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ORIGINAL ARTICLE

A randomized trial of amifostine as radioprotector in the radiotherapy of head and neck cancer

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Summary

Purpose: *Radiotherapy (RT) for head and neck cancer typically involves the major salivary glands bilaterally and can cause acute and chronic xerostomia and mucositis.*

The degree of xerostomia has been reported to depend on the radiation dose and the salivary gland volume irradiated. In this study, we evaluated the efficacy of the radioprotector amifostine to improve xerostomia and mucositis in head and neck cancer patients who received RT.

Patients and methods: *A total of 53 patients with head and neck cancer entered this prospective randomized study. Patients were randomly assigned to undergo RT or RT plus short intravenous (i.v.) infusion of amifostine 210 mg/m² before each RT fraction.*

Results: *No statistically significant difference was seen between the 2 arms in terms of mucositis. Acute xerostomia occurred in 31 (93.9%) patients in the amifostine arm and all of the patients in the RT-alone arm ($p < 0.05$). Grade 3 acute xerostomia occurred in 13 (39.3%) patients in the amifostine arm, and in 9 (45%) patients in the RT-alone arm ($p=0.04$). Late xerostomia occurred in 19 (57.5%) patients in the amifostine arm, and in 14 (70%) patients in RT-alone arm ($p=0.03$).*

Conclusion: *The administration of amifostine in head and neck cancer patients receiving RT improved significantly acute and late xerostomia, while did not offer protection in the prevention of mucositis. Further prospective studies are needed in order to better define the role of this agent.*

Key words: amifostine, head and neck cancer, mucositis, radioprotector, radiotherapy, xerostomia

Introduction

While RT is an effective treatment in head and neck cancers, its efficacy in locoregional disease control can be compromised because of toxicities related to both dose intensity and the cumulative dose. Mucositis and xerostomia, therefore, are often severely limiting factors in the treatment of head and neck cancers and a major cause of decreased quality of life [1,2].

Xerostomia disrupts normal activities including eating and speaking and may lead to sequelae including dental caries and teeth loss with the secondary risk of osteonecrosis. The degree of xerostomia reportedly depends on the radiation dose and the salivary glands volume irradiated. Amifostine selectively protects normal cells but not tumor cells from radiation-induced toxicities. Intravenous administration of amifostine before each RT fraction significantly reduces the severity of acute and late xerostomia and mucositis [3].

Intravenous administration of amifostine 200 mg/m², 15-30 min before each RT fraction is the usually recommended schedule for radioprotection. Although amifostine was generally well tolerated in most trials, nausea,vomiting, and hypotension were the most commonly reported side effects [4].

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Patients and methods

A total of 53 patients with head and neck cancer entered this prospective randomized study between October 2000 and November 2002. Patients were randomly assigned to undergo RT or RT plus i.v. administration of amifostine, according to their file number (0, 1).

Patient characteristics are listed in Table 1.

The primary study objective was to measure the incidence of grade 2-3 acute xerostomia and mucocitis according to the Radiation Therapy Oncology Group (RTOG) toxicity criteria.

Baseline studies included physical examination, full blood count, serum biochemistry, chest X-rays, and head and neck computerized tomography. Full blood count, serum urea and creatinine levels and serum liver function tests were assessed once weekly during RT.

All patients with head and neck cancer had local and/or regional disease that justified extended – field irradiation of the whole neck and primary tumor area. A standard fractionation regimen was used in all cases: 2 Gy/fraction, 5 fractions/week. Co 60 was used for the irradiation of all of the patients.

The primary tumor area and the neck received 46-50 Gy. Boost fields were used to increase the dose to 64-70 Gy in patients with high risk for local recurrence.

Amifostine 210 mg/m^2 was given as 15 min i.v. infusion with 8 mg dexamethasone, 20 min before each RT fraction. Blood pressure was monitored during amifostine administration and just before RT. In case of grade 3-4 mucositis, RT should be interrupted until regression of mucositis to grade 1. Patients with oropharyngeal mucositis were treated with analgesics and antifungal oral therapy.

Whole saliva production was quantitated pre-RT and regularly during RT and follow-up. Saliva was collected for 5 min after the patients had received paraffin as stimulant. Patients evaluated their symptoms using a special questionnaire during and after treatment. Statistical analysis was carried out by the chi-square test.

Table 1. Patient characteristics

Characteristic	*RT+amifostine (n=33) n (%)*	*RT-alone (n=20) n (%)*
Age, years		
median (range)	53 (16-60)	49 (36-70)
Sex		
male	22 (66.6)	17 (85)
female	11 (33.3)	3 (15)
Stage		
N0	7 (21.2)	8 (40)
N+	24 (72.7)	12 (60)
Site of disease		
larynx	10 (30.3)	12 (60)
nasopharynx	10 (30.3)	4 (20)
tonsil	1 (3)	–
salivary gland	1 (3)	–
mouth	4 (12)	2 (10)
hypopharynx	1 (3)	–
lymphoma	5 (15)	1 (5)
unknown primary	1 (3)	1 (5)
RT		
adjuvant	21 (63.3)	14 (70)
definitive*	12 (36.6)	6 (30)

*given in patients with inoperable disease and those who refused surgery

Results

Mucositis

As shown in Table 2, the incidence and grade of mucositis showed no important differences between the 2 arms.

No patient developed grade 4 mucositis in either arm. In general, mucositis occurred during the second week of treatment. Grade 3 mucositis was encountered in 12 (36.3%) patients in the amifostine arm and in 7 (35%) patients in the RT-alone arm (p=0.99). In these patients RT was interrupted until regression of mucositis to grade 1.

Xerostomia

Acute xerostomia occurred in 31 (93.9%) patients in the amifostine arm and all of the patients in the RT-alone arm. Grade 3 acute xerostomia occurred in 13 (39.3%) patients in the amifostine arm and in 9 (45%) patients in the RT-alone arm (p=0.04; Table 3). Late xerostomia occurred in 19 (57.5%) patients in the amifostine arm, and in 14 (70%) patients in RT-alone arm (p=0.03).

Table 2. Mucositis (RTOG criteria)

Grade	*RT + amifostine (n=33) n (%)*	*RT-alone (n=20) n (%)*	*p-value*
0	3 (9)	4 (20)	NS
1	8 (24.2)	3 (15)	NS
2	10 (30.3)	6 (30)	NS
3	12 (36.3)	7 (35)	NS
4	–	–	–

NS: non-significant

Table 3. Acute xerostomia (RTOG criteria)

Grade	*RT + amifostine (n=33) n (%)*	*RT-alone (n=20) n (%)*	*p-value*
0	2 (6)	0	NS
1	9 (27.2)	4 (20)	0.048
2	9 (27.2)	7 (35)	0.03
3	13 (39.3)	9 (45)	0.04
4	–	–	–

NS: non-significant

Other side effects

Loss of taste and dysphagia occurred in 21 (63.6%) patients in the amifostine arm compared with 15 (75%) patients in the RT-alone arm (p=0.05).

The range of salivary flow stimulated with paraffin was 60-98.5% (median 74.5%) in the amifostine arm, and 50-83.3% (median 71.6%) in the RT-alone arm (p=0.01).

The decrease of salivary pH was 10-29.3% (median 22.3%) in the amifostine arm, and 16-28.2 (median 25.3%) in the RT-alone arm (p=0.04).

In the amifostine arm grade 1 nausea was noted in 10 (30.3%) patients and transient grade 1 hypotension in 13 (39.9%) patients immediately after the amifostine administration.

In the same arm 2(6%) patients developed generalized rash throughout their body, lasting for 1-6 h after amifostine administration. Also in 2 (6%) patients arrhythmia was noted during amifostine infusion. In one of them amifostine was withdrawn after the 15th day of treatment because of continuation of arrhythmia.

In all of the patients in both arms serum calcium levels were normal during treatment.

Discussion

Amifostine has been used as a radioprotective agent in oncology. Many preclinical and clinical studies show that amifostine can minimize acute and late side effects of irradiation [5,6].

The major salivary glands produce about 90% of the saliva. Standard RT for head and neck cancers typically delivers high radiation dose to the major salivary glands bilaterally, resulting thus in marked reduction of saliva output [7]. Xerostomia is the most important late side effect of radiation for head and neck cancers. Several authors have reported encouraging results using amifostine as radiation protector [1,8]. The degree of xerostomia has been reported to depend on the radiation dose and the salivary gland volume irradiated. Sparing salivary function can be achieved by recording the radiation dose to the salivary glands or using a radiation protector, such as amifostine.

Several studies have shown that low amifostine doses of 200 mg/m^2 are sufficient to avoid the side effects of RT [9,10].

Different time schedules of amifostine administration have been used. Most authors give the agent as short infusion over 15 min [2,3]. Clinical trials document the efficacy of amifostine in decreasing the effects of irradiation on normal tissues without decreasing the cytotoxic effects on malignant tumors. In dose escalation trials, patients with head and neck cancer received amifostine 100 or 200 mg/m^2 before each RT fraction and demonstrated a good preservation of their salivary function with both dosage schedules [3,4,10].

The recommendations of the American Society of Clinical Oncology regarding amifostine state that this agent may decrease the incidence of acute and late xerostomia in certain patients undergoing fractionated RT for head and neck cancer, although the present data are insufficient to recommend its use for the prevention of RT-associated mucositis [7,11,12].

In this study, amifostine did not diminish the severity of mucositis. Grade 2-3 mucositis did not differ significantly between the two arms.

Xerostomia was assessed by the treating physician using the RTOG criteria, by quantitating the saliva flow.

Two major toxicities associated with amifostine include hypotension and emesis. A number of further side effects are known such as allergic reaction, hypocalcemia, and metallic taste. The onset of nausea and vomiting generally appears within 15-30 min from the start of the infusion, and resolves spontaneously. Pretreatment with dexamethasone and antiemetics can reduce the incidence of this acute side effect. Hypotension is a potentially serious side effect. It is generally systolic, lasting 5-15 min, without central nervous system, renal or cardiovascular consequences [4,13].

Hypocalcemia is clinically significant in approximately 1% of the patients and can be usually managed with oral calcium.

Allergic reactions occur in fewer than 1% of the patients.

In the present study, patients with head and neck cancer treated with RT tolerated amifostine quite well. Although early toxicities did not differ statistically between the 2 arms, late xerostomia was reduced

with amifostine administration (p=0.03). The reduction of late xerostomia (a typical radiation-associated side effect) was also reported by Brizel et al. and Buntzel et al. in phase III trials [5,13]. Reduction of loss of taste, fibrotic reaction, and posttherapeutic pain is also very important for the patient's quality of life and further investigations will be necessary because late toxicities create major problems in long-term survivors.

Based on amifostine ability to protect normal tissues, it may be possible to safely administer more intensive regimens to improve antitumor efficacy.

The i.v. administration of amifostine 200-350 mg/m^2, 20-30 min before each RT fraction is the usually recommended schedule for radioprotection.

Several problems still need to be addressed regarding radioprotection in head and neck cancer RT. These include understanding the role of this drug in the treatment schemes that use modified fractionation schedules and/or concurrent chemoradiation, and delineating more clearly the mucoprotective effects, if any, of amifostine. The answers will help define the role of this drug in clinical practice.

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