The Effect of Amifostine on Acute and Late Radiation Side Effects in Head and Neck Cancer Patients

Baş ve Boyun Kanseri Hastalarında Radyasyonun Akut ve Geç Yan Etkileri Üzerine Amifostinin Etkisi

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ABSTRACT Objective: We aimed to investigate the effect of amifostine on acute and late side effects, and its tolerability in head and neck cancer patients treated with radiotherapy (RT). **Material and Methods:** The study included 87 patients with primary head and neck cancers and cervical lymph node metastases from unknown primary cancers treated with RT alone or combined with chemotherapy (CT). Forty-one patients (47%) received amifostine combined with RT (ART group) and 46 patients (52%) received RT without amifostine (RT group). The patients were evaluated every week during the treatment and at month 1 and 2 after the completion of RT for acute side effects and month 3, 6, 9, 12, and 24 after the treatment for late side effects according to SOMA/LENT scale. Amifostine was administered prior to RT, along with anti-emetic prophylaxis. The two groups were compared with the Student's t and Mann-Whitney U and Chi-square tests. **Results:** The ART group had significantly less toxicity (grade 1 mucositis, grade 2 fibrosis) than patients in the RT group (p=0.001, p=0.03, respectively). At week 3 of RT grade 2 mucositis developed in two patients (5%) in the ART group and 10 patients (22%) in the RT group (p=0.02). The protective effect of amifostine on skin reactions developed at week 4 of RT (p=0.05). Grade 3 xerostomia at 9, 12, and 15 months of follow-up (p=0.02, p=0.02, and p=0.02, respectively), grade 2 xerostomia at 18 and 24 months (p=0.02 and p=0.01, respectively) and fibrosis at 15, 18 and 24 months (p=0.05, p=0.02 and p=0.02, respectively) decreased markedly in the ART group compared with the RT group. Emesis was the most common adverse effect of amifostine. **Conclusion:** Daily administration of amifostine during RT was effective in avoiding late grade 2-3 xerostomia, as well as grade 2 fibrosis.

Key Words: Radiotherapy; head and neck cancer; amifostine; xerostomia

ÖZET Amaç: Amifostinin radyoterapi (RT) ile tedavi edilmiş baş ve boyun kanseri hastalarında akut ve geç yan etkiler üzerindeki etkisini ve tolerabilitesini araştırmayı amaçladık. **Gereç ve Yöntemler:** Çalışmaya, tek başına RT veya RT ve eş zamanlı kemoterapi (KT) ile tedavi edilmiş primer baş ve boyun kanseri olan ve primeri bilinmeyen bir kanserden servikal lenf düğümlerine metastaz yapmış 87 hasta dâhil edildi. Kırk bir hastaya (47%) RT ile birlikte amifostin (ART grup) ve 46 hastaya (52%) amifostin olmaksızın RT (RT grubu) verildi. Olgular, tedavi sırasında akut yan etkiler açısından her hafta ve RT bittikten sonra 1. ve 2. ayda, geç yan etkiler açısından ise tedavi bittikten sonra 3., 6., 9., 12., ve 24. aylarda SOMA/LENT skalasına göre değerlendirildiler. Amifostin RT'den önce antiemetik profilaksi ile beraber uygulandı. İki grubun, komplikasyonlar üzerindeki etki açısından karşılaştırılmasında Student-t ve Mann Whitney-u testleri kullanıldı. **Bulgular:** ART grubunda toksisite, RT grubu hastalarında olduğundan daha az (evre 1 mukozit, evre 2 fibrozis) ortaya çıktı (p=0,001, p=0,03, sırasıyla). RT'nin 3. haftasında ART grubunda iki hastada (%5) ve RT grubunda on hastada (%22) evre 2 mukozit gözlemlendi (p=0,02). RT'nin 4. haftasında amifostinin deri reaksiyonları üzerinde koruyucu etkisi görüldü (p=0,05). Evre 3 kserostomi 9., 12. ve 15. ay takiplerinde (sırasıyla p=0,02, p=0,02, ve p=0,02), evre 2 kserostomi 18. ve 24. ay takiplerinde (sırasıyla p=0,02 ve p=0,01) ve fibrozis 15., 18. ve 24. ay takiplerinde (sırasıyla p=0,05, p=0,02 ve p=0,02) RT grubuna kıyasla ART grubunda belirgin olarak azaldı. Amifostinin en sık ortaya çıkan yan etkisinin kusma olduğu belirlendi. **Sonuç:** Günlük amifostin uygulaması, RT'ye bağlı geç evre 2-3 kserostomi ve evre 2 fibrozisinden korunmada etkili olmuştur.

Anahtar Kelimeler: Radyoterapi; baş ve boyun kanseri; amifostin; kserostomi

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Treatment of head and neck cancer with radiotherapy (RT) is associated with side effects that compromise the quality of life, including coherence of salivary secretion, mucositis, dysphagia, dental decay, and most importantly, xerostomia-specifically via damage to the parotid gland and oral microflora.[1-10] Among these, xerostomia is a long-term side effect and its treatment remains controversial. Preclinical studies reported that while amifostine (Ethyol®) decreased the level of damage to the parotid gland due to its cytoprotective property, it also protected normal tissues other than the parotid gland against the side effects of RT and chemotherapy (CT).[11-18] Amifostine is a phosphorylated aminothiol (WR2721) prodrug that preferentially accumulates in the salivary gland where it is metabolized to its active form by alkaline phosphatase, WR1065.[19] This active metabolite acts as a free radical scavenger and is considered the effective cytoprotector against side effects of both CT and RT.[20-22] This cytoprotection has been shown to be mostly effective on normal cells without any interaction with the tumour cells and the anticancer treatment.[16,23-26] The present study aimed to evaluate the effect of amifostine on the acute and late side effects of RT, and its tolerability in patients receiving RT for the treatment of head and neck cancer.

MATERIAL AND METHODS

This study included 87 consecutive patients referred to the Uludağ University Medical Faculty, Department of Radiation Oncology and was approved by the Uludağ University Medical Faculty Ethics Committee. All patients provided written informed consent before the treatment. The inclusion criteria were having a diagnosis of primary head and neck cancer with lymph node involvement, cervical lymph node metastases from unknown primary cancers and at least 75% of both parotid glands to be included within the irradiation volume. Patients with parotid or other salivary gland cancers, history of RT to the neck, distant metastasis, and Karnofsky Performance Scale score <60 were excluded from the study.

The patients were divided into two groups-amifostine plus RT (ART) group and RT group. Prior to treatment, all the patients underwent physical examination, complete blood count and biochemical tests that included renal and hepatic function tests, chest X-ray, and computed tomography scanning of the primary cancer site and neck.

RADIOTHERAPY

Patients were immobilized using a thermoplastic mask while in the supine position, and simulated. Computed tomography scanning was routinely used for the treatment planning and parotid glands were delineated in each case. While the primary tumor site and the upper cervical nodes were treated with two parallel opposed lateral fields, the lower part of the neck nodes was treated with an anterior field if necessary. The total radiation dose was 66-70 Gy (1.8-2 Gy per fraction) for definitive treatment and 50-60 Gy for adjuvant treatment. The total dose to the spinal cord was kept at 45 Gy. Median total RT dose was 60 Gy (range: 50-72 Gy) for both groups. The mean dose for 75% of the volumes of both parotid glands included within the radiation fields was ≥40 Gy.

CHEMOTHERAPY

Weekly cisplatin (30-40 mg/m²) CT was concomitantly administered to patients with adverse risk factors. Concomitant CT was administered to 21 patients (51%) in the ART group and 23 patients (50%) in the RT group.

AMIFOSTINE ADMINISTRATION

Amifostine (200 mg/m²) was administered intravenously 15-30 minutes prior to each RT session, along with anti-emetic prophylaxis. Blood pressure was measured before and after amifostine administration, and after RT.

FOLLOW-UP AND EVALUATION

Patients were evaluated with physical examination and blood tests every week during the treatment period. The first follow-up visit was performed two weeks after the last course of RT and thereafter follow-up visits were held monthly during the 1st year, every three months during the 2nd year, and every six months during the 3rd year. Clinical fol-

low-up visits included physical examination, computed tomography scanning and/or endoscopy. Patients were evaluated for acute side effects (mucositis, dysphagia, skin reactions, anemia, leukopenia, thrombocytopenia) every week during therapy and 1 and 2 months after the completion of RT. The late side effects (xerostomia, fibrosis) were recorded during follow-up examinations at 3, 6, 9, 12, 15, 18, and 24 months after the completion of RT. Radiation side effects were graded according to the SOMA/LENT scale, as approved by the Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC).

STATISTICAL ANALYSIS

Student's t and Mann-Whitney U tests were used for comparisons between the ART and RT groups for age, gender, cancer properties, and treatment properties. Comparisons of side effects in patients who did and did not receive amifostine were analyzed with the chi-square and Mann-Whitney U tests. SPSS v.16 software was used for statistical analysis. p value <0.05 was considered significant.

RESULTS

Overall, amifostine was administered to 41 patients (47%) during RT. In addition, patients that received RT+CT (n=44) were categorized in 2 subgroups-ART+CT (n=21, 47%) and RT+CT (n=23, 53%).

Mean follow-up time was 18.2 months (range 2-46 months) in the ART group and 19.5 months (range 5-48 months) in the RT group. Mean age of the patients in the ART group was 58 years (range 22-75 years) and 38 patients were male (93%). In the RT group, the mean age was 53.3 years (range 22-27 years) and 41 patients were male (89%). Patient characteristics were shown in Table 1.

Median overall survival was 24.3 months (range, 3-41 months) in the ART group and 24.7 months (range, 9-48 months) in the RT group. On the last follow-up visit, 17 (41%) patients in the ART group and 21 (45%) in the RT group were alive. While four patients (10%) had locoregional progression and 7 patients (17%) had distant metastasis in the ART group during the follow-up, 8 patients (13%) locoregionally recurred and distant metastasis developed in 10 patients (22%) in the RT group. Mean duration of RT was 43 days in the ART group (range 20-62 days) and 41 days in the RT group (range 30-63 days). Overall, 32 patients (78%) in the ART group and 25 patients (54%) in the RT group were treated with postoperative RT. The two groups did not show a significnat difference in total RT dose (p=0.94), duration of RT (p=0.57), time between surgery and RT (p=20), any break given during RT (p=0.86) and concomitant CT administration (p=0.81).

TABLE 1: Patient characteristics.

Properties	RT n (%)	ART n (%)	Total n (%)
Gender			
Male	41 (89%)	38 (93%)	79 (91%)
Female	5 (11%)	3 (7%)	8 (9%)
Localization of cancer			
Larynx	24 (52%)	18 (44%)	42 (48%)
Nasopharynx	4 (9%)	7 (17%)	11 (13%)
Hypopharynx	2 (4%)	4 (11%)	6 (7%)
Oropharynx	-	1 (2%)	1 (1%)
Oral Cavity	4 (9%)	1 (2%)	5 (6%)
Tongue	3 (7%)	7 (17%)	10 (11%)
Lower Lip	5 (11%)	-	5 (6%)
Paranasal Sinus	1 (2%)	1 (2%)	2 (2%)
Skin	1 (2%)	-	1 (1%)
Thyroid	1 (2%)	-	1 (1%)
Unknown Primary	1 (2%)	2 (5%)	3 (3%)
Histology			
Squamous cell carcinoma	44 (96%)	37 (91%)	81 (94%)
Undifferentiated carcinoma	-	3 (7%)	3 (3%)
Adenoid papillary carcinoma	1 (2%)	-	1 (1%)
Adenoid cystic carcinoma	1 (2%)	-	1 (1%)
Small cell carcinoma	-	1 (2%)	1 (1%)
Stage			
I	2 (4%)	-	2 (2%)
II	2 (4%)	3 (7%)	5 (6%)
III	8 (18%)	4 (10%)	12 (14%)
IV	31 (67%)	33 (81%)	64 (73%)
Recurrence	3 (7%)	1 (2%)	4 (5%)
Concurrent Chemotherapy	23 (53%)	21 (47%)	44 (51%)

ART: Amifostin combined with radiotherapy; RT: Radiotherapy without amifostin.

Based on the general analysis of the acute and late side effects, without considering time, grade 1 mucositis developed in nine patients (22%) in the ART group and 26 patients (57%) in the RT group. The effect of amifostine was statistically significant (p=0.001), whereas no difference was observed between the groups in terms of grade 2 and 3 mucositis (p=0.07, p=0.40, respectively). Grade 1 leukopenia was significantly more common in the ART group (n=13, 32%) than in the RT group (n=6, 13%) (p=0.03) The difference for grade 2 leukopenia was not significant between the groups. Acute side effects in patients who did and did not receive amifostine were listed in Figure 1. Few patients (n=6, 15% vs. n=16, 35%) who received amifostine had grade 2 fibrosis (p=0.03) while a greater number of patients (n=15, 37% vs. n=7, 15%) had no fibrosis (p=0.02). However, amifostine did not decrease the development of skin reactions, dysphagia, or xerostomia (Figure 2).

Side effects including mucositis, skin reactions, and dysphagia that occurred during RT and during the first and second months post-RT were recorded. During the third week of RT grade 2 mucositis was developed in two patients (5%) in the ART group and 10 patients (22%) in the RT group (p=0.02). Skin reactions developed in 16 patients (39%) who received amifostine and 31 (67%) who did not at four weeks of RT; this difference was borderline significant (p=0.05). The number of patients with grade 2 reactions was greater in the RT group (n=5) had compared to the ART group (n=1) at four weeks of RT. During week five, skin reaction developed in 27 patients (66%) in the ART group and 38 (83%) in the RT group (p=0.07). Amifostine did not have a significant impact on mucositis or skin reaction at six months of follow-up. The incidence of dysphagia during RT was not significantly different between the groups.

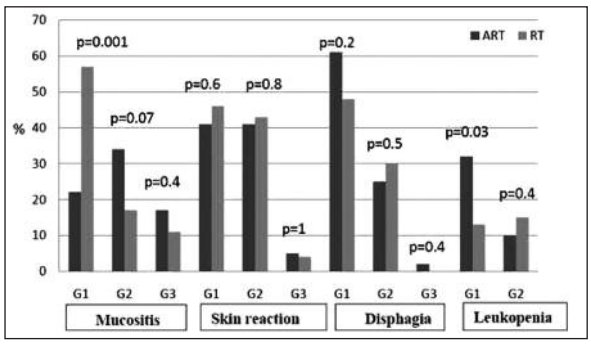

FIGURE 1: Acute side effects in the patients who did and did not receive amifostine.

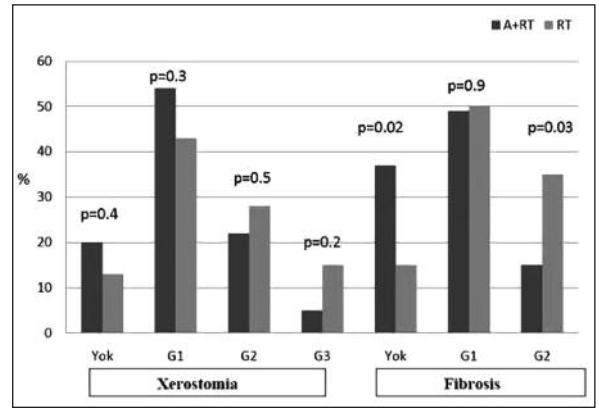

FIGURE 2: Late side effects in patients who did and did not receive amifostine.

In terms of late side effects, grade 1 xerostomia was surprisingly less common in the RT group than in the ART group (35% and 56%, respectively, p=0.04) at three months of follow-up. However, the effect of amifostine was remarkable on grade 2 and 3 xerostomia at the ninth month follow-up visit. At nine months of follow-up, grade 3 xerostomia was present in only one patient (2%) in the ART group and 4 patients (9%) in the RT group (p=0.02). At 12 and 15 month visits, grade 3 xerostomia was not observed in any patient in the ART group compared to 9% (n=6) and 9% (n=4) in the RT group, respectively (p=0.02 and p=0.02, respectively). Grade 2 xerostomia was noted in only five patients (8%) in the ART group and 13 patients (32%) in the RT group (p=0.02) at 18 months of follow-up. Grade 2 xerostomia did not develop in any patient who received amifostine, but was present in 8 patients (22%) who did not at 24 months of follow-up (p=0.01) (Table 2). While the occurence rate of grade 2 or greater xerostomia at 3 months was equal in both groups, it decreased after month 12 in favor of the ART group. The median time to the occurrence of grade 2 or greater xerostomia was 9 months in each group and this was not statistically significant (p=0.98) (Figure 3).

TABLE 2: Xerostomia rates according to the month of follow-up visits.

Month	Xerostomia	ART n (%)	RT n (%)	p
3	None	11 (27%)	22 (48%)	0.04
	Grade 1	23 (56%)	16 (35%)	0.04
	Grade 2	7 (17%)	6 (13%)	0.59
	Grade 3	0	2 (4%)	0.60
9	None	1 (27%)	15 (33%)	0.79
	Grade 1	19 (47%)	15 (33%)	0.99
	Grade 2	9 (22%)	12 (26%)	0.26
	Grade 3	1 (2%)	4 (9%)	0.02
12	None	2 (30%)	15 (37%)	0.79
	Grade 1	17 (42%)	17 (37%)	0.99
	Grade 2	11 (27%)	8 (17%)	0.26
	Grade 3	0	6 (9%)	0.02
15	None	11 (31%)	10 (22%)	0.35
	Grade 1	14 (40%)	21 (47%)	0.55
	Grade 2	10 (29%)	10 (22%)	0.51
	Grade 3	0	4 (9%)	0.02
18	None	11 (41%)	9 (22%)	0.96
	Grade 1	11 (41%)	16 (32%)	0.88
	Grade 2	5 (8%)	13 (32%)	0.02
	Grade 3	0	3 (7%)	0.58
24	None	14 (54%)	14 (38%)	0.26
	Grade 1	12 (46%)	12 (32%)	0.32
	Grade 2	0	8 (22%)	0.01
	Grade 3	0	3 (8%)	0.24

ART: Amifostin combined with radiotherapy; RT: Radiotherapy without amifostin.

Follow-up visits 12 months after RT showed that there was no significant difference in fibrosis between the two groups. At 15 months of follow-up grade 2 fibrosis was developed at a lower frequency rate in the ART group (n=5, 14%) than in the RT group (n=15, 33%), and the difference was borderline significant (p=0.05). At 18 and 24 months post-RT follow-up the frequency of fibrosis in the patients that received amifostine (n=17, 63%) was significantly lower than those in the RT group (n=32, 86%), (p=0.02 and p=0.02, respectively).

Patients were also analyzed in two subgroups (ART+CT and RT+CT) to determine if amifostine had any favorable impact on the side effects associated with the combined use of CT and RT. Grade 1 mucositis was noted only in eight patients (38%) in the ART+CT subgroup and 15 patients (65%) in the RT+CT subgroup (p=0.03). As a late side effect, fibrosis was present only in 12 patients (57%) in the ART+CT group and 22 patients (96%) in the RT+CT group; this difference was statistically significant (p=0.02). Although amifostine markedly decreased the incidence of fibrosis in patients that received CT, no difference was observed between the two subgroups, in terms of the severity of fibrosis. Amifostine did not have a protective effect against skin reaction, dysphagia, and xerostomia in patients treated with RT+CT. Similarly, no difference was observed between the two subgroups regarding anemia, leukopenia, and thrombocytopenia (Table 3).

The present study also assessed the side effects related to amifostine; grade 1 nausea occured in nine patients (22%), grade 2 nausea in four patients (9.7%), grade 3 nausea in two patients (5%), hypotension in five patients (12%), and skin rash in one patient (2%). One patient (2%) had syncope due to hypotension. Amifostine was withdrawn in two patients with hypotension including the one who experienced syncope and another patient who had skin rash during the last week of RT. There were no major changes in blood test results or biochemical parameters in any of the patients during or after treatment that were attributable to amifostine, except grade 1 leukopenia.

DISCUSSION

The acute and late side effects of RT and/or CT in head and neck cancers are dose-dependent factors. While xerostomia is the most severe and most common side effect of RT, amifostine remains the only

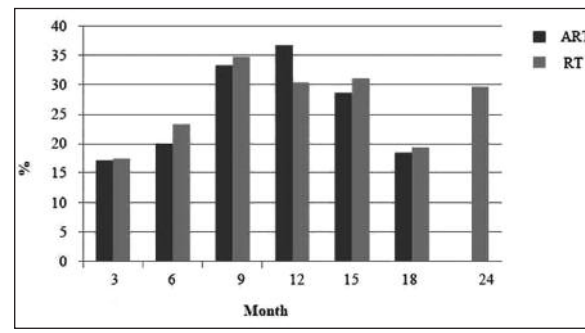

FIGURE 3: Grade 2 or more xerostomia according to time.

TABLE 3: The effect of amifostine on various side effects in patients who received RT+CT.

Side effect	ART+CT n (%)	RT+CT n (%)	p	Side effect	ART+CT n (%)	RT+CT n (%)	p
Mucositis				Fibrosis			
None	5 (24%)	3 (13%)	0.81	None	9 (43%)	1 (4%)	0.02
Grade 1	8 (38%)	15(65%)	0.03	Grade 1	9 (43%)	13 (57%)	0.64
Grade 2	3 (14%)	3 (13%)	0.99	Grade 2	3 (14%)	9 (39%)	0.12
Grade 3	5 (24%)	2 (9%)	0.80				
Skin reaction				Leukopenia			
None	2 (9.5%)	2 (9%)	0.99	None	12 (57%)	15 (65%)	0.89
Grade 1	9 (43%)	11 (48%)	0.85	Grade 1	7 (33%)	4 (17%)	0.91
Grade 2	8 (38%)	10 (43%)	0.85	Grade 2	2 (9%)	4 (17%)	0.46
Grade 3	2 (9.5%)	0	0.78				
Dysphagia				Thrombocytopenia			
None	2 (9%)	5 (22%)	0.66	None	17 (81%)	20 (87%)	0.96
Grade 1	14 (67%)	12 (52%)	0.80	Grade 1	2 (9%)	2 (9%)	1
Grade 2	5 (24%)	6 (56%)	0.85	Grade 2	2 (9%)	1 (4%)	0.80
Xerostomia				Anemia			
None	3 (14%)	3 (13%)	0.95	None	21 (100%)	21 (91%)	0.99
Grade 1	11 (52%)	8 (35%)	0.86	Grade 1	0	2 (9%)	0.73
Grade 2	5 (24%)	9 (39%)	0.7	Grade 2	0	0	
Grade 3	2 (9%)	3 (13%)	0.88				

ART: Amifostin combined with radiotherapy; CT: Chemotherapy; RT: Radiotherapy without amifostin

potent drug for preventing toxicity during long-term follow up.[27-30] Nonetheless, parotid sparing intensity modulated RT, which is reported to be superior to conventional RT and amifostine, resulted in a remarkable decrease in xerostomia.[31] The present study assessed the acute and late side effects of RT within weeks to months in patients who did and did not receive amifostine during conventional RT, and the results revealed a significant decrease in the development of xerostomia and fibrosis during the late follow-up period.

Wagner et al. studied patients that were treated with and without amifostine during RT. In the ART group, 71.4%, 28.5%, and 0% of the patients had grade 1, 2, and 3 xerostomia, 36%, 28.5%, and 0% had grade 1, 2, and 3 skin reactions, 36%, 14%, and 0% had grade 1, 2, and 3 mucositis, and 41% and 7% had grade 1 and 2 dysphagia, respectively. In the RT group 0%, 36%, and 57% of the patients had grade 1, 2, and 3 xerostomia. 0%, 41%, and 7% had grade 1, 2, and 3 skin reactions, 14%, 57%, and 28.5% had grade 1, 2, and 3 mucositis, and 42.8% and 87% had grade 1 and 2 dysphagia, respectively. Based on their results, they concluded that acute and late side effects occurred significantly less frequently in the ART group than in the RT group.[32]

Bourhis et al. reported that amifostine reduced the frequency of severe mucositis and the duration of mucositis induced by very accelerated RT; however, it was not well tolerated.[33] Ozsahin et al. evaluated side effects in patients treated with amifostine during accelerated RT and reported that grade 3 dysphagia, grade 3 mucositis, and grade 3 erythema occurred in 39%, 42%, and 43% of the patients, respectively. In terms of late side effects, grade 3 xerostomia and grade 3 fibrosis occurred in 15% and 0% of the patients, respectively, but their study did not include a control group to compare the efficacy of amifostine.[34] Brizel et al. reported the results of a multi-center, randomized phase III study on the efficacy of amifostine that included 315 patients.[35] Assessments were performed weekly before and during RT, and at certain intervals after RT. Grade 2-3 xerostomia was developed in 51% of the patients that received amifostine and 78% of the patients in the control group; the difference

was statistically significant. In addition, xerostomia and mucositis developed later in patients that received amifostine than in those who did not. They concluded that amifostine did not have a favorable effect on mucositis. In the present study, a significant impact of amifostine on grade 2-3 xerostomia and fibrosis was observed at 9 and 15 months of post-RT follow-up, whereas overall amifostine did not prevent acute or late side effects. This might have been due to the limited number of patients that tolerated amifostine well.

The effect of amifostine typically starts 12 months after RT.[36] In a study by Mc Donald et al., salivary secretion decreased during the first weeks of RT in patients with head and neck cancers who received amifostine. This decrease remained constant for six weeks in unstimulated saliva and there was 20% improvement in saliva secretion 12 months after RT. Significant side effects did not develop in eight patients that completed the protocol and amifostine was well tolerated.[37] Similarly, Wasserman et al. reported that unstimulated saliva production at 12 months in patients receiving amifostine was much higher than in those that did not receive amifostine, and this effect continued up to 24 months.[14] The administration of amifostine prior to RT has been shown to mostly reduce the incidence of grade ≥2 acute and late side effects.[35,38] A recent update of the study by Brizel et al. confrmed that the incidence of late grade ≥2 xerostomia decreased in the amifostine group.[36] In a study by Buntzel et al., the difference in grade 2 xerostomia was significant between ART and RT arms (p=0.0001).[39] By contrast, Munter et al. did not show any difference in comparison to other studies; however, the majority of the patients recieved RT without CT.[31] In the present study the effect of amifostine on saliva became significant starting at nine months of follow-up and persisted thereafter. The incidence of grade 3 xerostomia at 9, 12, and 15 months of follow-up was higher in the RT group than in the ART group. Similarly, at 18 and 24 months of follow-up, the incidence of grade 2 xerostomia was higher in the RT group than in the ART group.

Amifostine has also been reported to decrease the occurrence of acute side effects in patients receiving RT+CT. In a randomized phase II study by Buntzel et al. patients with locally advanced head and neck cancer were managed either with RT+CT or ART+CT. While grade 3-4 mucositis was noted in 12 out of 14 patients (86%) in the RT+CT group, it did not develop in any of the patients in the ART+CT group. Grade 2 xerostomia developed in 100% of the patients in the RT+CT group versus 12% of those in the ART+CT group. During 12 months of follow-up, significantly fewer patients in the ART+CT group had grade 2 xerostomia than those in the RT+CT group (17% vs. 55%), and amifostine significantly decreased the rate of severe dermatitis, loss of taste, and dysphagia.[39,40]

In a series of 50 cases, Antonadou et al. compared patients that underwent RT+CT with or without amifostine and side effects were recorded at certain intervals.[38] They reported that treatment was interrupted due to grade 4 mucositis in six patients (28%) in the amifostine group and in 12 patients (52%) in the control group. During the third week, grade 2 mucositis developed in 9.1% of the patients in the amifostine group versus 100% of the patients in the control group. Evaluations at four and seven weeks showed that the incidence of grade 3-4 mucositis and dysphagia was higher in the control group than in the amifostine group. In terms of late side effects, grade 1 xerostomia developed more frequently in the amifostine group than in the control group during the third month (54.5% and 17.4%, respectively) and a significant decrease was observed in grade 2 xerostomia (27% and 78%, respectively). At 18 months, 4.5% of the patients in the ART+CT group and 30.4% of the patients in the RT+CT group had xerostomia; the difference was statistically significant.

In our study 38% of the patients in the ART+CT subgroup and 65% of the patients in the RT+CT subgroup had grade 1 mucositis (p=0.03). The fibrosis incidence rate in the ART+CT subgroup was significantly lower than in the RT+CT subgroup (57% vs. 96%, p=0.02). In the patients that received RT+CT, amifostine had no protective effect in terms of skin reactions, xerostomia, and dysphagia. Acute side effects were analyzed according to weeks and months, and 5% of the pa-

tients that received amifostine had grade 2 mucositis at three weeks, versus 22% of the control group (p=0.02). At four weeks, skin reactions were present in 39% of the patients in the ART group (grade 1 skin reactions were more prominent) compared to 67% of the patients in the RT group. Among the patients that received amifostine, grade 3 xerostomia developed less frequently at 9 and 12 months of follow-up (p=0.02, p=0.02). At 18 and 24 months of follow-up grade 2 xerostomia was developed significantly less frequently (p=0.02, and p=0.01, respectively) in the ART group compared to the RT group. The difference in grade 1 and 3 mucositis, dysphagia, and skin reactions between the two groups was not statistically significant.

Amifostine is known to have a favorable impact on hematologic side effects related to RT. Betticher et al. reported that amifostine considerably decreased neutropenic fever in patients that received CT in their randomized phase III study.[41] In another study, grade 3-4 thrombocytopenia and leukopenia were not observed in any of the patients that received amifostine during RT, and the difference between the patients that did and did not receive amifostine was significant.[39,40] Momm et al. reported that only the leukocyte count was maintained in patients that received amifostine.[42] In contrast, Antonadou et al. did not observe a protective effect of amifostine against hematologic side effects.[38.] Amifostin had no benefit regarding anemia, thrombocytopenia, or leukopenia in the current study and did not improve the results of hematologic side effects in the patients treated with concomitant CT.

To the best of our knowledge, no randomized study has evaluated fibrosis. In the present study, grade 2 fibrosis developed in 14% of the patients who received amifostine and 33% of those who did not at 15 months of follow-up; the difference was borderline significant (p=0.05). Although the protective effect of amifostine on fibrosis was significant at 18 and 24 months (p=0.02 and p=0.02), it was not superior in terms of the severity of fibrosis between the two groups.

The tolerability of amifostine remains as a dilemma. The main side effects related to amifostine include nausea/vomiting and hypotension.[35,38] Bourhis et al. reported diffuse erythema and an increase in liver enzymes, and therefore amifostine treatment was interrupted.[40] Although subcutaneous administration was tolerated to a greater degree than intravenous administration, hypotension and nausea were reported to be the most common side effects.[18,39,43,44] Koukourakis et al. reported nausea in 28%, vomiting in 4%, and fatigue in 16% of patients that received amifostine subcutaneously, whereas hypotension was not observed in any of the patients.[44] In a study by Ozsahin et al., despite the fact that amifostine was interrupted due to nausea in 33% of patients and due to hypotension in 18%, it was well tolerated in nearly half of the patients.[34] Law et al. noted that grade 1 nausea/vomiting occurred in 35% of patients after subcutaneous administration.[18] Among the patients in the present study that received intravenous amifostine, 21.9%, 9.7%, and 4.8% had grade 1, 2, and 3 nausea, respectively, 2.4% had syncope, 9.7% had hypotension, and 2.4% had skin rash. Overall, amifostine treatment was interrupted in 3 patients due to syncope (n=1), diffuse skin rash (n=1), and nausea (n=1). These results were considered acceptable, as compared to those obtained with subcutaneous administration. We think that amifostine was well tolerated by the patients in the present study due to continuous hydration and supportive care during RT.

The most controversial issue concerning amifostine is its protective effect on cancer tissues, and its influence on survival. Several studies reported that the clinical outcome was not affected by amifostine.[33,38,39] In addition, the difference in overall survival rates in two studies was not significant between the groups.[14,35] In our study no significant difference was observed between the groups in terms of the median overall survival.

The current study showed that grade 1-2 mucositis and grade 2 fibrosis rates were significantly lower in patients that received amifostine during treatment in the general time-independent analyze. According to time-dependent evaluation, the effect

of amifostine on mucositis was favorable initially at three weeks, on skin reactions at four weeks, on xerostomia at nine months, and on fibrosis at 15 months of post-RT follow-up. Recent studies that used subcutaneous administration of amifostine reported significant decreases in the incidence of side effects; thus, subcutaneous administration of amifostine is currently being used in our department.

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