Feasibility and Efficacy of Subcutaneous Amifostine Therapy in Patients With Head and Neck Cancer Treated With Curative Accelerated Concomitant-Boost Radiation Therapy

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Objective: To assess the feasibility and efficacy of subcutaneous amifostine therapy in patients with head and neck cancer treated with curative accelerated radiotherapy (RT).

Design: Retrospective study.

Setting: University of Lausanne, Lausanne, Switzerland.

Patients: Thirty-three consecutive patients (male-female ratio, 4:5; median age, 54 years [age range, 39-76 years]).

Interventions: Between November 2000 and January 2003, the 33 patients were treated with curative definitive (n=19) or postoperative (n=14) RT with (n=26) or without (n=7) chemotherapy. All patients received conformal RT. Fractionation schedule consisted of concomitant-boost (Friday afternoon session) accelerated RT using 70 Gy (2 Gy per fraction) in 6 weeks in patients treated with definitive RT and 66 Gy (2 Gy per fraction) in 5 weeks and 3 days in the postoperative setting. Parotid glands received at least 50 Gy in all patients. Amifostine was administered to a total dose of 500 mg subcutaneously, 15 to 30 minutes before morning RT sessions.

Results: All patients received their planned treatment (including chemotherapy). Ten patients received the full schedule of amifostine (at least 25 injections), 9 received 20 to 24 doses, 4 received 10 to 19 doses, 5 received 5 to 9 doses, and 5 received fewer than 5 doses. Fifteen patients (45%) did not show any intolerance related to amifostine use. Amifostine therapy was discontinued because of nausea in 11 patients (33%) and hypotension in 6 patients (18%), and 1 patient refused treatment. No grade 3, amifostine-related, cutaneous toxic effects were observed. Radiotherapy-induced grade 3 acute toxic effects included mucositis in 14 patients (42%), erythema in 14 patients (42%), and dysphagia in 13 patients (39%). Late toxic effects included grade 2 or more xerostomia in 17 patients (51%) and fibrosis in 3 patients (9%). Grade 2 or more xerostomia was observed in 8 (42%) of 19 patients receiving 20 injections or more vs 9 (64%) of 14 patients receiving fewer than 20 injections (P=.15).

Conclusions: Subcutaneous amifostine administration in combination with accelerated concomitant-boost RT with or without chemotherapy is feasible. The major adverse effect of subcutaneous administration was nausea despite prophylactic antiemetic medication, and hypotension was observed in only 6 patients (18%).


Radiation therapy (RT) is widely used in head and neck cancer as a single treatment modality or used in combination with surgery with or without chemotherapy. Skin, mucosa, subcutaneous tissues, bone, and salivary glands are often affected when RT is given in curative intent. Salivary glands, particularly parotid glands, are frequently included in the planning treatment volume. Their functional damage depends on the RT dose and the exposed volume. Serous cells present in the parotid glands are very radiosensitive and die mostly by apoptosis. Xerostomia, one of the most important RT-induced late toxic effects, can alter the quality of life. Amifostine, or WR-2721 (Ethylol; Essex-Chemie AG, Lucerne, Switzerland), is an organic thiophosphate protecting normal tissues from free radicals produced by RT and/or chemotherapy. Many prospective studies have demonstrated the radioprotective effect of amifostine in several cancers.

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The major toxic effect of amifostine is hypotension, along with severe nausea and vomiting, especially when used intravenously. When administered subcutaneously, amifostine has the same bioavailability compared with its intravenous use. Thereafter, the subcutaneous administration of amifostine was developed and subsequently reported to be well tolerated, less...
time consuming, and less toxic, but the clinical experience is limited. In the present study, we report our experience using subcutaneous amifostine in patients with head and neck cancer treated with curative accelerated concomitant-boost RT with or without chemotherapy.

## METHODS

Between November 2000 and January 2003, 33 consecutive patients included in this retrospective study were treated with curative definitive (n=19) or postoperative (n=14) RT with (n=26) or without chemotherapy. The male-to-female ratio was 4.5:1, and the median age was 54 years (range, 39-76 years). All patients were assessed by our multidisciplinary head and neck tumor board consisting of the head and neck surgery, radiation oncology, medical oncology, pathology, diagnostic radiology, dental care, and nutritional care teams. Inclusion criteria consisted of nonmetastatic locally advanced head and neck cancer to be treated with postoperative or definitive RT with or without chemotherapy, age younger than 80 years, good performance status (World Health Organization scale, 0-1), no history of cancer other than nonmelanoma skin cancer or in situ cervical cancer, and parotid glands to be included in the planning RT volume. Exclusion criteria consisted of any severe cardiovascular disease, age 80 years or older, previous RT or chemotherapy, metastatic disease, or unilateral or bilateral parotid gland protection. Patient characteristics are given in Table 1. Full diagnostic workup, including complete history review, physical examination, computed tomography and/or magnetic resonance imaging of the head and neck region, chest radiography, complete blood cell count and chemistry tests, and electrocardiography, was performed in all patients. Bone scintigraphy and/or thoracoabdominal computed tomographic scan was performed when needed. The T classification according to the International Union Against Cancer included 10 patients with T1 to T2 tumors and 23 with T3 to T4 tumors. The N classification included 15 patients with N0 to N1 disease and 18 with N2 to N3 disease. Postoperative RT was indicated because of positive surgical margins, extracapsular nodal infiltration, 3 or more positive nodes, or pT4 tumors. All but 1 patient treated with definitive RT received concomitant chemotherapy (100 mg/m² of cisplatin intravenously on days 1, 22, and 43 in combination with 1 g/m² of fluorouracil given in continuous intravenous perfusion on days 1-5, repeated every 3 weeks). Of 14 patients treated with postoperative RT, 8 received 100 mg/m² of adjuvant concomitant cisplatin chemotherapy on days 1, 22, and 43. All patients received 3-dimensional conformal RT evaluating dose-volume histograms not only for target volume but also for parotid glands. Patient immobilization was accomplished using individualized thermoplastic masks, and the irradiation source was either a telecobalt unit or a linear accelerator using 6-MV photons and electrons. Radiotherapy consisted of a concomitant-boost accelerated schedule delivering a total dose of 66 Gy in the postoperative setting or 70 Gy in patients treated with definitive RT. Fractionation was 2 Gy per fraction. The duration of the treatment was 5 weeks and 3 days in postoperative patients and 6 weeks in definitive RT patients. Radiotherapy was delivered with a single daily fraction from Mondays to Thursdays and in 2 fractions (6-hour interval) on Fridays. Parotid glands received at least 50 Gy in all patients. All patients were pretreated with a daily 200-mg dose of oral dolasetron mesylate (Anzemet; Sanofi-Aventis, Geneva, Switzerland) 1 to 2 hours before the subcutaneous injection of amifostine. A total dose of 500 mg of amifostine was diluted in 2.5 mL of isotonic sodium chloride solution and injected subcutaneously in 1 site of the abdominal area, alternating every day, 15 to 30 minutes before every RT fraction except Friday afternoon sessions. Blood pressure was monitored daily before amifostine injection and after RT session. Acute and late toxic effects were scored according to the National Cancer Institute Common Toxicity Criteria version 2.0 and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer system, respectively.

Means were compared using the unpaired, 2-tailed t test, and proportions were compared using the chi-squared test or the Fisher exact test for values of 5 or greater or using the Fisher exact test for those less than 5. Survival rates were computed using the product-limit method. All causes of death were considered as an event, and living patients were censored.

All patients received their planned treatment (including chemotherapy). According to the dose-volume histogram analyses, all patients fulfilled the criteria of the International Committee on Radiation Units, and parotid glands were bilaterally included in the elective RT volume receiving at least 50 Gy.

Ten patients (30%) received the full schedule of amifostine (ie, at least 25 subcutaneous amifostine injections during the first 5 weeks of treatment when the parotid glands were included in the RT volume). Nine patients (26%) received 20 to 24 doses, 4 (14%) received 10 to 19 doses, 5 (15%) received 5 to 9 doses, and 5 (15%) received fewer than 5 doses. Fifteen patients (45%) did not show any intolerance related to amifostine. Amifostine therapy was discontinued because of nausea and vomiting in 11 patients (33%) and hypotension in 6 patients (18%), and 1 patient refused treatment. No grade 3, amifostine-related, cutaneous toxic effects were observed. Radiotherapy-induced

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%) (N = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (82)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (18)</td>
</tr>
<tr>
<td><strong>Site of primary tumor</strong></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Larynx</td>
<td>4 (12)</td>
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<tr>
<td><strong>Radiotherapy</strong></td>
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<tr>
<td>Definitive</td>
<td>19 (58)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>14 (42)</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Cisplatin alone</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Cisplatin and fluorouracil</td>
<td>18 (55)</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>7 (21)</td>
</tr>
</tbody>
</table>

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acute and late toxic effects are given in Table 2. Prophylactic percutaneous endoscopic gastrostomy was performed in 18 patients (55%) according to our institutional indications.19 Seven patients (21%) did not require any nutritional support, whereas a nasogastric feeding tube was required in 8 patients (24%). Weight loss ranged between 0 and 13 kg (median, 4.5 kg). Late toxic effects included grade 2 or more xerostomia in 17 patients (51%) and fibrosis in 3 patients (9%). Grade 2 or more xerostomia was observed in 8 (42%) of 19 patients receiving 20 amifostine injections or more vs 9 (64%) of 14 patients receiving fewer than 20 injections (P = .15).

During a median follow-up period of 2 years (range, 8-37 months), 2-year overall survival was 74% (95% confidence interval, 56%-92%) (Figure). One patient died of chemotherapy-related toxic effects. The 2-year locoregional control rate was 81% (95% confidence interval, 65%-97%). Seven patients relapsed: nodal progression occurred in 4 patients (one with local relapse and another with distant metastases), and systemic progression alone occurred in 3 patients.

### Table 2. Acute and Late Toxic Effects According to NCI CTC Version 2.016 and the RTOG/EORTC System, Respectively

<table>
<thead>
<tr>
<th>Toxic Effect</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xerostomia</td>
<td>0</td>
<td>4 (12)</td>
<td>16 (49)</td>
<td>13 (39)</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0</td>
<td>5 (16)</td>
<td>14 (42)</td>
<td>14 (42)</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>9 (27)</td>
<td>10 (30)</td>
<td>14 (43)</td>
<td>0</td>
</tr>
<tr>
<td>Skin erythema</td>
<td>0</td>
<td>2 (6)</td>
<td>4 (12)</td>
<td>4 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Late</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xerostomia</td>
<td>4 (13)</td>
<td>12 (36)</td>
<td>12 (36)</td>
<td>5 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>7 (21)</td>
<td>23 (70)</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: NCI CTC, National Cancer Institute Common Toxicity Criteria; RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

### Figure

Overall survival in 33 patients with locally advanced head and neck cancer treated with definitive or postoperative radiotherapy with or without chemotherapy.

Many prospective phase 2 or 3 studies in different cancers using intravenous amifostine as a radioprotector showed its efficacy in significantly decreasing late toxic effects.6-10,29 In a phase 3 randomized trial comparing RT with or without intravenous amifostine, Brizel et al6 reported that grade 2 or more acute or late xerostomia was significantly decreased in favor of the amifostine arm without any influence either on survival or locoregional control. A phase 2 randomized study comparing RT and concomitant chemotherapy with or without intravenous amifostine revealed that grade 2 xerostomia was significantly decreased in favor of the amifostine arm.30 With the radioprotection doses (200-300 mg/m²), hypotension (5%-15%) and nausea and vomiting (5%-10%) are the main adverse effects of amifostine, resulting in noncompliance by some patients.5,28

Intravenous administration of amifostine has been approved by the US Food and Drug Administration and recommended by the 2002 American Society of Clinical Oncology guidelines for xerostomia reduction during head and neck RT; however, subcutaneous administration has not yet been approved.31 Subcutaneous use of amifostine was introduced to decrease its complications and improve the daily practice by reducing the duration of its administration and the necessity of specialized nurs-
ing, therefore, lowering the cost of the treatment. When used subcutaneously, a 20- to 60-minute interval between amifostine administration and RT session is recommended by different authors. Our choice was an interval between 15 and 30 minutes to obtain an increased differential uptake between the salivary glands and tumor. When used with conventional RT fractionation, subcutaneous amifostine-related (500-mg total dose) systemic grade 3 or 4 toxic effects consist mainly of asthenia (6%), fever (6%), allergic reactions (6%), and cutaneous rash (6%). Local erythema at the injection site occurs in about 10% of the patients. In our study, assessing the feasibility and the efficacy of amifostine in 33 patients treated with curative doses of accelerated concomitant-boost RT with or without chemotherapy, amifostine therapy was discontinued because of nausea and vomiting in 11 patients (33%), hypotension in 6 (18%), and patient refusal in 1 (3%). Fifteen patients (45%) did not show any intolerance related to amifostine. No grade 3, amifostine-related, cutaneous toxic effect was observed. Patients in our series experienced more nausea and vomiting or hypotension compared with the 3% of patients who experienced grade 2 or higher nausea and vomiting or hypotension reported by Koukourakis et al. A possible explanation is that most (79%) of our patients received concomitant chemotherapy, which makes it difficult to make a clear distinction between amifostine- and chemotherapy-induced toxic effects.

When used intravenously, prehydration is recommended to prevent amifostine-induced toxic effects. However, subcutaneous administration of amifostine is reported to be well tolerated in terms of hypotension and other adverse effects without needing prehydration. Nonetheless, patients are encouraged to consume several glasses of water before treatment to ensure adequate hydration. On the other hand, when administered with concomitant cisplatin, which is also a high-potential emetogenic drug, adequate antiemetic therapy, prehydration, and careful monitoring are warranted.

We conclude that subcutaneous amifostine administration with accelerated concomitant-boost RT is feasible. Compared with intravenous administration, the major adverse effect of subcutaneous administration was nausea and vomiting despite prophylactic antiemetic medication without prehydration, and hypotension was observed only in 18% of the patients.

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Author Contributions: Dr Ozsahin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES


Announcement

Trial Registration Required

In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Otolaryngology—Head & Neck Surgery will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov or http://controlled-trials.com). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the June issue of Archives of Otolaryngology—Head & Neck Surgery (2005;131:479-480). Also see the Instructions for Authors on our Web site: http://www.archoto.com.