*Annals of Oncology* **10**: 693–700, 1999.


# Original article

## Randomized study of a short course of weekly cisplatin with or without amifostine in advanced head and neck cancer

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**Summary**

*Background:* Cisplatin is one of the most active cytotoxic agents available for the treatment of patients with head and neck cancer. In a previous phase II study with weekly administration of cisplatin, a response rate of 51% was achieved. However, only in a minority of the patients the planned high dose intensity of 80 mg/m$^2$/week could be reached because of toxicity, mainly thrombocytopenia and ototoxicity. Amifostine is a cytoprotective drug that can diminish the toxicity of alkylating agents and platinum compounds. Therefore the effect of amifostine on toxicity and activity of weekly cisplatin was investigated in a randomized study.

*Patients and methods:* Patients with locally advanced, recurrent or metastatic head and neck cancer were eligible. Patients were randomized to weekly cisplatin 70 mg/m$^2$ for six cycles preceded by amifostine 740 mg/m$^2$, or cisplatin only. Cisplatin was administered in hypertonic saline (3% NaCl) as a one-hour infusion; amifostine was administered as a 15-minute infusion directly before the administration of cisplatin.

*Results:* Seventy-four patients were entered in the study. The median number of cisplatin administrations was 6 (range 2–6), equal in both arms. In both treatment arms the median dose intensity of cisplatin achieved was the planned 70 mg/m$^2$/week. In the cisplatin only arm 6 out of 206 cycles were complicated by thrombocytopenia grade 3 or 4 *versus* 1 of 184 cycles in the amifostine arm ($P$ = 0.035). Hypomagnesaemia grade 2 + 3 was significantly less observed in the amifostine arm ($P$ = 0.04). Neurotoxicity analyzed by serial vibration perception thresholds (VPT) showed a diminished incidence of subclinical neurotoxicity in the amifostine arm ($P$ = 0.03). No protective effect on renal and ototoxicity could be shown. Hypotension was the main side effect of amifostine but only of relevance in one patient. The antitumor activity of cisplatin was preserved as 63% of the evaluable patients in the amifostine arm responded compared to 50% of the evaluable patients in the cisplatin alone arm.

*Conclusion:* Our study indicated that in combination with weekly administered cisplatin amifostine reduced the risk of thrombocytopenia, hypomagnesemia as well as subclinical neurotoxicity, but did not result in a higher dose intensity of cisplatin. Addition of amifostine did not compromise the antitumor effect of cisplatin.

**Key words**: amifostine, cisplatin, cytoprotection, head and neck cancer

### Introduction

Approximately 50%–60% of the patients with head and neck cancer present at diagnosis with a locally advanced tumor stage III or IV. Treatment usually consists of surgery followed by radiotherapy or of high dose radiotherapy. However, these treatments yield a cure rate of only 30%–40%. Most patients will recur locoregionally, while 10%–15% will die from distant metastases [1]. Locally advanced head and neck cancer is highly responsive to chemotherapy. The combinations of cisplatin with both bleomycin and methotrexate or with a 96-hour continuous infusion of fluorouracil are considered to be the most active regimens with response rates of 60%–90%, of which 30%–35% complete [2, 3]. The contribution of induction chemotherapy on survival in locally advanced head and neck cancer is however, not clear [4]. In locally recurrent or metastatic disease the results of chemotherapy are very disappointing with response rates of only 20%–30%, of short duration and without demonstrable effect on survival [4].

For cisplatin a dose-response relation is suggested in several tumor types [5]. Therefore clinical studies with high-dose and high-dose intensity regimens are attractive. As nausea and vomiting can be treated more efficiently and as with vigorous hydration and the administration of cisplatin in hypertonic saline the risk of nephrotoxicity can be reduced [6, 7], neuro- and ototoxicity are now the most cumbersome cisplatin toxicities. In a phase II study of weekly cisplatin at a planned dose of 80 mg/m$^2$/week for six cycles in locally far advanced head and neck cancer a response was obtained in 51% of the patients, suggesting that cisplatin administered at a higher dose intensity is more active than at standard

doses. With this weekly schedule hematologic toxicity, especially thrombocytopenia, was the main reason for treatment delays or the reason to take patients off study. Other major toxicities were hypomagnesemia grade 2 + 3 in 20%, ototoxicity grade 2 + 3 in 18% and nephrotoxicity grade 2 + 3 in 5% of the patients [8]. Because of these side effects, only 9 out of 59 patients completed the treatment without interruption and reached the planned dose intensity of 80 mg/m$^2$/week.

Amifostine (WR-2721; Ethyol®) is an organic thiophosphate. In preclinical and clinical studies amifostine showed selective protection of normal tissues against radiation-induced toxicities and toxicities induced by alkylating agents and platinum compounds without influencing the anti-tumor effects of these treatments [9–14]. Amifostine is a prodrug that has to be converted into the active metabolite, the free thiol WR-1065. Selective protection of normal tissues is explained by the more rapid uptake of WR-1065 in normal cells as compared to tumor cells, which is due to the difference in membrane- and capillary bound alkaline phosphatase and differences in pH between normal and tumor cells [15]. As amifostine has a very short plasma half-life (< 10 minutes), the drug has to be administered directly before the administration of chemotherapy [15, 16]. Specific side effects reported of amifostine are hypotension, nausea, vomiting, sneezing, flushing, mild somnolence, hypocalcaemia (mostly asymptomatic) and very rarely allergic reactions [17, 18].

The EORTC Head and Neck Cancer Cooperative Group decided to explore the weekly cisplatin regimen in a randomized study comparing weekly cisplatin to weekly cisplatin with amifostine.

## Patients and methods

Patients in this study were required to have a histologic proof of squamous cell carcinoma of the mucous membranes of the head and neck, locally advanced disease stage III or IV, locally recurrent disease after previous radiotherapy and/or surgery or with distant metastases and with measurable lesions on CT-scan or MRI. Prior chemotherapy was not allowed with the exception of neoadjuvant chemotherapy > 12 months before entering this study. Further entry criteria included age between 18 and 70 years. WHO performance status ≤ 2, WBC count ≥ 4.0 × 10$^9$/l, platelet count ≥ 100 × 10$^9$/l, serum creatinine ≤ 120 μmol/l or creatinine clearance > 60 ml/min, liver function tests and bilirubin < 2.0 × the upper limit of the normal range, no suspicion of active infection. Excluded from the study were patients with undifferentiated carcinoma of the nasopharynx, patients with hypertension requiring more intensive medication than diuretics only, patients with concomitant neurological, psychological or medical disorders making them unsuitable for treatment or follow-up per protocol and patients with CNS involvement. All patients gave written informed consent.

Before the start of treatment patients had a full clinical work up with medical history, physical examination, measurement of indicator lesions, full hematological counts and serum chemistries, creatinine clearance, ECG, chest X-ray, baseline audiometry and neurologic examination, including estimation of the vibration perception threshold (VPT). The VPT was measured at the dorsum of the second metacarpal bone of both hands. All centers made use of a Vibrameter type IV (Somatic AB, Stockholm, Sweden).

During treatment the patients had weekly a medical history and physical examination taken, weekly determination of full blood counts, serum chemistries and creatinine clearance. Neurologic examination and audiometry were repeated after the 3rd and 6th cisplatin administration and, if possible, three and six months later.

Patients were registered and randomized at the EORTC New Drug Development Office in Amsterdam. Patients were stratified by institution and by disease extent (locally advanced *versus* locally recurrent or metastatic disease).

Response to treatment was assessed two weeks after the last cisplatin dose. The WHO criteria for evaluation of response were used; toxicity, with exception of amifostine-induced hypotension, was graded according to the NCI–CTC criteria.

For grading of amifostine related hypotension a modified grading system was used:

| | |
|---|---|
| Grade 0 | No hypotension. |
| Grade 1 | Hypotension not requiring amifostine interruption. |
| Grade 2 | Hypotension requiring interruption once. |
| Grade 3 | Hypotension requiring interruption more than once. |
| Grade 4 | Prolonged hypotension requiring dose reduction. |
| Grade 5 | Hypotension accompanied by complications or requiring other therapy than rapid saline infusion. |

*Study design*

Before starting the randomized study a feasibility study was performed in 14 patients to estimate the optimal amifostine dose and antiemetic schedule [19]. The feasibility study was considered necessary because experience with weekly administration of amifostine with cisplatin was lacking. An amifostine dose of 740 mg/m$^2$ was in that study better tolerated than the usual 910 mg/m$^2$. The subject of the randomized study was to compare toxicity and efficacy of both schedules. Based on the results of other studies, which showed considerable reduction of nephro- and neurotoxicity [11, 12], it was postulated that 30 fully evaluable patients per treatment arm would be sufficient to detect a significant reduction in nephro- and neurotoxicity [20]. After the randomized study a cisplatin-dose escalation study was planned in case a significant protective effect of amifostine was shown.

*Treatment schedule*

Patients were hospitalized weekly for 24 hours

*Antiemetic regimen*

The antiemetic regimen consisted of tiëthylperazine 6.5 mg p.o. four hours and 30 minutes before chemotherapy combined with ondansetron 8 mg 30 minutes before and 8 mg eight hours after chemotherapy plus dexamethasone 20 mg 30 minutes before and eight hours after chemotherapy.

*Cisplatin*

Standard prehydration consisted of 1 liter of normal saline or dextrose/saline with suppletion of 20 mmol KCl and 2 g $MgSO_4$ and was given over two hours. Cisplatin powder was dissolved in 250 ml of hypertonic saline (NaCl 3%) and administered at a dose of 70 mg/m$^2$ over one hour followed by posthydration with 4 liters of normal saline or dextrose/saline (with 80 mmol KCl and 8 g of $MgSO_4$) over 24 hours. In case of urine output < 100 ml/hour 100 ml of mannitol 20% and/or 10 mg furosemide was administered depending on the local practice of the institute.

*Amifostine*

Amifostine was supplied by USB Pharma Ltd, Watford, UK. Amifostine was dissolved in normal saline to a concentration of 50 mg/ml and was administered at a dose of 740 mg/m$^2$ as a rapid infusion over 15 minutes directly before the cisplatin was given. During the amifostine administration patients were kept in the supine position and blood pressure was measured at least every five minutes.

Before starting amifostine a threshold blood pressure was determined under which value amifostine had to be interrupted. The threshold mean systolic blood pressure was calculated by taking the average of three blood pressures taken within two hours before the amifostine administration.

The guideline for interruption of amifostine was:

| | Mean baseline blood pressure in mm Hg | | | | |
|---|---|---|---|---|---|
| | <100 | 100–119 | 120–139 | 140–180 | >180 |
| Decrease in systolic BP (mmHg) | 20 | 25 | 30 | 40 | 50 |

In case of a drop in blood pressure below the calculated threshold the amifostine infusion was interrupted and infusion of normal saline started. In case of return of blood pressure above the threshold within five minutes the amifostine infusion was restarted. In case the hypotension lasted >5 minutes amifostine was further withheld for that cycle and for the next cycle the amifostine dose was reduced by 25%.

Dose reductions of cisplatin were not allowed in this study. If at planned retreatment WBC were $<2.5 \times 10^9$/l and/or platelets were $<75 \times 10^9$/l the treatment was postponed until recovery above these values In case of a treatment delay >2 weeks patients were taken off study. The development of nephro- or neurotoxicity grade 2 and the development of clinical hearing loss were also reasons to take a patient off study.

### Statistics

Percentages were compared using the chi-square test (without correction for continuity). Variables with an approximately continuous distribution were compared between treatment groups with the signed-rank Mann–Whitney U-test. For comparisons over time within treatment groups the signed rank test of Wilcoxon was used (Stata 3.1; Stata Corporation, TX).

## Results

Seventy-four patients were randomized in the study. The patient characteristics are shown in Table 1. Both groups were well balanced according to gender, age and disease extent. Three patients pretreated with neoadjuvant chemotherapy >1 year before, were randomized to the cisplatin-amifostine arm. One patient randomized to the cisplatin-amifostine arm never started treatment and is excluded from the analysis.

In the amifostine arm in total 184 cycles of cisplatin were administered compared to 206 cycles in the cisplatin only arm ($P = 0.06$). In both treatment arms the median number of cisplatin administrations was 6 (range 2–6). The median cisplatin dose intensity achieved was equal in both treatment arms: 70 mg/m$^2$/week. The results are given in Table 2.

In the cisplatin–amifostine arm 20 patients completed six cycles (56%) *versus* 28 patients in the cisplatin only arm (76%) ($P = 0.07$). The main reason for this difference between both arms is the early death of three patients in the amifostine arm (two patients with known cardiovascular disease died at home, one patient died of asphyxia). Other reasons not to complete the six cycles in the combination arm were: progressive disease in three patients, delay due to leucopenia >2 weeks in four patients, ototoxicity in three patients, pneumonia in one patient, a protocol violation in one patient and in one patient the reason was 'physicians preference' because of planning of additional radiotherapy. The reasons not to complete six cycles in the cisplatin only arm were progressive disease in one patient, delay >2 weeks due to hematologic toxicity in four patients (neutropenia in two and combination of neutro-and thrombocyto-

*Table 1.* Patient characteristics randomized study.

| | Cisplatin + amifostine | Cisplatin only |
|---|---|---|
| Number of patients entered | 37 | 37 |
| Number of patients treated | 36 | 37 |
| Sex | | |
| Male | 27 | 28 |
| Female | 10 | 9 |
| Age (in years) | | |
| Median | 54 | 54 |
| Range | 35–69 | 36–67 |
| Performance status | | |
| Median | 1 | 1 |
| Range | 0–2 | 0–1 |
| Disease status | | |
| Locally advanced | 29 | 29 |
| Locally recurrent | 5 | 7 |
| Metastatic | 3 | 1 |
| Prior radiotherapy | 9 | 7 |
| Prior neoadjuvant chemotherapy | 3 | 0 |
| Localization primary tumor | | |
| Oral cavity | 4 | 7 |
| Oropharynx | 17 | 15 |
| Hypopharynx | 10 | 11 |
| Larynx | 3 | 3 |
| Nasopharynx | 2 | 1 |
| Maxillary sinus | 1 | 0 |
| Differentiation grade | | |
| Well differentiated | 19 | 15 |
| Moderately differentiated | 14 | 15 |
| Poorly differentiated | 4 | 7 |

*Table 2.* Treatment results randomized study.

| | Cisplatin + amifostine | Cisplatin | *P*-value |
|---|---|---|---|
| Number of patients treated | 36 | 37 | |
| Total number of cycles | 184 | 206 | 0.06 |
| Number of cycles per patient | | | |
| Median | 6 | 6 | |
| Range | 2–6 | 2–6 | |
| Patients completing six cycles | 20 | 28 | 0.07 |
| Without delay | 15 | 20 | 0.29 |
| Number of patients with delays | 5 | 9 | |
| For myelosuppression | 2 | 8 | 0.08 |
| Total number of weeks delayed for myelosuppression | 15 | 25 | 0.17 |
| Median cisplatin dose intensity achieved (mg/m$^2$/week) | 70 | 70 | |
| Reasons for <6 cycles | | | |
| Progressive disease | 3 | 2 | |
| Early death | 3 | 0 | |
| Hematologic toxicity | 4 | 3 | |
| Ototoxicity | 3 | 3 | |
| Infection | 1 | 1 | |
| Protocol violation | 1 | 0 | |
| Physician preference | 1 | | |

*Table 3* Toxicity analysis. CTC-grading, worst toxicity per patient.

| | Cisplatin + amifostine (grade) | | | | Cisplatin only (grade) | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Anemia | 11 | 19 | 2 | 0 | 14 | 15 | 3 | 0 |
| Leucopenia | 8 | 11 | 2 | 2 | 4 | 10 | 5 | 0 |
| Neutropenia | 5 | 9 | 8 | 2 | 5 | 6 | 10 | 1 |
| Thrombocytopenia | 19 | 7 | 0 | 1 | 11 | 4 | 2 | 3 |
| Nephrotoxicity | 6 | 2 | 0 | 0 | 4 | 0 | 0 | 0 |
| Ototoxicity | 6 | 6 | 3 | 0 | 3 | 10 | 4 | 0 |
| Neurotoxicity | 4 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| Nausea | 12 | 13 | 3 | 0 | 18 | 6 | 2 | 0 |
| Vomiting | 9 | 13 | 3 | 2 | 6 | 9 | 3 | 0 |
| Diarrhea | 2 | 0 | 1 | 0 | 5 | 2 | 0 | 1 |
| Stomatitis | 2 | 1 | 0 | 0 | 2 | 0 | 0 | 0 |
| Hypocalcemia | 6 | 2 | 2 | 0 | 7 | 2 | 1 | 0 |
| Hypokalemia | 7 | 0 | 0 | 1 | 7 | 5 | 0 | 0 |
| Hypomagnesemia | 8 | 6 | 0 | 0 | 7 | 7 | 7 | 0 |
| Hyponatremia | 13 | 4 | 0 | 0 | 17 | 4 | 3 | 0 |
| Hypophosphatemia | 5 | 1 | 1 | 0 | 7 | 0 | 0 | 0 |
| Alopecia | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Weight loss | 6 | 3 | 0 | 0 | 8 | 3 | 0 | 0 |
| Hypotension[a] | 4 | 6 | 2 | 3 | | | | |

[a] Amifostine induced hypotension, for grading see 'Patients and methods'.

penia in two), ototoxicity in three patients and a pneumonia in one patient.

*Toxicity analysis*

*Hematologic toxicity*

The hematologic toxicity is presented in Table 3. There was no difference in the occurrence of leucopenia ($P = 0.76$) and neutropenia ($P = 0.98$) between the two arms when analyzed per patient, nor when analyzed per cycle ($P = 0.130$ and $P = 0.953$, respectively). In the cisplatin only arm thrombocytopenia grade 3 + 4 was observed in five *versus* one patients in the combination arm ($P = 0.10$) and in 6 of 206 cycles in the cisplatin only *versus* 1 of 184 cycles in the combination arm ($P = 0.035$). In the combination arm four patients were taken off study because of treatment delay > 2 weeks due to slow bone marrow recovery (three patients with leucopenia and one patient with both leuco-and thrombocytopenia) and three patients in the cisplatin alone arm (two patients because of thrombocytopenia and one patient because of neutropenia). The total number of weeks delayed because of haematologic toxicity was not different between both arms: 15 weeks delay in the combination arm and 25 weeks in the cisplatin only arm ($P = 0.17$).

*Nephrotoxicity*

Nephrotoxicity grade 2, based on serum creatinine levels, was reported in two patients in the amifostine arm; one of the patients was taken off study after the fourth cisplatin administration during neutropenic fever and in the second patient grade 2 nephrotoxicity was reported after completion of treatment. In both patients the serum creatinine returned to baseline level during follow-up. Nephrotoxicity grade 1 was reported in five patients in the cisplatin only and in six patients in the combination arm. When creatinine clearances (calculated with the Cockroft–Gault formula) were compared cycle by cycle no differences between both treatment arms could be shown (Table 4). Although the median creatinine clearance decreased in the cisplatin only arm from 97 ml/min to 81 ml/min after six cisplatin cycles while the median clearance remained at least stable in the cisplatin–amifostine arm this difference was not statistically significant ($P = 0.12$; Mann–Whitney U-test).

*Table 4.* Renal toxicity.

| Cycle | Number of patients | | Median creatinine clearance[a] ml/min | | |
|---|---|---|---|---|---|
| | Cisplatin + amifostine | Cisplatin only | Cisplatin + amifostine | Cisplatin only | *P*-value |
| 1 | 36 | 37 | 82 | 97 | 0.09 |
| 2 | 36 | 37 | 82 | 91 | 0 38 |
| 3 | 34 | 35 | 87 | 90 | 0.44 |
| 4 | 31 | 34 | 86 | 85 | 0.82 |
| 5 | 27 | 31 | 87 | 85 | 0.46 |
| 6 | 20 | 28 | 84 | 82 | 0 83 |
| Post 6 | 20 | 28 | 89 | 81 | 0.32 |

[a] Calculated creatinine clearance by Cockroft–Gault formula.

*Hypomagnesemia/hyponatremia*

Hypomagnesemia grade 2 + 3 was observed in six patients in the combination arm *versus* in 14 patients in the cisplatin only arm ($P = 0.04$); there were 8 cycles in the combination arm complicated by hypomagnesaemia > grade 1 *versus* 27 cycles in the cisplatin only arm ($P = 0.004$). Clinical side effects related to hypomagnesemia were not reported. In the cisplatin only arm four patients had hyponatremia grade 3 + 4 *versus* none in the amifostine-arm ($P = 0.04$), but when hyponatraemia is analysed cycle by cycle this difference is not significant ($P = 0.163$).

There were no significant differences between both treatment arms in the occurrence in hypokalaemia, hypocalcaemia or hypophosphatemia.

*Neurotoxicity*

Clinical neurotoxicity grade 1 was reported in four patients in the combination arm and five patients in the cisplatin only arm. As neurotoxicity can develop after cessation of treatment the clinical neurotoxicity grading was based on worst symptoms up to three months after treatment. For the same reason the VPT analysis was done in patients in whom three-month VPT values were available. The mean cumulative cisplatin dose in the analyzed patients was 394 mg/m$^2$ in the combination arm *versus* 401 mg/m$^2$ in the cisplatin only arm. Details are shown in Table 5. VPT was measured at the dorsum of the second metacarpal bone of both hands and was recorded in micrometers of skin displacement. Per VPT-

examination three measurements were done and the mean of these three values was taken as value for the VPT as described previously [25]. In the table the median of these VPT-means are reported. The VPTs of the left hand show less increase in the amifostine arm compared to the cisplatin alone arm ($P = 0.03$). Due to an imbalance at baseline for the cisplatin–amifostine arm for VPT values of the right hand (due to the limited number of data) the increase of the VPTs for the right hand is not significant different ($P = 0.07$). This imbalance is probably caused by the low number of patients analyzed at three months as the median VPT for the right hand at baseline, when all patients in the amifostine arm are considered, was 0.73, identical to the VPT-values of the left hand.

*Table 5.* Neurotoxicity. VPT analysis (median values).

| | Cisplatin + amifostine | Cisplatin |
|---|---|---|
| Left hand baseline (all patients) | 0 77 | 0.77 |
| Right hand baseline (all patients) | 0.73 | 0.74 |
| Left hand baseline[a] | 0.70 | 0.65 |
| Left hand three months[a] | 0.85 | 1.13[b] |
| Right hand baseline[a] | 0.58 | 0 75 |
| Right hand three months[a] | 0.86 | 1.15[c] |

[a] Patients with VPT values at baseline and after three months follow-up. Fourteen patients in the cisplatin + amifostine arm; twenty patients in the cisplatin only arm.
[b] $P = 0.03$ and [c] $P = 0.07$ for difference in increase of VPT after treatment.

*Ototoxicity*

Although tinnitus was reported less frequent in the amifostine arm there was no difference in the occurrence of clinical ototoxicity grade 2 + 3 between both treatment arms ($P = 0.24$). Ototoxicity grade 3, clinical hearing loss, was reported in three patients in the combination arm and four patients in the cisplatin alone arm. Analysis of the serial audiometries in both arms of the study showed that hearing loss was only seen at the high-frequency levels (4000 and 8000 Hz). At 4000 Hz the median hearing loss was 15 decibels (db) in both ears, equal in both treatment arms. At 8000 Hz the median hearing loss was 30 db in both ears in the amifostine arm and 25 db in the right and 35 db in the left ear in the cisplatin only arm.

As many patients had already impaired hearing function at baseline, patients with 'normal' ears at baseline (<30 db hearing loss at 4000 and 8000 Herz) were analyzed separately. Also in this small subgroup (only six patients in the amifostine arm and nine in the cisplatin only arm) no difference in the audiologic parameters could be shown.

*Gastrointestinal toxicity*

Nausea and vomiting were reported slightly more frequent in the combination arm, not unexpected, as amifostine itself could cause these side effects. Vomiting grade 4 was reported in two patients in the amifostine arm. Other gastrointestinal side effects were equal in both treatment arms.

*Amifostine toxicities*

Hypotension (for grading system see section 'Patients and methods') during the infusion of amifostine was reported in 17 patients (47%) and in 45 out of 184 cycles (24%). Hypotension grade 3 was reported in two patients (three cycles) and grade 4 hypotension in three patients (four cycles), and occurred only during the first or second amifostine administration. In two patients hypotension did not recur after a 25% dose reduction according to the protocol. In one patient, grade 4 hypotension recurred despite dose reduction and amifostine was further withheld in this patient.

One patient died shortly after the second amifostine administration. This patient, with an obstructive local recurrence of oropharyngeal cancer, suffered from a hypotension (RR 70/50) nine minutes after the start of amifostine and the administration was interrupted. Shortly thereafter the patient became dyspnoeic because of airway obstruction by tough sputum, became unconsciousness and died shortly thereafter. The postmortem revealed asphyxia due to mechanical obstruction and pulmonary edema.

Other, minor, side effects of amifostine reported were dizziness (seven patients), flushing (six patients), feelings of anxiety (two patients), palpitations (three patients) and collapse (one patient) due to episodes of hypotension. A typical amifostine side effect is sneezing. This side effect was reported by six patients. Dizziness was also reported by five patients in the cisplatin only arm.

*Response analysis*

Although the main goal of the randomized study was comparison of toxicity all X-rays, CT-scans and MRI's of all responding patients as well as an at random selection of non-responding patients were independently reviewed by a radiologist experienced in head and neck oncology. In case of discrepancies between the response classification of the reviewer and the treating clinician the CT-scans or MRI's were reviewed by a team of the author's but in doubt the response was always rounded down to the least favorable response category. Ten patients were considered not evaluable for the following reasons: initial measurements performed with other techniques than at follow-up (five patients), missing CT-scans one patient, early death three patients, lost to follow-up one patient. In the amifostine group two patients obtained a complete response and 17 a partial response out of 30 evaluable patients (63%; 53% of eligible patients); in the cisplatin only arm 34 patients were evaluable for response and 17 had a partial response (50%; 46% of eligible patients). In patients with locally advanced disease there were 23 evaluable patients in the amifostine arm (1 CR and 15 PR: response rate 70%) and 26 in the cisplatin only arm (partial response

in 13 patients: 50%). The low number of complete responders can be attributed to the early time of response evaluation and the very strict criteria with which CT-scans and MRI's were judged. As all patients with locally advanced disease had radiotherapy starting two weeks after the last cisplatin administration and the treatment was left free for the other patient categories no information can be given on response duration. Analysis of survival will be a subject of a later report.

As a significant protection by amifostine of renal function and hearing could not be demonstrated with this cisplatin schedule the group decided not to embark on the dose escalation study.

## Discussion

The incidence of head and neck cancer in the western world is still rising and most patients present at diagnosis with stage III or IV tumors. In locally advanced disease cisplatin containing neoadjuvant chemotherapy is frequently given although the real value of neoadjuvant chemotherapy still has to be proven [4]. The combination of cisplatin with continuous infusion of fluorouracil is generally considered to be the standard regimen. However, side effects of this regimen (nausea, vomiting, lengthy hospital stays, phlebitis- or the need for central venous access) are a frequent cause of patient noncompliance. Regimens with shorter hospital stays might be more attractive to this particular patient group.

We previously explored a regimen with weekly administration of cisplatin, aiming at a treatment with a high dose intensity. The patient compliance in that study was good and 60% of the evaluable patients responded [8]. Toxicity, mainly thrombocytopenia, ototoxicity and renal toxicity, precluded completion of the six planned cycles in 40% of the patients, however, and the median cisplatin dose intensity achieved was 60 mg/m$^2$/week in stead of the planned 80 mg/m$^2$/week. Measures to reduce the toxicity of this schedule were thus considered worthwhile to explore.

Amifostine (WR-2721) is one of several cytoprotective drugs that entered clinical trials the last decade. WR-2721 is a prodrug; the active metabolite, the free thiol WR-1065 accumulates rapidly in normal cells but slowly in tumor cells [22]. WR-1065 is a potent scavenger of oxygen-free radicals and binds to active platinum species thereby preventing platinum-DNA adduct formation [23]. Because of the short half life of WR-1065 the drug was administered directly before cisplatin and for the same reason cisplatin was administered over one hour. As the phase I studies of amifostine suggested that patients with head and neck cancer are more prone to hypotension than patients with other tumor types we started a feasibility study first to test the combination of amifostine and cisplatin in a weekly regimen. With an amifostine dose of 740 mg/m$^2$ the risk of hypotension was low. In the randomized study hypotension grade 3 + 4 occurred in five patients and always during the first or second cycle. Other side effects reported, palpitations, feelings of anxiety and drowsiness, were mainly related to the hypotensive episodes and were of minor importance. A typical side effect is sneezing.

In the present study the comparison of cisplatin toxicities was the main interest. Protection of bone marrow toxicity by amifostine was limited to protection of thrombocytopenia only. Treatment delays due to hematologic toxicity never occurred before the fourth cycle. The number of cycles delayed because of hematologic toxicity was not different between both arms and. the cisplatin dose-intensity after three cycles and over-all are equal between both arms. The observation of protection against thrombocytopenia is in agreement with observations in animal studies with carboplatin and fluorouracil where amifostine selectively protected the animals from developing thrombocytopenia [22]. It is also in agreement with other randomized studies in patients treated with various cytotoxic agents (alkylating agents, platinum compounds, mitomycin C) with or without amifostine [12–14].

We could not show a protective effect on renal toxicity in this study. The incidence of renal toxicity was low in both arms of the study. Therefore, any additional effect of amifostine would have been difficult to show. This low incidence can be explained by the use of hypertonic saline and the vigorous hydration program in this study. In a large randomized study in ovarian cancer a significant protective effect of amifostine on the renal function was shown [12]. In that study, patients were treated with cisplatin-cyclophosphamide with or without amifostine every three weeks. Apart from the addition of cyclophosphamide, a less vigorous hydration schedule and a higher dose of cisplatin per cycle may have contributed to the higher incidence of renal toxicity as in the group treated without amifostine 30% of the patients had a decrease of $>40\%$ in the calculated creatinine clearance.

With respect to the development of hypomagnesemia, an indication of tubular damage induced by cisplatin [24], the occurrence of grade 2 and 3 hypomagnesemia was significantly less in the combination arm, which is in agreement with the results of the study of Kemp et al. [12]. Although major symptoms such as epileptic seizures, ventricular tachycardias and cortical blindness fortunately occur only in a minority of patients, minor complaints such as muscle weakness, anorexia and nausea are frequently reported. Several randomized studies showed the importance but also the limited succes of magnesium supplementation [25] making the protective effect of amifostine of value in the subgroup of patients at risk for this side effect.

The third cisplatin toxicity on which amifostine showed a protective effect in a previous study is neurotoxicity [11]. In our study measurement of the VPT was selected as VPTs are a more objective and sensitive indicator of neurotoxicity than the clinical CTC criteria [26, 27]. As cisplatin neurotoxicity can become manifest up to three months after the last cisplatin dose [28] VPTs were separately analyzed in the patients with three months

follow-up. Unfortunately the number of patients with long-term follow-up was less than expected which hampers a complete analysis. The increase in VPT was less in the amifostine arm and VPT values stayed well below the values we obtained in previous studies with cisplatin only, which is highly suggestive of a protective effect of amifostine [28]. Additional studies with more patients and more complete follow-up data will be needed.

The fourth major cisplatin toxicity in which we were interested, and which is reported frequently in high-dose schedules, is ototoxicity. In contrast to neurotoxicity, the risk of ototoxicity is more dependent on the cisplatin dose per cycle than the cumulative dose. Also the cisplatin peak plasma levels, which are high with a one-hour infusion, are of influence [29, 30].

In this study a protective effect was not shown, neither when analyzed by audiometry nor when graded on complaints. A recently published study on protection of cisplatin induced ototoxicity in hamsters showed that amifostine had no effect while sodium thiosulfate was more active [30]. This preclinical study fits well with our observation and further studies on prevention of ototoxicity are of utmost importance.

Amifostine itself had manageable side effects. The drug compares in this way favorable with other cytoprotective agents. Diethyldithiocarbamate (DDTC), a heavy metal chelating agent, is an effective protector in animal studies. However, its side effects in patients limit its use [32]. Sodiumthiosulfate and probenecid [33, 34] have the disadvantage that they only protect the kidneys while for sodiumthiosulphate inhibition of cisplatin activity is suggested [34]. A recently published randomized phase II trial in advanced gastric cancer, treated with a weekly chemotherapy regimen of cisplatin 40 mg/m$^2$ plus or minus reduced gluthation (GSH), showed significantly less neurotoxicity and less treatment delays due to thrombocytopenia in the GSH arm [35]. In that study no clinical ototoxicity was observed, probably related to the low cisplatin dose per cycle. Data on nephrotoxicity or mineral disorders were not reported.

The response rate we observed in locally advanced disease of 70% in the combination arm and 50% in the cisplatin only arm is somewhat lower than reported for most combination regimens [2–4], however, the patients in our study all had extensive irresectable disease. The fear that amifostine would not only protect normal tissues but also tumor tissue is not confirmed as the response rate in the amifostine arm was even slightly higher than in the cisplatin only arm. Amifostine thus showed a protective effect in this study on three organ systems. However, in the combination arm the cisplatin-dose intensity was not higher than in the cisplatin only arm. For this reason, and due to the lack of protection on ototoxicity, it was decided not to continue with the planned dose-escalation study. As amifostine also protects normal tissues from late radiation damage [11] further studies with amifostine and cisplatin or carboplatin plus radiotherapy in head and neck cancer are warranted.

## Acknowledgements

The authors wish to thank the otolaryngologists and radiologists of the participating hospitals for their skillful evaluation of patients, the neurologists for their help in the evaluation of neurotoxicity, the research nurses for their assistance during chemotherapy administrations and the data managers for their continuous support during this study. We are very grateful to P. I. M. Schmitz, PhD, for his help of the statistical analysis.

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Received 28 January 1999; accepted 20 April 1999.

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