (Ethyol), are equivalent following intravenous or subcutaneous administration in cynomolgus monkeys. Oncology *67*: 187-193, 2004.
27 Cassatt DR, Fazenbaker CA, Kifle G and Bachy CM: Subcutaneous administration of amifostine (ethyol) is equivalent to intravenous administration in a rat mucositis model. Int J Radiat Oncol Biol Phys *57*: 794-802, 2003.
28 Cassatt DR, Fazenbaker CA, Kifle G and Bachy CM: Effects of dose and schedule on the efficacy of ethyol: preclinical studies. Semin Oncol *30(Suppl)*: S31-39, 2003.
29 Bourhis J, De Crevoisier R, Abdulkarim B *et al*: A randomized study of very accelerated radiotherapy with and without amifostine in head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys *46*: 1105-1108, 2000.
30 Lyass O, Lotem M, Edelmann D *et al*: Protective effect of amifostine (AMF) on doxil/caelyx-induced palmar-plantar erythrodysesthesia (PPE) in patients (PTS) with advanced cancer. Proc Am Soc Clin Oncol *20*: 99b, Abstract 2148, 2001.

Received February 2, 2006
Accepted March 17, 2006