

RESEARCH COMMUNICATION

Weekly Cisplatin versus Standard Three-weekly Cisplatin in Concurrent Chemoradiotherapy of Head and Neck Cancer: the Baskent University Experience

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Abstract

Background: The majority of patients with head and neck cancer are treated with concurrent chemoradiotherapy. However, toxicity is substantial so that alternate schedules of cisplatin have been tried to overcome this problem. No formal comparison, however, has been reported between alternate schedules and reference regimen. **Patients and methods:** Fifty-five eligible patients treated with concurrent chemoradiotherapy were retrospectively analyzed. The patients treated with weekly cisplatin were defined as group A, while the patients treated with standard regimen were defined as group B. Basic demographics and clinical characteristics, overall survival rate, locoregional or systemic relapse rates, and time to local/systemic relapse were recorded. **Results:** One, two, and three-year probability of survival in groups A and B were 75% to 65% after one year, 63% to 56% after two, and 63% to 52% after three, respectively. Although time to local and systemic relapse was higher in group B as compared to group A, a statistical analysis was failed to show any significant difference. Furthermore, there was no significant difference between groups with respect to major toxicity. **Conclusion:** In patients with head and neck cancer, concurrent chemoradiotherapy with weekly cisplatin might be as effective as concurrent chemoradiotherapy with bolus cisplatin.

Keywords: Head and neck cancer - concurrent chemoradiotherapy - cisplatin schedule

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Introduction

Head and neck cancer is the fifth most common cancer in the world (Sankaranarayanan et al., 1998). Smoking and alcohol abuse are the primary risk factors. The majority of cases are diagnosed at a locally advanced stage. Concurrent chemoradiation has become a standard modality for this disease (Traynor et al., 2010). A meta-analysis of studies showed that addition of chemotherapy to radiotherapy yielded an absolute benefit of 8% at five years in term of overall survival compared with radiotherapy alone (Haddad et al., 2008; Pignon et al., 2000). Single agent bolus cisplatin in every three weeks at a dose of 100 milligram per square meter is accepted as standard reference regimen in the setting of definitive chemoradiation (Forastiere et al., 2003). Reference regimen was also successfully tested in adjuvant setting with significant survival benefit (Bernier et al., 2004; Cooper et al., 2004). This regimen is, however, usually associated with significant increase in acute toxicities such as higher rate of mucositis, hematological complication, and renal complication. Occurrence of these side effects can be resulted with early treatment termination or at

least, decrease in treatment compliance (Adelstein et al., 2003; Bernier et al., 2004; Cooper et al., 2004; Traynor et al., 2010). For example, in these trials only 74 to 85 % of patients were treated with an intended cisplatin dose (Adelstein et al., 2003; Bernier et al., 2004). Therefore, splitting full dose three-weekly cisplatin as a weekly cisplatin schedule might decrease toxicities and increase compliance while maintaining dose intensity seem to logical. The Head and Neck Intergroup conducted a phase III trial comparing radiation therapy alone with chemoradiotherapy with weekly cisplatin at a dose of 20 milligram per square meter. This trial, however, was a negative study. Although response rate was higher in the chemoradiotherapy group, overall survival was too short and not statistically different between groups (Haselow RE., 1990). Though, there are other studies suggesting weekly cisplatin regimen to be feasible in literature, no randomized comparison has been made between weekly and three weekly cisplatin regimens.

In this study, we report a retrospective analysis of fifty five head and neck cancer patients who were treated at adjuvant or definitive setting with weekly or three weekly cisplatin regimens. The main aim of this study was to

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make comparison between these regimens and define a subgroup of patients in which we can safely substitute alternate weekly cisplatin with standard regimen.

Materials and Methods

Patients and methods

Retrospective chart review of patients with histologically confirmed head and neck cancer who were followed in Baskent University between 2007 and 2009 was carried out. Radiation dose administered to the primary and neck was between 50 and 70 Gy and administered as fractions of two Gy for five days in week. Patients were divided into two groups based on their chemotherapy regimens. The patients who were treated with weekly cisplatin (30 mg/m²/week) during radiotherapy were the group A, while the patients who were treated with standard regimen (100 mg/m²/cycle, every 21 days) were group B. Medical charts were reviewed systematically considering demographic and clinical characteristics including age, sex, body surface area, Eastern Cooperative Oncology Group (ECOG) performance score, stage of disease, and tumor location. Additionally chemotherapy regimens, total cisplatin dose during radiotherapy, whether or not taking neoadjuvant chemotherapy, major toxicities, local or systemic relapse rates, time to local relapse and time to systemic relapse, and overall survival rates were documented. Excel 4.0, 2007 (Microsoft, Redmond, WA) was used for data entry.

Statistical analysis

All results are presented as rate for categorical values or mean and median for continuous variables. Overall survival (OS) was determined as time between histological diagnosis and death. Time to local relapse and time to systemic relapse were determined as time between histological diagnosis and local/systemic relapse (TTloR, TTsyR), respectively. Survival curves were estimated according to the Kaplan-Meier method and log-rank tests were used for univariate statistical comparisons. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were used for estimation. All data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL) and a p value of <0.05 was considered statistically significant.

Results

Medical charts of 55 patients with histologically confirmed head and neck cancer were reviewed. The patient’s clinical and demographic characteristics are summarized in Table 1. No significant difference was observed between the treatment arms comparing age, sex, history of cigarette smoking, presence of co-morbidity, whether or not taking neoadjuvant chemotherapy, and performance status. There was a significant difference for total cisplatin dose between group A and B (p<0.0001). Patients in group B received higher total cisplatin dose during radiotherapy as compared with group A (Table 1). Median overall survival time was not reached for both groups. One, two, and three-year probability of survival for patients in group A and B were 75% and 65% in one

Table 1. Clinical Characteristics

	Group A(32)	Group B(23)	Total(55)
Age (years, range)	58 (31-80)	60 (37-90)	59 (31-90)
Sex			
Male	26 (81%)	18 (78%)	44 (80%)
Female	6 (19%)	5 (22%)	11 (20%)
Co-morbidity	5 (16%)	8 (34%)	13 (24%)
Cigarette smoking	25 (80%)	18 (78%)	43 (78%)
Performance status			
0	16 (50%)	11 (48%)	27 (49%)
1	14 (44%)	9 (40%)	23 (42%)
2	2 (6%)	3 (12%)	5 (9%)
Primary tumor site			
Oral cavity	5 (16%)	1 (4%)	6 (11%)
Oropharynx	9 (28%)	4 (17%)	13 (24%)
Hypopharynx	0	2 (9%)	2 (4%)
Larynx	18 (56%)	14 (60%)	32 (58%)
Nasopharynx	0	2 (9%)	2 (4%)
Overall stage			
II	3 (9%)	2 (9%)	5 (9%)
III	15 (47%)	67(30%)	22(40%)
IV	14 (44%)	14 (61%)	28 (51%)
Neoadjuvant chemo	8 (25%)	5 (17%)	12 (22%)
Total cisplatin(mg/m ² -range)	162(85-240)	210 (71-300)	181 (72-300)

year, 63% and 56% in two year, and 63% and 52% in three year, respectively (Figure 1). Although median overall survival rate was higher for patients those who were treated with weekly cisplatin, this did not reach statistically significant level.

Similar results were seen for time to progression

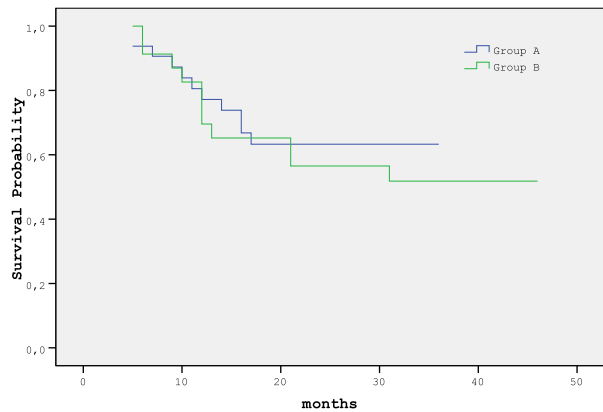


Figure 1. Predicted Survival for Patients Treated with Weekly Cisplatin (group A) versus the Standard Regimen (group B)

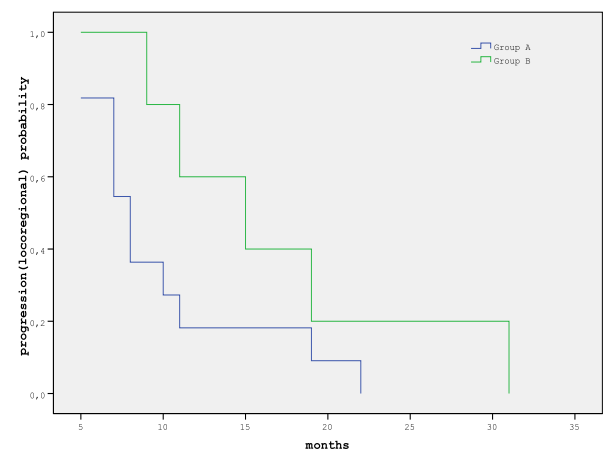


Figure 1. Predicted Time to Local Relapse (TTloR) for Patients Treated with Weekly Cisplatin (group A) versus the Standard Regimen (group B)

Table 2. Toxicity during Concurrent Chemotherapy

	Group A(32)	Group B(23)	Total(55)
Hematologic toxicity			
Grade 0	4 (13%)	3 (13%)	7 (13%)
Grade I-II	25 (78 %)	17 (74%)	42 (76%)
Grade III-IV	3 (9%)	3 (13%)	6 (11%)
Mucositis			
Grade I-II	9 (28%)	9 (41%)	18 (33%)
Grade III-IV	23 (72%)	13 (59%)	36 (67%)
Renal toxicity			
	4 (13%)	2 (9%)	6 (11%)

rates. Locoregional relapse and distant metastases rate were seen in whole group with rate of 16(29%) and 11(20%), respectively. Statistical analysis was failed to show significant difference between groups with regard to locoregional and distant metastases rate ($p>0.05$). During follow-up period, eleven and five patients were experienced locoregional relapse of disease in groups A and B, respectively. TTloR was 9 months in whole patient group (95% confidence interval [95%CI], 5-12.9). TTloR for group A and B were 8 months (95% confidence interval [95%CI], 6.1-9.8) and 15 months (95% confidence interval [95%CI], 6.4-23.5), respectively. Four patients in group A and seven patients in group B were experienced systemic relapse. TTsyR for whole group was 7 months (95% confidence interval [95%CI], 3.7-10.2). TTsyR for group A and B were 6 months (95% confidence interval [95%CI], 4-7.9) and 9 months (3.8-14), respectively. TTloR and TTsyR were higher in group B as compared to group A, though none of these values reached to statistically significance level (Figure 2, 3).

Toxicities during treatment are detailed in Table 2. No differences were found between the treatment groups in terms of renal toxicity, grade III-IV hematological toxicity, and grade III-IV mucositis. However, myelosuppression was more common in group B, while grade III-IV mucositis was higher in group A.

Patients those with grade III-IV mucositis during chemoradiotherapy had significantly higher median overall survival rate than patients those with grade I-II mucositis. Only grade III-IV mucositis during treatment showed significant effect on OS in univariate analysis.

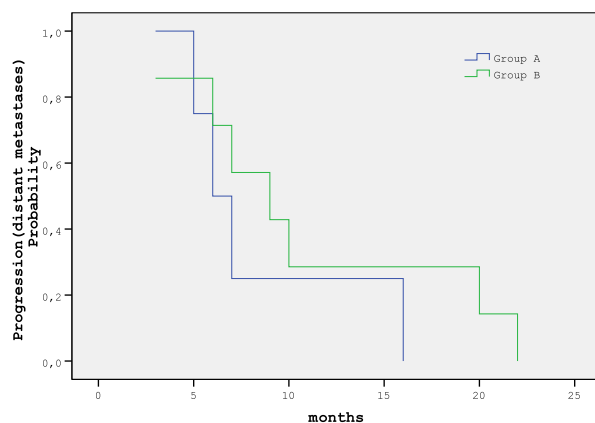


Figure 1. Predicted Time to Systemic Relapse (TTsyR) for Patients Treated with Weekly Cisplatin (group A) versus the Standard Regimen (group B)

Discussion

A Head and neck cancer was diagnosed in more than half million people worldwide in every year (Haddad and Shin, 2008). Majority of patients are diagnosed at advanced stage. One hundred milligram per square meter cisplatin every three week with radiotherapy was accepted standard regimen for either in case of high risk adjuvant treatment or definitive chemoradiotherapy. This report summarizes significant number of head and neck cancer patients' data including basic demographic and clinical characteristic. There was no significant difference between the group A and group B with respect to parameters such as age, sex, smoking habit, disease stage, presence of co-morbidity, whether or not taking neoadjuvant chemotherapy, and performance status. Patients in group B had been exposure to significantly higher total cisplatin dose as compared to Group A. Though study design was retrospective, baseline characteristics of patients were similar. Median overall survival time was not reached for both groups. One, two, and three-year probability of survival for patients in group A and B were 75% to 65% in one year, 63% to 56% in two years, and 63% to 52% in three years, respectively. TTloP and TTsyP for group A and B were 8 to 15 months and 6 to 9 months, respectively. No significant differences were detected with regard to OS, TTloR and TTsyR between two groups. Additionally no significant difference was seen between treatment arms with respect to local or systemic toxicities.

A pooled analysis of trials with head and neck cancer showed an absolute benefit of 8% favored concurrent chemoradiotherapy compared with radiotherapy alone (Cooper et al., 2008). Though three weekly high dose bolus cisplatin is preferred regimen, there has been no optimal chemotherapy regimen during radiotherapy. Because bolus three weekly regimens were associated with severe local and systemic toxicities, most clinics reserved it for patients with better performance score (Forastiere et al., 2003; Adelstein et al., 2009). Additionally, alternate regimens of cisplatin seem to have better tolerability. These regimens were consisted of 6mg/m²/day, 20 mg/m²/day for five days on weeks one and five, 30-40 mg/m²/week cisplatin (Haselow et al., 1990; Bachaud et al., 1996; Jeremic et al., 1997; Huguenin et al., 2004; Traynor et al., 2010). In one trial, radiotherapy with alternate cisplatin schedule showed significantly higher rate of survival and local control rates as compared to radiotherapy alone (Jeremic et al., 1997). Although these regimens have not been compared with standard regimen, they are suggested as reasonable options in setting of concurrent chemoradiotherapy. In current study, even total cisplatin dose in group B was significantly higher than group A, statistical analysis failed to show any significant difference between two groups in term of OS. Indeed one, two, and three year OS rates were better for patients in group A as compared to group B. Therefore current study suggested that alternate schedule with weekly cisplatin was as effective as standard dose three weekly cisplatin.

After curative treatment, patients with head neck cancer can relapse by locally and/or distant metastases. It has been clearly demonstrated that addition of

chemotherapy to radiotherapy increases overall survival rates by improving loco regional control rates rather than preventing distant metastases (Haddad and Shin, 2008). Even addition of induction chemotherapy to concurrent chemoradiotherapy failed to decrease distant metastases rate in head and neck cancer (Forastiere et al., 2003; Posner et al., 2007; Vermorken et al., 2007). In current study, local and systemic relapse rates for group A and B were consisted with literature. Though, TTloR and TTsyR in group B was higher compared with group A, statistical analysis failed to show significant difference between these two groups.

Chemoradiotherapy was one of the main curative treatment modality for head and neck cancer. But its toxicities can be life threatening (Haddad and Shin, 2008). Splitting the dose of cisplatin can help minimize these toxicities. In present study, we were not able to show significant difference between treatment groups in term of all measured toxicities. Though myelosuppression was seen in higher rate in group B and severe mucositis was seen higher rate in group A. This finding was somewhat different than what we are expecting. We did not have any explanation for that. But our study suggested that weekly cisplatin was effective but not less toxic regimen than high dose bolus cisplatin. However, we did not use any parameter that was accepted as 'cumulative high dose' cisplatin toxicity such as frequency of marked nausea and vomiting, peripheral neuropathy, and hearing loss in both groups and treatment cessation rate due to mentioned toxicities. This was the weakness of current study. Therefore, it would be inappropriate to conclude that these schedules have same toxicity by using only these data.

In conclusion, alternate schedule with weekly cisplatin during radiotherapy is as effective as three weekly cisplatin with respect to OS, locoregional/systemic relapse rates, TTloR and TTsyR time. Last but not least, we were not able to show that alternate regimen was less toxic than standard regimen. However, our study did not include whole toxicity parameters which would be needed to reach firm conclusion about treatment toxicity.

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