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International Journal of Current Research
Vol. 8, Issue, 10, pp.40551-40555, October, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

WEEKLY VERSUS THREE-WEEKLY CISPLATIN DELIVERED CONCURRENTLY WITH RADIOTHERAPY FOR PATIENTS WITH HEAD AND NECK SQUAMOUS CELL CARCINOMA:A RANDOMIZED CONTROLLED TRIAL

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ARTICLE INFO

Article History:
Received 11th July, 2016
Received in revised form
18th August, 2016
Accepted 29th September, 2016
Published online 30th October, 2016

Key words:

Chemoradiotherapy,
Cisplatin,
Head and Neck Cancer,
Radiotherapy,
Toxicity.

ABSTRACT

Background and Aim: The standard chemoradiotherapy (CRT) protocol in head and neck cancers (HNC) consists of three cycles of high-dose cisplatin every three weeks. This study compared the acute toxicity profiles of these two concomitant CRT protocols in squamous cell carcinoma of the head and neck.

Methods and Materials: 89 locally advanced head and neck cancers (HNC) patients' candidate for CRT randomly assigned into two groups. Forty-seven patients to arm A (40 mg/m2 weekly cisplatin) and 42 patients to arm B (100mg/m2 triweekly cisplatin). According to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, weekly assessment and grading of acute toxicities were done.

Result: Our results did not show any statistically significant difference between the rate of treatment interruption and acute hematologic and non-hematologic toxicity profiles of the two schedules of cisplatin administration. Only there was a trend of more grade≥3 mucositis in the weekly cisplatin arm, but the difference was not significance.

Conclusion: in terms of acute treatment toxicity the weekly administration of cisplatin concomitant with RT has the similar objective result with the triweekly schedule. However, because we did not assess the locoregional recurrence-free survival (LRFS) and overall survival (OS) in this trial, thus, we cannot suggest that weekly cisplatin CRT can be the alternative protocol for the standard triweekly schedule.

Citation: Hodjatollah Shahbazian, Shole Arvandi, Sayed Mohammad Hosseini, Sasan Razmjoo, Ali Bagheri, Maedeh Barahman and Somaye Barihi, 2016. "Weekly versus three-weekly cisplatin delivered concurrently with radiotherapy for patients with head and neck squamous cell carcinoma: A randomized controlled trial", *International Journal of Current Research*, 8, (10), 40551-40555.

INTRODUCTION

Definitive radiotherapy (RT) was the historical standard treatment in locally advanced head and neck cancers (HNC). But recent evidence indicated superior results by combining cytotoxic chemotherapy (CT) with RT (Halperin *et al*., 2013). A meta-Analysis by Pignon *et al*. compared the results of chemotherapy in Head and Neck Cancer (MACH-NC), only concurrent chemoradiotherapy (CRT) to other forms of adding CT to RT, and revealed significant improvement in local tumor control and survival rate versus RT alone (Pignon *et al*., 2009). Also in the adjuvant setting, Radiation Therapy Oncology Group (RTOG), 9501 trial showed that postoperative concomitant CRT, only in subgroups of patients with either positive surgical margins or extracapsular extension, improves locoregional tumor control in comparison with single modality RT (Cooper *et al*., 2012). The most widely used CRT protocols consist of three cycles of 80-100 mg/m2 of cisplatin once every three weeks on days 1, 22 and 43 of RT (Forastiere *et al*., 2003). However, because of significant toxicity compliance that is a major problem and approximately one-third of patients do not receive all planned cycles of CT (Halperin *et al*., 2013), some authors suggest cumulative doses more than 200 mg/m2 are sufficient for achieving the maximal benefit from concurrent CRT, therefore, weekly cisplatin regimens have been developed. With the assumption that more frequent administration of smaller doses of cisplatin during the RT course will minimize adverse effects without compromising treatment efficacy, these studies deliver nearly the same cumulative doses as three weekly schedules (Jeremic *et al*., 2000; Ang, 2004). But interestingly, despite the common belief that weekly cisplatin has less toxicity than every three-

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week regimen, a recent meta-analysis that evaluated 10 trials and 779 patients from 1982 to 2015, indicated that weekly schedule results in higher risk of dermatitis, therapy delay, and interrupt but lower gastrointestinal reactions. Also in subgroup analysis, grade ≥3 mucositis in non-nasopharynx HNC was higher in the weekly regimen. Overall survival rate and locoregional recurrence-free survival were not different between two groups (Yue Zhang *et al*., 2015). To address these concerns and to shed light on the efficacy and adverse events of treatment protocols, we conducted this randomized controlled trial (RCT) to evaluate the common impression of better tolerability and ease of administration of weekly schedules by directly comparing acute toxicities of weekly versus triweekly cisplatin regimen in concomitant CRT protocols for head and neck squamous cell carcinoma (SCC).

MATERIALS AND METHODS

Study design

This was a single-blind randomized clinical trial RCT conducted at the Clinical Oncology Department of Golestan Hospital (Ahvaz Jundishapour University of Medical Sciences, Ahvaz, Iran). Registration was done in the Iranian Registry of Clinical Trials (IRCT.ir) (number IRCT2015112225185N1). The study procedure was explained to all patients and written informed consent was obtained, moreover, the study protocol was approved by The Ahvaz Jundishapur University of Medical Sciences ethics and scientific committees approved the study protocol according to the Helsinki declaration (ajums.REC.1393.382). The patients were enrolled from February 2015 to February 2016. The patients with histopathologically confirmed head and neck squamous cell carcinoma (SCC) that were planned to be treated with CRT, were randomized into two groups. In the first group, patients treated with weekly low dose cisplatin during radiotherapy (RT) (arm A) and in the second group, patients received concomitant high-dose cisplatin once triweekly (arm B). In both arms, patients received definite or adjuvant CRT with curative intent. Acute treatment toxicity was the primary end.

Eligibility

Eligible patients were 18–70 years old with a biopsy- proven non-metastatic head and neck SCC, Eastern Cooperative Oncology Group (ECOG) performance status 0 –2, white blood cell count ≥4000/mm3, platelet count ≥100000/mm3, hemoglobin concentration ≥10 gr/dl, serum creatinine concentration ≤1.5 mg/dl, serum aminotransferase less than twice of the upper limit of normal range and a total bilirubin concentration ≤2 mg/dl.

Chemotherapy

At an outpatient setting, arm A patients received weekly low dose cisplatin (40 mg/m^2) on days 1,8,15,22,29,36 and 43 of RT and in arm B, patients were treated with concomitant once triweekly schedule at a dose of 100 mg/m2 on days 1, 22 and 43. Both arms of this study received adequate pre-chemotherapy hydration and antiemetic prophylaxis with dexamethasone plus 5HT3 antagonist plus aprepitant. Also in all patients, cisplatin dose was reduced by 25% in subsequent CT cycles if severe toxicities were encountered (Chu and DeVita Jr. 2008).

Radiotherapy

After immobilization with a head and neck thermoplastic mask and computed tomography simulation, RT was delivered with 6 MV photon beams produced by a linear accelerator using three-dimensional conformal techniques (3DCRT). Radiation dose to the primary tumor and gross lymphadenopathy in definitive CRT protocols and tumor bed boost in the adjuvant setting was 70Gy and 64-66Gy with conventional fractionation (2Gy fractions, five fractions per week) respectively. In addition, if clinically indicated, elective nodal irradiation was carried out to at least 44Gy. The spinal cord dose was kept below maximum tolerance by using off cord fields after 44Gy and posterior cervical lymph nodes were boosted with electron beams if needed.

Toxicity evaluation

Weekly assessment and grading of acute toxicities were done by a trained assistant during treatment according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (2010). In addition, treatment interruption was defined as completion of less than five and two chemotherapy cycles in arms A and B, respectively (Homma *et al*., 2011).

Statistical analysis

Data were analyzed using SPSS version 22. Categorical data are presented as numbers (%), and continuous data as mean ± SD. We used the Chai_2 or Fisher's exact test to compare categorical variables and the Student's t-test, to compare continuous variables. $\alpha < 0.05$ was considered significant. Acute toxicities, cumulative cisplatin and mean RT dose and rate of chemotherapy interruption were compared in the two arms of this trial.

RESULTS

Totally 89 consecutive patients (76 males and 13 females) were enrolled in this trial, of which 47 patients randomly assigned to arm A (40 mg/m2 weekly cisplatin) and 42 patients to arm B (100mg/m2 triweekly cisplatin). Patient demographics, primary tumor site location, and pre-treatment lab data are shown in table 1.The most common site was the larynx (43 patients).In nasopharyngeal carcinoma, we enrolled only patients with SCC, not non-keratinizing differentiated or undifferentiated carcinoma. RT and cisplatin dose, treatment type plus treatment interruption rate is outlined in table 2 and the difference between the two groups was not significant. The cisplatin CRT was stopped in 25 patients (53.1%) in arm A due to 5 cases of grade 3 nausea and vomiting, 12 cases of grade 3 mucositis and 8 cases of grade 3 pharyngitis. 22 patients (52.3%) in arm B was stopped CRT before completion of all courses due to 10 cases of grade 3 mucositis, 8 cases of grade 3 pharyngitis, 1 case of Gastrointestinal Bleeding (GIB) and 3 cases of grade 3 nausea and vomiting. In addition, there was not a statistically significant difference between grade ≥ 3 and grade < 3 acute hematologic and non-hematologic toxicities between the two arms of this trial (table 3, 4). Grade 3 anemia was observed in 4.3% of arm A (weekly CRT) and 2.4% of arm B (triweekly CRT) which was statistically not significant (P= 0.57). We did not detect liver and renal toxicity, but one grade 2 GIB was observed in arm B with no surgical intervention and no mortality.

Table 1. Patient characteristics at baseline

	Arm A (Weekly cisplatin) (40 mg/m²) (N=47)	Arm B (Three weekly cisplatin) (100 mg/m²) (N=42)	P-value
Sex			
Male	39 (83%)	37 (88.1%)	0.495
Female	8 (17%)	5 (11.9%)	
Mean age	56.1±10.1 year	55.2±9.1 year	0.68
Primary site			
Oral cavity	1 (2.1%)	0 (0%)	1.00
Oropharynx	5 (10.6%)	1 (2.4%)	0.20
Hypopharynx	15 (32%)	11 (26.2%)	0.82
Nasopharynx	7 (14.9%)	6 (14.3%)	1.00
Larynx	19 (40.4%)	24 (57.1%)	0.45
Lab data			
Hb (gr/dl)	12.2±1.2	12.4±1	0.31
WBC (/mm³)	6066±1454	6449±1560	0.235
Plt (/mm³)	308×10³±91×10³	287×10³±110×10³	0.334

Hb Hemoglobin concentration; WBC White blood cell count; Plt Platelet count

Table 2. Treatment characteristics in two groups

Characteristic	Arm A (Weekly cisplatin) (40 mg/m²) (N=47)	Arm B (Three weekly cisplatin) (100 mg/m²) (N=42)	P-value
Treatment Type			
Definitive	39(82%)	29(69%)	0.14
Adjuvant	8(17%)	13(30%)	
Mean RT dose (Gy)	65.6±3	68±2.2	0.51
Cumulative cisplatin dose			
<200 mg/m²	5 (10.6%)	5 (11.9%)	1
≥200 mg/m²	42 (89.4%)	37 (88.1%)	
Mean	319.6±81	310±80	0.57
Chemotherapy Interruption	25 (53.1%)	22 (52.3%)	1

Table 3. The frequency of acute Hematologic toxicity in two groups

Toxicity	Arm A (Weekly cisplatin) (40 mg/m²) (N=47)	Arm B (Triweekly cisplatin) (100 mg/m²) (N=42)	P-value
Anemia			
Normal Hb	34 (72.3%)	26 (61.9 %)	0.5
<grade 3	11 (23.4%)	15 (35.7%)	0.57
≥grade 3	2 (4.3%)	1 (2.4%)	
Leukopenia			
Normal WBC	37 (78.7%)	34 (80.9%)	1
<grade 3	10 (21.3%)	8 (19.1%)	1
≥grade 3	0 (0%)	0 (0%)	
Thrombocytopenia			
Normal Plt	42 (89.3%)	41 (97.6%)	0.2
<grade3	5 (10.6 %)	1 (2.4%)	1
≥grade 3	0 (0%)	0 (0%)	

Hb Hemoglobin concentration; WBC White blood cell count; Plt Platelet count

Table 4. The frequency of acute Non-Hematologic toxicity in two groups

Toxicity	Arm A (Weekly cisplatin) (40 mg/m²) (N=47)	Arm B (Triweekly cisplatin) (100 mg/m²) (N=42)	P-value
Dermatitis			
<grade3	47 (100%)	42 (100%)	1
≥grade 3	0 (0%)	0 (0%)	
Pharyngitis			
<grade3	36(76.6%)	28(66.7%)	0.34
≥grade 3	11(23.4%)	14(33.3%)	
Mucositis			
<grade3	33 (70.2%)	35 (83.3%)	0.211
≥grade 3	14 (29.8%)	14 (29.8%)	
Nausea/Vomiting			
<grade3	40 (85.1%)	33 (78.6%)	0.581
≥grade 3	7 (14.9%)	9 (21.4%)	
Renal dysfunction			
<grade3	0 (0%)	0 (0%)	1
≥grade 3	0 (0%)	0 (0%)	
Fever			
<grade3	1 (2.1%)	3 (7.1%)	0.339
≥grade 3	0 (0%)	0 (0%)	
Liver dysfunction			
<grade3	0 (0%)	0 (0%)	1
≥grade 3	0 (0%)	0 (0%)	

Hb Hemoglobin concentration; WBC White blood cell count; Plt Platelet count

Grade 3 mucositis was observed in 14 patients (29.8%) in arm A and 7 patients (16.7%) in arm B which was not statistically significant between the two arms (P =0.21). No grade 3 dermatitis was observed in either arm.

DISCUSSION

According to CRT protocols in HNC, which is based on multiple well-designed phase III RCT's, high dose triweekly cisplatin is considered the standard of care. Weekly low dose cisplatin is commonly used for chemoradiotherapy in uterine cervical SCC (Pearcey *et al*., 2002). In current practice, the efficacy and adverse events of two treatment approaches were not different significantly. However, as oppose to our results, many investigators have hypothesized that more frequent administration of low doses of cisplatin during RT improves treatment results and decreases side effects. A model described by Marcu *et al*. in 2006 showed that "daily administration of cisplatin resulted in a 35% improvement of tumor control as compared to radiation alone, while weekly cisplatin has improved radiotherapy only by 6%" (Marcu *et al*., 2006). Harmoniously a review by Marcu *et al*. in 2003 revealed Daily low-dose cisplatin increased tumor control with less toxicity as compared to weekly high-dose drug delivery (Marcu *et al*., 2003). However, the results of previous trials were not consistent and a study by Tsan *et al*. in 2012 indicated higher compliance, and lower acute toxicity in three-weekly high-dose cisplatin treatment group than weekly low-dose cisplatin treatment (Tsan *et al*., 2012). Despite the widely conception that weekly cisplatin administration during head and neck RT is better tolerated than triweekly schedule, recent evidence is contrary and a systematic review and meta-analysis in 2015 by Zhang *et al*. showed similar risks for neutropenia and anemia and interestingly, even more, treatment interruption, dermatitis and grade≥3 mucositis (only when the primary disease was located in the oral cavity, oropharynx, hypopharynx or larynx) with the weekly regimen. Also, this analysis did not show any statistically significant difference in terms of efficacy, i.e. overall survival (OS) and locoregional recurrence-free survival (LRFS) between the two groups (Yue Zhang *et al*., 2015). Compatible with the majority of the available evidences, our experience did not find any statistically significant difference between the rate of treatment interruption and acute toxicity profiles of the two schedules of cisplatin administration. Only there was a trend of more grade≥3 mucositis in the weekly cisplatin arm, but this did not reach astatistical significance probably because of insufficient sample size. In terms of patient demographics, pretreatment laboratory data, treatment type (adjuvant or definitive), total irradiation and cumulative cisplatin dose, the two arms of this trial were well balanced. One of the main limitations of this study was that the cisplatin-based CRT impact on the compliance of therapy, for example, the body weight loss and the tube-feeding rate was not assessed. The results of this study cannot be extrapolated to post intensity modulated radiation therapy (IMRT) era; because the irradiation technique used in this study was 3DCRT and its more conformal RT modality that nowadays are widely used in HNC can spare more normal tissue; and therefore, it reduces local treatment side effects. Another limitation of this study was that oncologic outcomes, such a LRFS and OS, were not assessed.

Conclusion

In terms of acute treatment toxicity, the weekly administration of cisplatin concomitant with RT has similar objective results with the triweekly schedule. However, because we did not assess the LRFS and OS in this trial, thus, we cannot recommend that weekly cisplatin CRT can be the alternative protocol for the standard triweekly schedule.

Acknowledgements

Ahvaz Jundishapur University of Medical Sciences supported this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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