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Report

Tolerability of the cytoprotective agent amifostine in elderly patients receiving chemotherapy: a comparative study

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In order to determine if age and comorbidity influence the tolerability of the cytoprotective agent amifostine, we compared side effects related to amifostine in patients ⩾70 years (group I) with patients <70 years (group II). We evaluated 268 consecutive administrations of amifostine (119 in group I and 149 in group II, respectively), given i.v. at a dose of 740 mg/m^2 just before platinum-, taxol- or cyclophosphamide-based chemotherapy. Transient hypotension was the most common side effect occurring in association with amifostine. Decreases in systolic blood pressure >20 mmHg were of similar frequency in both groups (27.1 versus 28.8% of amifostine infusions in group I and II, respectively). Hypotension did not result in medical sequelae in any of the patients. The amifostine infusion was interrupted 16 times in group I and 8 times in group II, respectively, mainly due to hypotension, but could be restarted after a few minutes in all patients except for three cases in group I. Patients in group II more often suffered from nausea/vomiting than in group II (20.8 versus 10.0% in group I). Other subjective symptoms (e.g. warmed, flushed sensation, sneezing, metallic taste, mouth dryness, dizziness and sleepiness) and hypocalcemia occurred with a similar frequency in both groups. Adverse effects associated with amifostine were not observed more frequently in elderly patients than in younger ones, although more elderly patients had a comorbidity than the younger ones. [© 2001 Lippincott Williams & Wilkins.]

Key words: Amifostine, cancer, chemoprotectant, comorbid conditions, elderly.

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Introduction

Due to the aging of the population, a steady increase in the number of elderly tumor patients is expected in the coming decades. Aging is usually associated with alterations in pharmacokinetics, particularly decreased activity of hepatic drug-metabolizing enzyme activity and a decrease in the glomerular filtration,[1] explaining the reported higher toxicity of cytotoxic drugs in elderly patients. Amifostine is a thiol compound of special interest in the treatment of elderly patients with cancer due to its wide cytoprotective activity encompassing, for instance, hematologic toxicity from alkylating agents, platinum-induced nephrotoxicity and neurotoxicity.[2,3] However, amifostine, which may have clinically significant side effects, has not been adequately evaluated in the elderly. Therefore, it is unknown how elderly patients, who often present with comorbid diseases, e.g. cardiovascular diseases and/or hypertension, in addition to the malignant tumor, tolerate amifostine. In this study, we compared side effects related to amifostine given i.v. at a dose of 740 mg/m^2 in combination with chemotherapy in patients 70 years and older and in younger patients in order to determine if age and comorbidity impair the tolerability of amifostine.

Patients and methods

Patients

A total of 63 patients who had received amifostine in combination with chemotherapy at our institution were retrospectively analyzed after being stratified in two groups according to age (Table 1).

Table 1. Patient groups according to age, disease and treatment

Group/patient age	No.	Disease	Chemotherapy
Group I: ⩾70 years	24	all patients with high-grade NHL	CHOP
Group II: <70 years	39	26 patients with NHL	CHOP
		8 patients with pancreatic cancer	platinum–gemcitabine
		1 patient with NSCLC	platinum–gemcitabine
		1 patient with metastatic esophageal carcinoma	platinum–taxol–5-fluorouracil
		3 patients with metastatic breast carcinoma	taxol–epirubicine-gemcitabine, or taxol alone, or epirubicine–cyclophosphamide

The group of patients ⩾70 years (group I) gathered a total of 24 patients with agressive non-Hodgkin's lymphoma (NHL) who received amifostine combined with CHOP polychemotherapy. The group of patients <70 years (group II) collected a total of 39 patients, and consisted of 26 patients with NHL (24 patients with agressive NHL and two patients with mantle cell lymphoma) who also received amifostine combined with CHOP polychemotherapy; 11 patients with solid tumors who received amifostine to reduce the toxicity of a polychemotherapy containing platinum or cyclophosphamide (eight patients with pancreas carcinoma, one patient with non-small cell carcinoma of the lung (NSCLC), one patient with metastatic breast carcinoma and one patient with metastatic esophageal carcinoma); and two patients with metastatic breast carcinoma treated with polychemotherapy containing paclitaxel who received amifostine on a compassionate basis.

Patient groups, underlying diseases and chemotherapy are summarized in Table 1. For each patient the following data were noted: age, sex, presence of a significant, i.e. medically treated, cardiovascular disease and/or hypertension.

Treatment plan and monitoring

All patients received 250 ml of 0.9% normal saline over 30 min before amifostine. Amifostine was given at a dose of 740 mg/m^2, administered as a 15-min i.v. infusion 30–15 min prior to the first chemotherapy infusion (adriamycin in the CHOP regimen, paclitaxel or platinum for the other patients). During the amifostine infusion, patients remained in a supine position and their blood pressure was monitored every 5 min. Amifostine was interrupted for a 20–50 mmHg decrease in systolic blood pressure, depending on the patient's baseline level, according to the recommendations of the published guidelines.[4] Amifostine was restarted after the systolic blood pressure returned to baseline values, provided the patient was asymptomatic.

For all patients, the premedication included a serotonin antagonist, i.e. ondansetron 8 mg given i.v. For those receiving CHOP polychemotherapy, no dexamethasone was administrated since all patients received 100 mg prednisone as oral medication before the beginning of amifostine. For patients receiving paclitaxel, the premedication consisted of ondansetron 8 mg, ranitidin 50 mg and dexamethasone 16 mg given i.v. Patients receiving a polychemotherapy containing platinum had a premedication with 8 mg dexamethasone.

In addition to the control of arterial blood pressure during each amifostine administration, patients were monitored for adverse events developing from the beginning of amifostine until 1 h after the end of the infusion. Changes in the systolic and/or diastolic blood pressure, and occurrence of other adverse effects were thus compared between the two groups of patients.

Results

Patients characteristics

Patients characteristics are summarized in Table 2. In patients ⩾70 years (group I), the median age was 75.5 years; in group II (patients <70 years), the median age was 64 years. The proportion of men and women was similar in the two groups. In group I, 70.8% of patients had hypertension and/or a cardiovascular disease requiring medication compared with 47.3% in group II. The proportion of patients treated with antihypertensive drugs was not significantly different in the two groups (41.6% in group I versus 36.8% in group II). In each group, one patient presented with slight renal or hepatic impairment.

Adverse events

A total of 268 consecutive administrations of amifostine was evaluated: 119 in group I and 149 in group II.

The major side effect of amifostine was hypotension. The effect of amifostine on systolic blood pressure and the incidence of symptomatic hypotension are reported in Table 3. A decrease in systolic blood pressure was observed in 86.5 and 81.9% of amifostine administrations in group I and II, respectively. A decline in systolic blood pressure >20 mmHg for over 5 min or symptomatic hypotension or symptomatic hypotension occurred in 27.1 and 28.8% of the amifostine administrations in group I and II, respectively. Other adverse effects and their frequency in both groups are reported in Table 4. They included flushing, nausea and vomiting, sneezing, metallic taste or mouth dryness, dizziness, and sleepiness. These adverse effects were mild and of short duration. Hiccups or chills did not occur in any patients and no idiosyncratic reaction such as fever or rash was observed.

Serum calcium levels were monitored before and after a total of 146 of 268 amifostine administrations (71 amifostine administrations in group I and 75 amifostine administrations in group II, respectively). Serum calcium levels were measured 4–6 h or 1 day after the amifostine infusion. Hypocalcemia defined as a value under 2.2 mmol/l occurred in about 88% of amifostine administrations in both groups (Table 5). Because hypocalcemias were asymptomatic, no calcium supplementation was required.

Table 2. Patient characteristics

Characteristics	Group I ($\geqslant$70 years)	Group II ($<$70 years)
No.	24	39
Age (years)		
median	75.5	64
range	70–87	42–69
Gender		
male	12 (50%)	17 (43.6%)
female	12 (50%)	22 (56.4%)
Cardiovascular disease and/or hypertension	17 (70.8%)	18 (46.1%)
Patients with antihypertensive drugs	10 (41.6%)	14 (35.9%)
Patients with renal or hepatic impairment	1 (4.1%)	1 (2.5%)

Table 3. Effect of amifostine infusion on blood pressure and incidence of symptomatic hypotension

	Group I ($\geqslant$70 years)	Group II ($<$70 years)
Amifostine administrations	$n=119$	$n=149$
Decrease in systolic blood pressure	103 (86.5%)	122 (81.9%)
symptomatic	5 (4.2%)	14 (9.4%)
$\leqslant$20 mmHg	71 (59.6%)	79 (53%)
21–40 mmHg	29 (24.6%)	33 (22.1%)
$>$40 mmHg	3 (2.5%)	10 (6.7%)
Decrease in diastolic blood pressure	84 (70.6%)	94 (63%)
symptomatic	4 (3.4%)	7 (4.7%)
$\leqslant$20 mmHg	82 (68.9%)	83 (55.7%)
21–40 mmHg	2 (1.7%)	10 (6.7%)
$>$40 mmHg	0 0	1 (0.7%)

Table 4. Other observed adverse effects of amifostine administration

	Group I ($\geqslant$70 years)	Group II ($<$70 years)
Amifostine administrations	$n=119$	$n=149$
Warmed, flushed sensation	31 (25.2%)	51 (34.2%)
Nausea, vomiting	12 (10%)	31 (20.8%)
Sneezing	8 (6.7%)	17 (11.4%)
Metallic taste, mouth dryness	5 (4.2%)	7 (4.7%)
Dizziness, light-headedness	3 (2.5%)	8 (5.3%)
Sleepiness	1 (0.8%)	0 (0%)

The amifostine infusion was interrupted 16 times in group I and 8 times in group II, respectively, mainly due to hypotension. However, the amifostine infusion could be restarted after a few minutes, when the blood pressure had returned to baseline, in all but three cases in group I (Table 6).

None of the observed adverse effects resulted in medical sequelea in any of the patients.

Discussion

Amifostine has shown promise as a supportive treatment in patients receiving therapy with antineoplastic agents and irradiation, particularly in patients receiving platinum or cyclophosphamide. It reduces the incidence of hematologic toxicity (granulocytopenia and thrombocytopenia) of these agents and some other toxicities including platinum-induced neuro- and nephrotoxicity, allowing better tolerance of different regimens.[5–7] Because there is no evidence from clinical trials that amifostine reduces the efficacy of cytotoxic chemotherapy, interest in this cytoprotective agent has grown over recent years. Since the expansion of the aging population makes cancer in the elderly increasingly common and because the toxicity of antineoplastic chemotherapy is augmented in older individuals, the use of amifostine in this group of patients offers an interesting possibility. However, amifostine has not been adequately evaluated in the elderly and therefore is not yet recommended for use in these patients.[8]

Table 5. Occurrence of hypocalcemia after amifostine administration

	Group I ($\geqslant$70 years)	Group II ($<$70 years)
Amifostine administrations	$n=119$	$n=149$
With calcemia monitoring	$n=71$	$n=75$
Hypocalcemia $<$2.2 mmol/l	62 (87.3%)	66 (88%)
No hypocalcemia	9 (12.6%)	9 (12%)

Hypocalcemia: range 1.54–2.19 mmol/l, median 2.02 mmol/l.

Table 6. Interruption of the amifostine infusion

	Group I ($\geqslant$70 years)	Group II ($<$70 years)
Amifostine administrations	$n=119$	$n=149$
With amifostine interruption	16 (13.4%)	8 (5.3%)
due to hypotension alone	10	3
due to hypotension and symptoms	6	5
Definitive interruption	3	0

We retrospectively evaluated the side effects of amifostine at a dose of 740 mg/m^2, administered prior to chemotherapy in patients $\geqslant$70 years (group I) and in patients $<$70 years (group II). As expected, more patients in group I presented with cardiovascular disease and/or hypertension. As already reported in other studies,[5–7] we found that the clinically most significant adverse effect of amifostine was hypotension. More than 80% of the amifostine administrations in each group were associated with a drop in systolic blood pressure. A decrease in systolic blood pressure $>$20 mmHg was observed with the same frequency in both groups. Although antihypertensive agents were not interrupted before treatment with amifostine in our patients, the occurrence of hypotension was not more frequent, as compared with the reported incidence of 25% by Kemp *et al.*[5] with an amifostine dosis of 910 mg/m^2 or of 31% in the study of Schiller *et al.*[6] at the 740 mg/m^2 dose level. The lack of symptoms associated with decreases in systolic blood pressure in most instances may be explained by rare drops $>$20 mmHg in diastolic blood pressure. Overall, reduction in blood pressure was transient and tended to occur toward the end of the amifostine infusion. While the interruption of the amifostine infusion was more frequently necessary among older patients in our study (13.4% in group I versus 5.3% in group II), this event was rare compared to other studies.[6,7]

Nausea and vomiting are usually reported as the second major side effect with incidences of 54–82% of courses of amifostine.[8] In our study, these symptoms were observed in only 20.8% of the amifostine administrations in group II and less frequently in older patients (only 10%). This low incidence of nausea and vomiting in both groups may be explained by pretreatment with corticosteroids and serotonin antagonists. The even lower incidence in elderly patients may be explained by the observation that, in general, emesis occurs less frequently in older compared with younger patients.[9]

The development of flushing was the second most common side effect after hypotension in our study. Sneezing, metallic taste, dizziness, light-headedness and sleepiness were, as noted in other studies, minor side effects.

Hypocalcemia is a well-known adverse effect of amifostine and occurs particularly with daily administration schedules.[10] It is due to inhibition of parathyroid hormone secretion and direct inhibition of bone resorption.[11] Mean total serum calcium levels have been reported to decrease significantly by 18% after each of 18 courses of i.v. amifostine.[11] However, as in

most other studies without consecutive daily administrations of amifostine, development of hypocalcemia was asymptomatic and required no treatment.

Conclusion

The administration of amifostine in combination with chemotherapy is associated with an acceptable toxicity profile in patients $\geqslant$70 years. Although comorbidity, and especially the presence of a cardiovascular disease and/or hypertension, was more frequent in our elderly patients, amifostine-related side effects did not occur more often than in younger patients. However, because only a few patients in our study presented with renal or hepatic impairment, the use of amifostine in these circumstances needs to be evaluated further.

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