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ORIGINAL ARTICLE

The comparison of weekly and three-weekly cisplatin chemotherapy concurrent with radiotherapy in patients with previously untreated inoperable non-metastatic squamous cell carcinoma of the head and neck

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Abstract
Purpose Several studies have shown that the concurrent administration of chemotherapy (CHT) and radiotherapy (RT) is superior to RT alone in patients with inoperable non-metastatic squamous cell carcinoma of the head and neck (InSCCHN). We compared the efficacy and safety profile of RT and concurrent cisplatin CHT given in two different schedules to patients with previously untreated InSCCHN.
Methods Fifty patients with previously untreated InSCCHN admitted to our oncology department were included in the study. Thirty of 50 (60%) patients with a younger age or good performance status (PS) (ECOG 0-1) received cisplatin 100 mg/m^2 on a 21-day schedule (group A). Other 20 (40%) patients with older age or poor PS (ECOG 2) received cisplatin 40 mg/m^2 on a 7-day schedule (group B). Each of the 50 patients received concurrent conventional dose RT according to primer tumor location.
Results The median follow-up is 12 months for group A and 12.5 months for group B. Twenty-eight (93.3%) patients in group A and 18 (90%) in group B were evaluable for response. The complete response rate was 50% in group A and 40% in group B ($P > 0.05$). The objective response rate was 92% in group A and 90% in group B ($P > 0.05$). All grade 3–4 toxic events were seen in 16 (53.3%) of group A patients and 8 (40%) of group B patients ($P > 0.05$).
Conclusions Comparison between two treatment modalities appears to result in statistically similar response rates and adverse event profile. A randomized phase III trial is required to confirm the safety and efficacy of weekly cisplatin therapy in patients with poor PS and/or older age at diagnosis.

Keywords Inoperable head and neck cancer · Squamous cell · Weekly cisplatin · Three weekly · Cisplatin · Concurrent chemoradiotherapy

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Introduction

Radiation therapy (RT) has been considered the standard treatment for inoperable non-metastatic squamous cell carcinoma of the head and neck (InSCCHN), but response rates are relatively low and systemic relapse occurs in 20–30% of cases [1–3]. On the other hand, the superiority of the concurrent administration of chemotherapy (CHT) and RT compared with RT alone in patients with InSCCHN

has been previously reported in several studies. For that reason, chemo-radiotherapy (CHTR) has become the standard of care for InSCCHN [4, 5]. Platinum-based regimens were applied as the most effective regimens. Although the benefits of CHTR are proven, acute toxicities are significantly increased, especially in elderly patients with or without poor performance status [4, 6].

In concurrent CHTR, the dose of cisplatin has ranged from three-weekly higher dose (100 mg/m^2) to low dose daily (6 mg/m^2) or weekly (40 mg/m^2) administration [4, 7–10]. A complete response (CR) rate of 71% and a 4-year survival of 34% were reported with RT with high-dose cisplatin (three-weekly 100 mg/m^2) by Radiation Therapy Oncology Group (RTOG) [11]. However, in the schedules of low dose weekly cisplatin (40 mg/m^2), a CR rate of 62% was documented [8]. High dose CHT should prevent the development of distant metastasis, but there were no data and weekly cisplatin has radio sensitizing effect. Moreover, although the response rates of two treatment schedules were similar, three-weekly cisplatin is less toxic compared with weekly dose [9]. In this study, we compared the efficacy and safety profile of RT and concurrent cisplatin CHT given at two different schedules in InSCCHN.

Materials and methods

Between January 2002 and December 2007, totally 50 patients with histologically confirmed and previously untreated InSCCHN with no evidence of distant hematogenous metastases, and admitted to our oncology department, were included in the study. InSCCHN was staged in accordance with American joint committee for cancer staging system [12] and the patients suffering from oropharynx, hypopharynx, oral cavity and larynx were evaluated.

The initial evaluations included a complete medical history and physical examination in a multidisciplinary clinic by a team of radiation oncologists, medical oncologists, and head and neck surgeons. The locoregional tumor extension was evaluated with endoscopy and CT or MRI scan of the head and neck region. Before treatment, complete blood count, electrolytes, liver enzymes, renal function tests, and lung X-ray were performed in all patients. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2, and be taking in adequate oral nutrition [not percutaneous endoscopic gastrostomy (PEG) dependent, at the initiation of therapy]. Laboratory requirements for the inclusion were having normal levels of bilirubin, hepatic enzymes, and renal functions. Hematologic requirements were a white blood cell count >3,000, absolute neutrophil count (ANC) > 1,000, and platelets >100,000 per mm^3.

The cases were divided into two groups according to ECOG performance status. Group A consisted of 30 patients with younger age and good performance status (ECOG 0-1) and received concomitant cisplatin 100 mg/m^2 on a 21-day schedule during radiotherapy. The remaining 20 patients with older age or poor performance status (ECOG 2) [group B] received 40 mg/m^2 cisplatin on a 7-day schedule. Radiotherapy was administered using 6-MV photons and the radiation doses given to the planning target volume that included primary tumor and involved nodal regions ranging between 66 and 70 Gy given in 33–35 fractions of daily 2.0 Gy each.

Aggressive hydration and antiemetic therapy were used with all cisplatin administration. The patients were evaluated regularly every week during treatment period. Acute systemic toxicities were documented using World Health Organization criteria and late toxicities were assessed using RTOG/European Organization for Research and Treatment of Cancer acute toxicity criteria [13, 14]. Informed written consent was obtained from each subject included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki [15], as reflected in prior approval by the local ethical committee.

Statistical analysis

Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA) software. Descriptives of the parameters are quoted as mean $\pm$ SD and 95% confidence intervals (CI). Normality of the data was tested using Kolmogorov–Smirnov test. Parameters normally distributed were compared with Student's t test. Mann–Whitney U test was applied for non-normally distributed data. Differences between groups in response rate and incidence of toxicity were evaluated using the Fisher's exact test. $P \leq 0.05$ were considered to be statistically significant.

Results

Main baseline characteristics of patient are shown in Table 1. From January 2002 until December 2007, 50 patients with previously untreated InSCCHN were analyzed; the majority of patients localized in larynx (68%, $n = 34$) and presented with stage IV disease (74%, $n = 37$). The patients were divided to two groups according to ECOG performance status and age. Group A included thirty patients of younger age or good performance status (ECOG 0-1). On the other hand, group B included 20 patients of older age or poor performance status (ECOG 2); median age 53.2 (range 43–71); 71 (range 52–80) years, respectively, in groups. There were significant differences between the two groups according to the age ($P = 0.02$). No

Table 1 Patient characteristics

	Group A *n* (%)	Group B *n* (%)	*P*
n	30 (60)	20 (40)	
Sex			
Male	24 (80)	15 (75)	
Female	6 (20)	5 (25)	
Age: median (range)	53.2 (43–71)	71 (52–80)	0.02
ECOG PS			
0	13 (43.3)	–	
1	17 (56.7)	–	
2	–	20 (100)	
Stage			
III	9 (30)	4 (20)	
IV	21 (70)	16 (80)	
Primary site			
Oropharynx	2 (6.6)	2 (10)	
Hypopharynx	5 (16.6)	3 (15)	
Larynx	22 (73.5)	15 (75)	
Oral cavity	1 (3.3)	–	
T and N stage (*n*)			
T1:T2:T3:T4	1:4:10:15	0:3:6:11	
N0:N1:N2:N3	2:5:12:11	2:3:6:9	
Tumor differentiation			
Well differentiated	10 (33.4)	3 (15)	
Moderately well differentiated	12 (40)	10 (50)	
Poorly differentiated	8 (26.6)	7 (35)	
Follow-up duration: median (month; range)	12 (1–33)	12.5 (1–43)	

ECOG PS Eastern Cooperative Oncology Group performance status

differences were identified between the treatment arms in sex, tumor stage and tumor differentiation ($P > 0.05$).

In group A, patients received cisplatin 100 mg/m^2 on a 21-day schedule. The remaining 20 patients (group B) received cisplatin 40 mg/m^2 on a 7-day schedule. In addition, all patients were treated with concurrent conventional dose RT according to primer tumor location as planned per protocol. A total dose of RT was 66–70 Gy (median 70 Gy) In group A, median cisplatin cycle was three. Three patients received two cycles three-weekly cisplatin because of the treatment toxicities in this group. The number of weekly cisplatin courses ranged from four to six (median six courses) in group B. Total treatment times ranged from 44 to 70 days, with a median of 64 days for group A and a median treatment time was 43 days (range 43–55 days) in group B. There was no difference with respect to total treatment times in groups.

Chemotherapy was administered without interruption in 74% ($n = 22$) and 65% ($n = 13$) of patients, respectively. Cisplatin courses were interrupted due to hematological (4 patients in group A, 6 patients in group B) or renal disfunction (4 patients in group A, 1 patient in group B). RT treatment interruptions were similar in two arms (43 vs. 40%). The most cause of interruption was mucosal toxicity due to RT in groups. Treatment interruptions because of toxicity were similar in two groups. There were no differences regarding the administration of CHT and RT ($P \geq 0.05$).

The features of toxicity in groups are listed in Table 2. All grade 3–4 toxic events were seen in 16 (53.3%) of group A patients and 8 (40%) group B patients. As for all grade 3–4 toxicity, no differences were detected ($P > 0.05$). Nausea and vomiting were similar in both treatment schedules. Grade 3–4 skin toxicity was observed in 13.3 and 15% of patients, respectively, in groups. Grade 3–4 mucous membrane toxicity was also similar in two groups (23.3 vs. 25%). Grade 3–4 nephrotoxicity was detected in 16.6% of group A patients. However, in group 2, Grade 3–4 nephrotoxicity was observed in only one patient (5%). These differences were not statistically significant ($P > 0.05$). Grade 3–4 hematologic toxicities were similar in all groups. Although neutropenia in group A was mildly higher than group B patients, there were no differences in two treatment schedules ($P > 0.05$). One patient died of febril neutropenia related to treatment in group A. Tube-feeding was performed in only 36.6% of the patients of group A. Moreover, 40% of group B patients underwent feeding procedure. There were no differences concerning enteral feeding procedure ($P = 0.75$). Hospitalization was needed to manage toxicity in three (10%) and four (20%) patients in groups, but no difference was statistically detected ($P = 0.66$).

The median follow-up is 12 (range 1–33) months for group A and 12.5 (range 1–43) months for group B. Twenty-eight patients (93.3%) and 18 patients (90%) were

Table 2 Grade 3 and 4 toxic events in groups

Toxicity[a]	Group A		Group B	
	No. (%)	Group 3/4	No. (%)	Group 3/4
Non-hematologic toxicities				
Nausea/vomiting	12 (40)	9/3	4 (20)	4/0
Nephrotoxicity	5 (16.6)	3/2	1 (5)	1/0
Stomatitis/esophagitis	7 (23.3)	6/1	5 (25)	3/1
Skin	4 (13.3)	3/1	3 (15)	2/1
Hematologic toxicities				
Neutropenia	6 (20)	5/1	3 (15)	3/0
Anemia	2 (6.6)	2/0	2 (10)	1/1
Thrombocytopenia	5 (16.6)	4/1	1 (5)	1/0

[a] World Health Organization acute toxicity and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late toxicity criteria

evaluable for response in groups. Locoregional CR was achieved in 50% of group A patients and in 40% of group B patients. There were no differences between two treatment groups regarding CR ($P > 0.05$). Furthermore, the objective response (OR) was detected in 92% of group A patients and in 90% of group B patients. OR was also statistically similar between group A and group B ($P > 0.05$).

Discussion

Although RT alone has been the standard management approach, because of relatively low response rates, concurrent CHRT has recently become the standard care for InSCCHN. However, the concomitant administration of CHT and RT could increase severe adverse events which reduce the PS of patients; CHRT is less tolerable, especially in elderly and patients with poor PS [1–5]. Some chemotherapeutic agents have been used concurrently with RT in InSCCHN. Several studies have suggested improved response rates with single agents cisplatin [4, 6, 8–10, 16, 17], fluorouracil [4, 18, 19], methotrexate [20] and mitomycin [21]. On the other hand, the regimens containing platinum were most effective.

In studies, cisplatin have been concurrently used with RT on a dose of high (three-weekly) and low (daily or weekly) [4, 7–10]. Geeta et al. [9] showed that three-weekly cisplatin therapy was less toxic than weekly. We also compared concurrent weekly and three-weekly cisplatin CHT with RT in InSCCHN. Grade 3–4 toxicity was detected in 53.3% of group A patients and 40% of group B patients in our study. The most common grade 3–4 toxic events were nausea and vomiting in group A, but mucous membrane toxicity in group B. However, the differences were not significant. Severe neutropenia was detected in 20 and 30% of patients. In our study treatment schedules, all grade 3–4 toxicities were similar compared with other studies [8–11].

Medina et al. [8] have shown that the most common acute toxicity was mucositis, which reached grade 3 in 85% of patients treated with weekly cisplatin. On the other hand, they have also detected grade 3 neutropenia (5%), grade 3 thrombocytopenia and anemia (3%) in their study. In other studies, grade 3–4 toxicity was reported in 85% of patients who received concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 of RT [4]. Our all grade 3–4 toxic events were more higher in group B than those in previous reported studies [8, 9, 11]. However, in group A, grade 3–4 toxicity was more less compared with literature [9]. Although all grade 3–4 toxicities for group B were more higher than those for group A, grade 3–4 neutropenia was more less in group B compared with group A as expected.

Two studies have identified CR in 40.2–90% of patients treated with three-weekly cisplatin [4, 17]. Furthermore, in patients who received weekly cisplatin, CR rate was reported as 66–73.3% [8, 10]. We detected a CR rate in 50% of patients treated with three-weekly cisplatin and in 40% patients who received weekly cisplatin. In addition, 92 and 90% OR rate, were observed in our study. The subgroup analysis of T and N stage could not be performed because of our similar OR rate and small number of patients in both groups. Our results were in concordance with literature.

Most of the patients completed the study treatment in groups without interruption due to both CHT and RT. In previous studies, treatment completion rates have been documented in 85.1% of patients treated with three-weekly cisplatin [4] and in about 95% of patients who received weekly cisplatin [8, 10].We detected different rates of treatment completion in groups, but this was not statistically significant. The cause of this difference can be explained with grade 3–4 mucositis which affected 25% of patients that received weekly cisplatin and the poor performance status of these patients.

Barzan et al. [22] suggested that age was not an independent prognostic factor for local control and survival in patients with head and neck cancer. They have also shown that stage appeared to be the most important prognostic factor. Furthermore, Dreyfuss et al. [23] indicated that age, sex, and performance status did not correlate with treatment outcome. In recently reported study by Geeta et al. [9], no influence of age and sex on treatment toxicity was shown. We detected difference regarding age and performance status in two treatment arms, but the impact of age and performance status on treatment response could not be suggested and response rates were also similar in two groups.

In conclusion, we detected statistically similar response rates and adverse events profile when two treatment modalities were compared. A randomized phase III trial is required to confirm the safety and efficacy of weekly cisplatin therapy in patients with poor performance status and/or older age at diagnosis. Our study is not a phase III trial, but especially in patients who were of older age and poor performance status with previously untreated InSCCHN, weekly cisplatin regimen may used with concurrent RT.

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