Radiol Oncol 1999; 33(2): 153-7.

# Chemical radioprotection (WR-2721) in patients with head and neck cancer

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***Background and methods.*** *Amifostine was given as daily intravenous application (200mg/m2) 10-15 minutes prior to radiotherapy in 36 patients with locally advanced head and neck tumors to spare normal tissues, such as the salivary glands and oral cavity, from irradiation. Postoperative radiotherapy was carried out to a complete dose of 60 Gy given in 30 days, with single doses of 2 Gy. Side effects of radiotherapy were assessed using the WHO-criteria.*

***Results.*** *According to the WHO-score, mucositis occurred in 10 patients (grade I) and 26 patients (grade II). Dysphagia was recorded in 10 patients as grade I and in 12 patients as grade II. Xerostomia was established as grade I in 14 patients and as grade II in 16 patients. Skin reactions were grade I in 9 patients and grade II in 13 patient. Drug-related toxicity was recorded in 12 patients: hypotension grade I and nausea grade I were observed in 3 patients, while vomiting grade I and grade II were documented in 3 and 1 patient respectively.*

***Conclusions.*** *According to the data from the literature, we believe that the application of amifostine is feasible, and amifostine is an effective radioprotector decreasing both acute and late side effects in patients irradiated for head and neck tumors.*

*Key words: head and neck neoplasms - radiotherapy; radiotherapy - adverse effects; radiation - adverse effects; amifostine*

## Introduction

Radiotherapy for head and neck tumors can produce significant acute and chronic side effects, such as mucositis and xerostomia, because in many cases most of the salivary glands as well as the major integral volume of the oral cavity are included in the irradiation portals.[1]

The degree and duration of radiation damage to the oral mucosa and to the salivary glands is related to the total dose of radiotherapy, to fractionation, to the volume of the treatment fields and the overall treatment time.[2-5] In some cases severe mucositis can lead to a pause in radiotherapy and therefore to treatment delay.6 In a particular situation every day of treatment delay will decrease the probability of remission rate.[6]

Received 30 June 1998
Accepted 15 December 1998

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On the other hand, xerostomia is one of the most severe and definitive side effects in patients with head and neck tumors. Xerostomia will significantly undermine the quality of life of those patients. In the past it had been impossible to avoid these side effects by modifying the schedule of radiation therapy or using oral mucosa protecting drugs.

After World War II, in 1949, investigations directed into finding an effective radioprotective agent were started at Walter Reed Army Institute of Research.[7] More than 4400 substances had been investigated, and in terms of side effects, WR-2721 or amifostine was the most effective and compatible agent.[7] Since 1995 the use of amifostine in medicine has been permitted in Germany. Hence, after the introduction of a new radioprotective agent there is a new approach to spare normal tissue.

Amifostine is a pro-drug and must be converted to the active free thiol by the membrane-bound alkaline phosphatase.[8,9] Yang *et al.* have shown that the number of membrane-bound alkaline phosphatase is significantly higher in normal than in tumor cells.[10] So amifostine will be dephosphorylated and activated faster in normal than in tumor cells.[11,12] During the first 30 minutes after infusion, the concentration of the agent in normal cells is 102 -103 times higher than in tumor cells.[12] This difference produces a selective protection of healthy cells while there is no protection of tumor cells, because of a very low concentration of the agent in tumor cells directly after infusion. In the cells amifostine works by direct protection of the DNA. The free thiol protects against radiation damage by acting as a free radical scavenger, and by donating hydrogen to repair damaged target molecules.[13-15] It is worth mentioning that so far the exact mechanism of action in radioprotection has not been fully understood. In the last years a series of normal tissues have been studied to evaluate tissue protection factors for amifostine.[16,17] Tissues with high protection factors are especially bone marrow (factor 3.0), immune system (factor 3.4), epidermis (factor 2.4), salivary glands (factor 2.0), oral mucosa (factor>1).[16,17] That is why amifostine is given recently as a radioprotector in patients with advanced head and neck tumors, because mucositis and xerostomia are severe acute and late side effects, which can decrease life quality.

## Patients and methods

Since 1995 we have treated 36 patients with advanced head and neck tumors applying amifostine daily before radiotherapy. Amifostine at a dosage of 200 mg/m$^2$ was given 10-15 minutes before irradiation. The substance was administered as short infusion over a period of 15 minutes.

During application, blood pressure was measured before, during and after infusion. All patients had given their informed consent to therapy. Patients with a blood pressure below 100 mmHg were excluded. All patients were male. Their median age was 52 years (range: 42-66).

All patients had undergone a complete resection of the gross tumor and a unilateral or bilateral neck dissection. Only patients with primary tumors were investigated.

It is very important that the irradiation takes place within 30 minutes after infusion because the difference in concentration between healthy and tumor cells will decrease significantly in correlation with time. Radiotherapy was given in 5 fractions per week, with single doses of 2 Gy over 6 weeks, to a total dose of 60 Gy. At least 75% of the salivary glands and 2/3 of the oral cavity were included in the irradiation fields. Postoperative irradiation was carried out on a linear accelerator (6 MV) using opposed irradiation portals. The target volume was defined as previous gross tumor site includ-

ing the area of regional lymph nodes. The target volume was irradiated up to a total dose of 36 Gy, given according to the above described fractionation. Afterwards, the irradiation fields were divided into anterior photon and posterior electron fields to spare the radiosensitive spinal cord. The choice of posterior electron energy was based on the axial CT-imaging defining the distance between the skin surface and the spinal cord. Retrospective analysis of the irradiation technique shows an absolute dose homogeneity for the complete target volume and especially for the salivary glands and oral cavity.

The irradiated parts of these had been included within the 100% isodose. The median follow-up for the patients is calculated to be 17 months (range: 3-24 months) up to now. The grade of irradiation-related side effects of as well as drug toxicity were documented using the WHO-score.[18] During radiotherapy, every patient underwent clinical check up once weekly. After completed radiotherapy, the patients were followed up clinically every month to evaluate late effects after irradiation.

## Results

Because of hypotension amifostine administration had to be discontinued in 12 patients. In every case the infusion could be completed within a few minutes without antihypotensive therapy. There were no cases of dizziness, sneezing or flushing, nor other allergic side effects observed. Nausea grade I was recorded in 3 patients, vomiting grade I and II in 3 and 1 patients, respectively. Hence, administration of amifostine proved to be feasible and non-toxic. Daily application of 200 mg/m$^2$ amifostine prior to radiotherapy entails no toxicity grade III or IV, according to WHO.

In terms of radioprotection, we have obtained the following results (Table 1):

**Table 1.** Different side effects according to the WHO-score in patients with and without amifostine

| WHO- grade | Grade I | Grade II |
|---|---|---|
| Mucositis | 10 | 26 |
| Dysphagia | 10 | 12 |
| Dermatitis | 9 | 13 |
| Xerostomia | 14 | 16 |

Mucositis grade I was documented in 10 patients, and grade II in 26 patients. Dysphagia grade I and II occurred in 10 and 12 patients, respectively. Dermatitis was evaluated as grade I in 9 patients, and as grade II in 13 patients. Xerostomia grade I was seen in 14 patients, and grade II in 16 patients. There were no cases of grade III or IV side effects due to high dose irradiation (60 Gy/30 days) recorded.

## Discussion

In our investigation, the use of radioprotector amifostine resulted in a marked decrease in typical side effects related to high-dose radiotherapy for head and neck tumors. The results are in agreement with a number of other studies.

In 1994, Mc Donald *et al.* described a decrease in xerostomia during and after radiotherapy in 9 patients measuring the salivary function.[1] In this investigation a good feasibility of the drug was documented, but no sparing of acute mucositis during radiation was found when amifostine was administered at a dosage of 100 mg/m $^2$.

Dendale and colleagues have investigated mucositis in rodents, using different doses of amifostine before irradiation.[19] In 3 groups altogether 24 animals got a total irradiation dose of 24 Gy, with single doses of 4 Gy after 40 mg/kg, 200 mg/kg and 400 mg/kg amifostine given intraperitoneally. The results were scored and there was no significant difference seen between the 3 doses of amifostine,

whereas the difference between any amifostine group and the crude radiotherapy group was highly significant.

Bohuslavizki *et al.* administered 500 mg/m$^2$ amifostine to patients with cancer of the thyroid before iodine therapy.[20] Although the number of patients was very small, xerostomia was calculated to be 37% in the group treated by radiotherapy alone (n=9), and none in the amifostine group (n=8).

From Munich we have got some preliminary results using amifostine in patients with ENT - relapses.[21,22] All the patients (n=40) received another dose of radiotherapy (40 Gy), combined with 350 mg/m$^2$ 5-FU and 300 mg/m$^2$ amifostine in the state of recurrence. A mucositis grade I or II was documented in 4 patients only. Buenzel *et al.* have published some reliable data from a prospective randomized phase-II study including 39 patients.[23,24] One group was given radiotherapy to a complete dose of 60 Gy in 30 days with concurrent administration of carboplatin (70 mg/m$^2$, day 1-5 + day 21-25) with or without 500 mg amifostine. There was a highly significant decrease in the incidence of mucositis, xerostomia and thrombopenia noted in the patients who received amifostine.

The follow-up time was 12 months, the disease free survival rate was 79% in the amifostine and 64% in the radiochemotherapy group, respectively. Complete response was 72% in the amifostine and 43% in the control group. Hence, this could be regarded as convincing evidence that there is no shielding of tumor cells. Similar data were reported by Füller and colleagues.[25]

Because of those promising preliminary data, the RTOG started a prospective randomized phase III-study in patients with head and neck tumors stage III and IV. In the study, a radiotherapy dose of 70 Gy was given in 35 fractions with or without amifostine 200 mg/m$^2$.[26] In the amifostine group the rate of xerostomia was reduced significantly (p=0,0004), and the time to the onset of xerostomia was significantly longer (p=0,0001). The preliminary results in the literature have shown that there is no sparing of tumor cells by amifostine[27], so that up to now survival time and disease free survival time have not been significantly different in amifostine and control groups.

In their investigation, Mc Donald *et al.* administered 100 mg/m$^2$ amifostine.[1] While this dose failed to prevent the onset of mucositis, doses between 200 mg/m$^2$ and 300 mg/m$^2$ amifostine proved successful in reducing this side effect.

Dendale *et al.* have shown a dose dependent correlation between incidence of mucositis and dose of amifostine.[19] The optimal dose of amifostine still remains to be established.

In conclusion, considering our data we believe that amifostine is an effective radioprotector able to decrease acute as well as late side effects in patients irradiated for head and neck tumors.

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