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Acute Side Effects of Combined Chemotherapy with Intensity-Modulated Radiotherapy in The Treatment of Nasopharyngeal Carcinoma

Nazofarengeal Karsinom Tedavisinde Yoğunluk Ayarlı Radyoterapi ile Kombine Kemoterapinin Akut Yan Etkileri

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ABSTRACT

Nasopharyngeal cancer is a very common head and neck cancer. Although concurrent chemotherapy plays an important role in controlling the disease, the risk of acute toxicity is high due to the anatomical location of the tumor. The aim of our study is to evaluate the acute side effects observed in nasopharyngeal carcinoma patients who underwent definitive chemoradiotherapy. A total of 64 patients (41 men, 23 women) between the ages of 20 and 82, who were diagnosed with nasopharyngeal cancer and treated, were included in the study. All patients received concurrent chemoradiotherapy along with intensity-modulated radiotherapy. While 70 Gy radiotherapy was applied to the tumor and positive lymph nodes, 60 Gy radiotherapy was applied to the entire nasopharynx and bilateral neck lymph nodes. Three cycles of cisplatin 100 mg/m^2 (days 1, 22 and 43) or weekly 40 mg/m^2 cisplatin chemotherapy were used for treatment. Acute side effects of the patients were noted and evaluated. Of the patients included in the study, 15 (23%) had stage II disease, 37 (58%) had stage III disease, and 12 (19%) had stage IV disease. The rates of grade 2 and 3 hematological toxicity in male patients were 47% and 20%, respectively. The rates of grade 2 and 3 hematological toxicity in male patients were 47% and 20%, respectively. A significant difference was found in the hematological toxicity rate between both groups (p=0.0001). In patients under the age of 65, grade 2 and 3 hematological toxicity rates were determined as 47% and 20%, respectively. In patients over 65 years of age, the rates of grade 2 and 3 esophagitis were 53% and 80%, respectively. There was a significant difference in the rate of esophagitis between both groups (p=0.0001). Our results are compatible with the literature in terms of acute side effects. Close monitoring and treatment of acute side effects can improve patient compliance with treatment, improve quality of life, and increase the effectiveness of treatment.

Keywords: Acute side effect, Chemoradiotherapy, Nasopharyngeal cancer

ÖZET

Nazofarenks kanseri çok yaygın bir baş ve boyun kanseridir. Kemoradyoterapide eş zamanlı kemoterapi hastalığın kontrolünde önemli rol oynamasına rağmen tümörün anatomik yerleşimi nedeniyle akut toksisite riski yüksektir. Çalışmamızın amacı definitif kemoradyoterapi uygulanan nazofaringeal karsinom hastalarında görülen akut yan etkilerin değerlendirilmesidir. Nazofaringeal kanser tanısı alan ve tedavi gören 20-82 yaş aralığında toplam 64 (41 erkek, 23 kadın) hasta çalışmaya dahil edildi. Tüm hastalara yoğunluk ayarlı radyoterapi ile birlikte eşzamanlı kemoradyoterapi uygulandı. Tümör ve pozitif lenf nodlarına 70 Gy radyoterapi uygulanırken, tüm nazofarenks ve iki taraflı boyun lenf nodlarına 60 Gy radyoterapi uygulandı. Tedavi için üç kür sisplatin 100 mg/m^2 (1., 22. ve 43. günler) veya haftalık 40 mg/m^2 sisplatin kemoterapisi kullanıldı. Hastaların akut yan etkileri not edildi ve değerlendirildi. Çalışmaya dahil edilen hastaların 15'i (%23) evre II, 37'si (%58) evre III, 12'si (%19) ise evre IV hastalığa sahipti. Erkek hastalarda 2. ve 3. derece hematolojik toksisite oranları sırasıyla %47 ve %20 şeklindeydi. Kadın hastalarda 2. ve 3. derece hematolojik toksisite oranları sırasıyla %53 ve %80 tespit edildi. Her iki grup arasında hematolojik toksisite oranında anlamlı fark bulundu (p=0.0001). 65 yaş altı hastalarda 2. ve 3. derece hematolojik toksisite oranları sırasıyla %47 ve %20 belirlendi. 65 yaş üstü hastalarda 2. derece ve 3. derece özofajit oranları sırasıyla %53 ve %80 idi. Her iki grup arasında özofajit oranında anlamlı fark görüldü (p=0.0001). Elde ettiğimiz sonuçlar akut yan etkiler açısından literatürle uyumludur. Akut yan etkilerin sıkı takibi ve tedavisi, hastanın tedaviye uyumunu artırabilir, yaşam kalitesini iyileştirebilir ve tedavinin etkinliğini artırabilir.

Anahtar Kelimeler: Akut yan etki, Kemoradyoterapi, Nazofarengeal karsinom

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INTRODUCTION

Nasopharyngeal cancer (NPC) is a very common head and neck cancer. However, it differs from other head and neck cancers with its course, histopathology, epidemiology and etiology, and staging. NPC is an uncommon tumor that accounts for 0.2% of all cancers in Western nations and has an endemic distribution. However, according to us, in eastern nations, particularly in China, this frequency can reach 20/100,000 annually, this may be associated with highly processed fish consumption and EBV infection. Greenland, North Africa, and Mediterranean nations, including our own, are ranked after Southeast Asian nations in terms of annual incidence, which is claimed to be 8-12/100.000 in these areas.[1] Although 51 is the average age for NPC diagnosis, it has been shown that this age group is biphasic in endemic areas. Between the ages of 15 and 25 and 40 and 50, it is seen in these shadows, and men are 2-3 times more likely to see it.[2,3] Radiotherapy (RT) is one of the primary treatment methods and comprehensive treatments for NPC since NPC is highly sensitive to it. However, different therapeutic approaches have been utilized for NPC at various stages. Radical radiation alone can produce an acceptable outcome for stage I (T1N0M0) NPC; nevertheless, chemoradiotherapy (CRT) is used in locally advanced stages.[4-6] The radiosensitizing activity of cisplatin was first reported in 1974. Cisplatin increases the potential lethal damage caused by radiation, inhibits the repair of sublethal damage, and increases the efficacy of RT by sensitizing hypoxic cells to radiation damage.[7] Traditional two-dimensional conformal radiation therapy (2D-CRT) has given way to three-dimensional conformal radiation therapy (3D-CRT), and finally to intensity-modulated radiation therapy (IMRT). RT procedures have improved, allowing for a reduction in adverse effects and an increase in survival.[8-10] However, local side effects may occur due to RT, and the concurrent chemotherapy used may increase these effects. Although concurrent chemotherapy plays a major role in disease control in chemoradiotherapy, it can also cause serious toxicities in the early and late periods.[11] The most common acute side effects of CRT in the treatment of NPC are dermatitis, mucositis, esophagitis, and hematological side effects. In particular, oropharyngeal mucositis is the most common acute non-haematological toxicity.[11] When side effects are encountered, changes to be made in the treatment and supportive treatments to be added are vital. In this study; Early side effects of patients with NPC who were treated in our clinic and treated with chemoradiotherapy were evaluated.

METHODS

Patient selection

This retrospective investigation has received permission from the institutional review board. (Date: 08.05.2017, Project No. 2017-77, Kardeniz Technical University Faculty of Medicine Scientific Research Ethics Committee). We retrospectively examined patients with NPC who had received CRT between January 2010 and May 2023 and who had been recorded in the Radiation Oncology Clinic database at the Karadeniz Technical University Faculty of Medicine. Initially, patients with metastatic disease with either prior or present cancer were excluded from the study. Patients with stage II and above disease who underwent CRT were included in the study. The study included patients with a Karnofsky Performance Score of at least 70 who had undergone whole-body fludoxyglucose F 18 (18 F-FDG) positron emission tomography (PET)-CT imaging without evidence of metastasis and had undergone biopsy-based pathological diagnosis.

Treatment and Patients

CRT was administered to patients with T2 or N1 M0 disease. While 70 Gy of radiotherapy was administered to the tumor and positive lymph nodes in all patients, 60 Gy of radiotherapy was administered to all nasopharyngeal and bilateral neck lymph nodes. Three rounds of cisplatin 100 mg/m^2 (days 1, 22, and 43) or 40 mg/m2 weekly chemotherapy were used for treatment. IMRT was used to treat all patients.

Acute Side Effect Evaluation

Early side effects were observed within 90 days of the initiation of RT, whereas late side effects were observed after 90 days. The National Cancer Institute-Common Toxicity Criteria (NCI-CTC) were used each week to assess acute adverse events. The blood/bone marrow, dermatology/skin, and gastrointestinal systems were evaluated. Dysphagia, esophagitis, odynophagia (painful swallowing): grade 0: none, grade I: mild dysphagia, but can eat regular diet, grade II: dysphagia, requiring predominantly pureed, soft, or liquid diet, grade III: dysphagia, requiring IV hydration, grade IV: complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation. Dermatology/skin, grade 0: none, grade I: mild, grade II: moderate, grade III: severe, grade IV: life-

threatening or disabling. Blood/bone marrow, leukocytes (total WBC), grade 0: regular, grade I: >3000/mm^3, grade II: 2000-3000/mm^3, grade III: 1000-2000/mm^3, and grade IV: <1000/mm^3. Mucositis due to radiation, grade 0: none, grade I: erythema of the mucosa, grade II: patchy pseudomembranous reaction (patches generally ≤1.5 cm in diameter and noncontiguous), grade III: confluent pseudomembranous reaction (contiguous patches generally >1.5 cm in diameter), grade IV: necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion. The Radiation Therapy Oncology Group (RTOG) guidelines were used to evaluate early radiation reactions.[12] Follow-up was done every three months for the first three years and every six months for the next three years.

Statistical Analysis

In our study, side effects (skin reaction, mucositis, esophagitis, and hematological) seen as a result of CRT were evaluated. The general characteristics of the patients and early side effects were compared. Frequency percentages were calculated for categorical variables. Mean standard deviation and median values were calculated for continuous variables. Pearson x^2 tests for hematological and non-hematologic toxicity were performed in the two groups. Statistical significance was set at $p<0.05$.

RESULTS

A total of 64 patients were included in this study. The mean age of the patients was 51.05±14.46 (range:20-82) years. 52 (81%) patients were younger than 65 years, and 12 (19%) were aged ≥65 years. 41 (64%) patients were male and 23 (36%) were female. Anemia was observed in 10 (16%) men and 7 (11%) women, according to the World Health Organization (WHO) criteria for anemia (hemoglobin <12 g/dL (female) or <13 g/dL (male)) by sex. After RT, 18 (28%) men and 14 (22%) women had low hemoglobin levels. According to T stage, 25 (39%) patients had T1 tumor, 19 (30%) patients had T2 tumor, 11 (17%) patients had T3 tumor and 9 (14%) patients had T4 tumor. According to the N stage, 12 (19%) patients were classified as N0, 13 (20%) as N1, 38 (59%) as N2, and 1 (2%) as N3. When patients were analyzed for stage, 15 (23%) were stage II, 37 (58%) were stage III, and 12 (19%) were stage IVA. According to the pathological types, 5 (8%) patients had WHO Type I, 12 (19%) patients had WHO Type IIA, and 47 (73%) patients had WHO Type IIB. Patient characteristics are shown in Table 1. The mean follow-up period for the side effect analysis was calculated as 8.6 months. For acute toxicity, skin, oral mucosal and esophageal side effects were noted at weekly follow-ups. In addition, complete blood counts were performed every week to determine the hematological toxicity of the patients. According to dermatitis grade, 3 (5%) patients had grade I, 22 (34%) patients had grade II, 27 (42%) patients had grade III and 12 (19%) patients had grade IV dermatitis. According to the mucositis grade, 1 (2%) patient had grade I, 10 (16%) had grade II, 49 (76%) had grade III, and 4 (6%) had grade IV mucositis. According to esophagitis grade, 2 (3%) patients had grade I esophagitis, 18 (28%) had grade II esophagitis, and 44 (69%) had grade III esophagitis. According to the hematological toxicity grade, not seen in 2 (3%) patients, 42 (66%) patients had grade I, 15 (23%) patients had grade II, and 5 (8%) patients had grade III hematological toxicity. Hematological side effects were more common in patients who received high-dose cisplatin CT every 3 weeks. Grade III hematological toxicity was observed in five (8%) patients in this group. Acute side effects are shown in Table 2. In male, the rates of grade 2 and 3 dermatitis were 55% and 59%, respectively. In female, the rates of grade 2 and 3 dermatitis were 45% and 41%, respectively. There was no significant difference in dermatitis rate between the 2 groups (z=2.405, p=0.520). In male, the rates of grade 2 and 3 mucositis were 40% and 53%, respectively. In female, the rates of grade 2 and 3 mucositis were 60% and 47%, respectively. There was no significant difference in the rate of mucositis between the 2 groups (z=2.684, p=0.265). In male, the rates of grade 2 and 3 esophagitis were 67% and 45%, respectively. In female, the rates of grade 2 and 3 esophagitis were 33% and 55%, respectively. There was no significant difference in the rate of esophagitis between the 2 groups (z=3.412, p=0.186). In male, the rates of grade 2 and 3 hematological toxicity were 47% and 20%, respectively. In female, the rates of grade 2 and 3 hematological toxicity were 53% and 80%, respectively. There was a significant difference in the rate of hematological toxicity between the 2 groups (z=16.882, p=0.0001). Acute side effects by gender are shown in Table 3. When patients were evaluated according to age, the rates of grade 2 and 3 dermatitis in patients younger than 65 years were 55% and 52%, respectively. In patients older than 65 years, the incidence rates of grade 2 and 3 dermatitis were 45%

and 48%, respectively. There was no significant difference in dermatitis rate between the 2 groups (z=1.124, p=0.583). The rates of grade 2 and 3 mucositis in patients aged <65 years were 60% and 53%, respectively. In patients aged >65 years, the rates of grade 2 and 3 mucositis were 40% and 47%, respectively. There was no significant difference in the mucositis rate between the 2 groups (z=1.788, p=0.424). The rates of grade 2 and 3 esophagitis in patients aged <65 years were 44% and 45%, respectively. In patients aged >65 years, the rates of grade 2 and 3 esophagitis were 56% and 55%, respectively. There was no significant difference in the esophagitis rate between the 2 groups (z=0.886, p=0.350). The rates of grade 2 and 3 hematological toxicities in patients aged < 65 years were 47% and 20%, respectively. In patients aged >65 years, the rates of grade 2 and 3 esophagitis were 53% and 80%, respectively. There was a significant difference in the esophagitis rate between the 2 groups (z=18.360, p=0.0001). Acute side effects by age are shown in Table 3.

Table 1. Patient characteristics

	Grade	n (%)
Gender	Male	23 (36)
	Female	41 (64)
T stage	1	25 (39)
	2	19 (30)
	3	11 (17)
	4	9 (14)
N stage	0	12 (19)
	1	13 (20)
	2	38 (59)
	3	1 (2)
Stage	II	15 (23)
	III	37 (58)
	IV	12 (19)
Pathological types	WHO I	5 (8)
	WHO IIA	12 (19)
	WHO IIB	47 (73)

Table 2. Distribution of early side effects

	Grade	n (%)
Dermatitis	1	3 (5)
	2	22 (34)
	3	27 (42)
	4	12 (19)
Mucositis	1	1 (2)
	2	10 (15)
	3	49 (77)
	4	4 (6)
Esophagitis	0	-
	1	2 (3)
	2	18 (28)
	3	44 (69)
Hematological toxicity	0	2 (3)
	1	42 (66)
	2	15 (23)
	3	5 (8)

Table 3. Comparison of early side effects by gender and age

	Grade	Male n(%)	Female n(%)	z	p	Age ≤65 n(%)	Age >65 n(%)	z	p
RTOG Dermatitis	2	12 (55)	10 (45)	2.40	0.520	12 (55)	10 (45)	1.12	0.583
	3	16 (59)	11 (41)			14 (52)	13 (48)		
RTOG Mucositis	2	4 (40)	6 (60)	2.68	0.265	6 (60)	4 (40)	1.78	0.424
	3	26 (53)	23 (47)			26 (53)	23 (47)		
RTOG Esophagitis	2	12 (67)	6 (33)	3.41	0.186	8 (44)	10 (56)	0.88	0.350
	3	20 (45)	24 (55)			20 (45)	24 (55)		
RTOG Hematological toxicity	2	7 (47)	8 (53)	16.88	0.0001	7 (47)	8 (53)	18.36	0.0001
	3	1 (20)	4 (80)			1 (20)	4 (80)		

DISCUSSION

The aim of head and neck cancers is to increase disease-free survival, improve the quality of life, and achieve a functional life by protecting the organs at risk as much as possible. The main goals are to gain a survival advantage by increasing local control with new technological treatment modalities and to prevent early and late side effects. Chemoradiotherapy is known to increase the risk of esophagitis, rashes, infections, and mucositis in patients with head and neck tumors.[13]

It also leads to hematological suppression. NPC is highly sensitive to both RT and chemotherapy. For this reason, chemoradiotherapy is administered to patients in all stages, except T1 tumor. Especially progression-free survival increases with concomitant treatment.[14] Kang et al. in patients with NPC who received chemoradiotherapy, the most acute side effects were leukopenia, neutropenia, decreased hemoglobin, nausea/vomiting, weight loss, and oral mucositis. The most important acute adverse reactions are nausea and vomiting.[9] In RT of NPC, the salivary glands are affected by irradiation, and changes in the amount, nature, and composition of saliva cause various complications. Oral mucositis develops as a result of decreased saliva and is the most common complication bothering patients. The incidence of oral mucositis is 80%, which is quite severe in half of all cases.[15] Oral mucositis is characterized by erythema and fused ulcers. Its main clinical symptoms include decreased salivation, dry mouth, mouth pain, dehydration, taste disturbance, and malnutrition. In addition, severe long-term reactions can lead to difficulties in swallowing and speaking, sleep disturbances, agousia, cavities and oral infections. In addition, severe oral mucositis leads to decreased adherence to treatment, reduced concomitant chemotherapy doses, or discontinuation of radiotherapy, resulting in a lower quality of life, weight loss, prolonged hospital stay, and additional analgesic and anti-infective drugs.[16,17] In our study, grade III mucositis was observed in 77% of patients. In a study by Minhas et al., oral mucositis was predominantly observed in male patients (62%).[18] In a study by Igor et al., oral mucositis was observed in men with a rate of 78.2%.[19] In our study, the incidence rate of grade III mucositis in men was 53%. Luo et al found the most common toxicity with chemoradiotherapy in NPC were grade III or IV oral mucositis (40%), pharyngo-esophagitis (12%), leukopenia (29.6%) and neutropenia (26.4%). Oral mucositis and pharyngo-esophagitis occurred around the 10th fraction of RT. They noted that the most severe oral mucositis and pharyngo-esophagitis occurred during the 20th to 25th fraction.[20] In our study, grade III esophagitis developed in 69% of the patients. In the study conducted by Du et al, the incidence of grade III-IV leukopenia, thrombocytopenia and anemia was found to be 10.1%, and radiation therapy was discontinued in 11 patients for an average of 9.2 days (6-14 days) due to acute toxicity.[21] Grade III hematological toxicity was observed in 8% of the patients in our study, and the treatment was interrupted for an average of 7.1 days (range 5-11). In the study of Maoleekoonpairoj et al., only a few patients had grade 3 and 4 hematological toxicity and there was no gender difference.[22] In the study of Dechaphunkul et al., myelosuppression occurred, including leukopenia (30%), neutropenia (20%), anemia (12%), and thrombocytopenia (6%).[23] In our study, the rate of grade II hematology toxicity was 23%, grade III toxicity was 5%, and grade III toxicity was higher in women.

CONCLUSION

Despite the technological treatment devices and methods, the risk of acute toxicity is high in the treatment of nasopharyngeal cancer due to its anatomical location. Our study is compatible with the literature in terms of acute side effects. Strict follow-up and treatment of acute side effects may increase patient adherence to treatment, improve the quality of life, and increase the effectiveness of treatment. To support this finding, more prospective randomized controlled clinical investigations are required.

Authorship contribution statement

Consept and desing: MK, AB, KA, BÇ.
Acquisition of data: MK, AB, KA, BÇ.
Analysis and interpretation of data: MK, AB, KA, BÇ.
Drafting of the manuscript: MK, AB, KA, BÇ.
Critical revision of the manuscript for important intellectual content: MK, AB, KA, BÇ.
Statistical analysis: MK, AB, KA, BÇ.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

This study was approved by the Faculty of Medicine Scientific Research Ethics Committee of Karadeniz Technical University (Protocol no: 2017/77).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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