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Weekly Versus Three-Weekly Cisplatin in Concurrent Chemoradiotherapy for Head and Neck Squamous Cancers: A Prospective Study

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Abstract

Concurrent chemoradiotherapy (CT-RT) is often used as definitive treatment for patients with locally advanced head-and-neck squamous cancers (HNSCC). Concurrent cisplatin administered 3-weekly (100 mg/m^2 on days 1, 22 and 43 of RT) is the accepted standard-of-care, but causes significant toxicity. This has resulted in altered administration schedules, including weekly (40mg/m^2) regimen, with conflicting reports on identifying optimal schedule. We compared acute toxicity and response rates between patients on CT-RT receiving weekly and 3-weekly cisplatin in this prospective study. 56 patients received either weekly (40 mg/m^2; 36 patients) or 3-weekly (100 mg/m^2; 20 patients) cisplatin concurrently with 3D-conformal radiotherapy (70 Gy/35#/7 weeks) based on physician or patient preference. Patients receiving weekly schedule were older (57.9 vs 50.3 years; p=0.03), but the groups were comparable in other variables including gender, primary site and stage.

Acute toxicities (myelosuppression, mucositis, dysphagia, weight loss, etc.) were frequent but similar betweengroups, excepting a significantly lower nausea/vomiting in weekly schedule (≥grade II in 8.3% vs. 50%; p=0.03). Two patients, both on weekly chemotherapy, expired of aspiration pneumonia during treatment. Complete response rates at 12 weeks were similar between the cohorts (77.7% vs 85% CR, respectively; p= 0.61). At median follow-up of 12 months (range: 4-21.5 months), the estimated disease-free survival (DFS) was comparable between regimens (72% and 78% at 15 months, respectively; p= 0.550). We conclude thatweekly-cisplatin is associated with lower incidence of nausea/vomiting, but has otherwise comparable acute toxicity profile to 3-weekly schedule. Response to treatment and DFS are similar between the two.

Keywords: Sensitizer Chemotherapy; Oral Cancers; Definitive Radiotherapy; Acute Toxicity; Treatment Compliance.

Introduction

Head and neck squamous cancer (HNSCC) is one of the commonest cancers in India, and constitutes about one-third of all cancers [1]. At our institution HNSCC accounts for around 30-40% newly registered cases, and 60-70% present with locally advanced disease. External beam radiotherapy with concurrent chemotherapy is the standard-of-care in locally advanced HNSCC, but has significant toxicity. Cisplatin administered on a three-weekly basis at 100 mg/m^2 on days 1, 22 and 43 of RT is considered as the standard concurrent chemotherapy administration schedule. However, due to severe toxicity of the regimen, alternative schedules that deliver smaller and more frequent doses of chemotherapy have been tried and reported [2-3]. Weekly cisplatin regimens have been increasingly used in large part because of their relative ease of administration and general impression of reduced toxicity [4-6]. Both schedules are being practiced at our center. This study attempts to compare standard 3-weekly Cisplatin and weekly Cisplatin concurrent chemotherapy in CT-RT for locally advanced HNSCC.

Materials and Methods

This prospective comparative study was conducted on patients who were considered for treatment with definitive CT-RT for HNSCC between October 2014 and June 2016 after getting institutional ethical committee clearance.Inclusion criteria included locally advanced disease (Stages III, IVa or IVb),Karnofsky Performance Score ≥60 % and normal baseline hematological and renal parameters. Patients on adjuvant CT-RT were excluded, as were those with associated medical illnesses that would render them unfit for concurrent Cisplatin andthose with metastatic disease at presentation. Patients who discontinued treatment for non-medical reasons were also excluded from further analysis.

Radiotherapy was administered to all eligible patients by 3D-Conformal Radiotherapy (3DCRT) to a dose of 70 Gy in 35# delivered over seven weeks. All patients were immobilized using a thermoplastic mask in a supine position with arms by the side, and treatment was delivered on Elekta PRECISE Linear accelerator using 6 MV photon beams.

All patients were planned for either weekly or 3-weekly concurrent cisplatin based on the discretion of the treating physician or preference of the patient. Patients considered for 3-weekly Cisplatin 100mg/m^2 were hydrated beginning 24 hours prior to administering chemotherapy. Chemotherapy was administered over 60 minuteswith adequate prehydration, intravenous mannitol and antiemetic coverage. Patients considered for weekly cisplatin received 40mg/m^2 delivered as infusion in normal saline over 60 minutes with adequate prehydration,intravenousmannitol and antiemetic coverage. All patients received post-chemotherapy hydration and symptomatic care as required. Consent was taken prior to starting of radiotherapy and prior to each chemotherapy injection.

Blood counts, renal parameters, serum electrolytes and acute toxicitieslike mucositis, dermatitis, nausea/vomiting, dysphagia, etc. experienced by the patients were recorded every week. Toxicities were graded according to RTOG and CTCAE guidelines [7,8].

The tumor response was determined at three months after the completion of treatment. Patients were classified as having residual disease if the disease persisted at three months following completion of RT. Loco-regional recurrence was defined as any new histopathologicallyconfirmed lesion at the primary site or regional lymph nodes, after a period of three months post treatment. Disease Free Survival (DFS) was defined as the period from the date of completion of radiotherapy to local, regional or systemic relapse.

Chi-square test was used to analyze the variation between the two regimens. Survival curves were estimated according to Kaplan-Meier method, and log-rank test was used for statistical comparison. All data were analyzed with Statistical Package for Social Science (version 15; Chicago, IL), and a p-value of < 0.05 was considered statistically significant.

Results

A total of 56 patients meeting the study requirements were enrolled into the study. Among them, 36 patients received weekly cisplatin and 20 patients received 3-weekly cisplatin. The mean age of the patients was 56 years (range: 30-70 years) with 47 patients (83.9%) being males. The distribution of demographic variables between the two groups is shown in Table 1.

Two patients (3.6%) expired while on treatment with suspected aspiration pneumonia. Both of them had received weekly chemotherapy. The remaining 54 patients completed the prescribed dose of radiotherapy, though 14 (25%) had rest-periods in between due to toxicity, mostly due to aspiration pneumonia (six patients). Febrile neutropenia was noted in one patient. The mean treatment duration was 47 days in both the study groups (p= 0.568). However, compliance to concurrent chemotherapy was significantly superior among patients receiving weekly cisplatin, with 22 patients (61.1%) receiving at least 85% of prescribed dose compared to six patients (30%) receiving 3-weekly Cisplatin (p=0.026).

Other treatment toxicities included hematological toxicity, predominantly leucocytopenia, and dyselectrolytemias, weight loss, oropharyngeal mucositis and xerostomia. Leucocytopenia and neutropenia set in earlier in the 3-weekly arm, with 65% (13 patients) experiencing ≥ grade I toxicity by the third week compared to 27.7% (10 patients) in weekly arm (p=0.024). However, the overall incidence of hematotoxicity during the entire course was similar between the two arms, and none of the patients developed grade IV toxicity. The details of other acute toxicities are shown in Table 2.

Excluding the two patients who expired during the course of treatment, patients were evaluated for response at the end of 12 weeks following treatment completion. In total, of the remaining 54 patients, 81.5% (44 patients) had complete response and 18.5%

(10 patients) had persisting residual disease at 12 weeks. Residual disease was most frequently observed in oral cavity (five patients) followed by larynx (three patients) and hypopharynx (two patients). The probability of harboring a residual disease after treatment completion was not statistically associated with the primary stage, sub-site or degree of differentiation. Similarly, on comparing the response rates between the chemotherapy regimens, there was no statistical difference (77.7% vs 85% complete response in weekly and 3-weekly arms, respectively; p= 0.61). On sub-group analysis, response rates were no different between the two groups with respect to stage of disease, node positivity or grade of tumor.

The patients were followed up for a median duration of 12 months (range: 4- 21.5 months) after treatment completion. Three patients who had complete response at 12 weeks assessment developed loco-regional recurrence on follow up. Metastatic disease as first evidence of recurrence was not noted in any patient. Disease-free survival (DFS) analysis was performed in 54 patients, after excluding the two patients who had expired while on treatment. The estimated DFS at 15 months was comparable between weekly and 3-weekly chemotherapy regimens (72% and 78%, respectively; p= 0.55) (Figure 3). Patients receiving all three courses of 3-weekly chemotherapy appeared to have a superior outcome compared to patients who received only two courses of 3-weekly cisplatin, but the difference in DFS was not statistically significant (p= 0.155). Similarly,there was no impact of treatment compliance on DFS among patients receiving weekly cisplatin. On sub-group analysis, DFS was comparable between the two arms irrespective of site of primary, stage of disease or presence of node metastasis.

Table 1: Distribution of patient characteristics between the weekly and 3-weekly arms

Variable	Study arms		P value
	Weekly chemotherapy (n=36)	3-weekly chemotherapy (n=20)	
Mean age in years (range)	**57.9 (31-70)**	**50.3 (30-68)**	**0.03**
Gender			
Males	30 (83.3%)	17 (85%)	0.871
Females	6 (16.7%)	3 (15%)	
Site of primary			
Oral cavity	6 (16.7%)	10 (50%)	0.182
Oropharynx	9 (25%)	4 (20%)	
Hypopharynx	10 (27.8%)	4 (20%)	
Other sites	11 (30.6%)	2 (10%)	
Grade of tumor			
Grade I	9 (25%)	10 (50%)	0.24
Grade II	15 (41.7%)	7 (35%)	
Grade III	12 (33.3%)	3 (15%)	
T stage			
≤ T2	7 (19.4%)	5 (25%)	0.431
≥ T3	29 (80.6%)	15 (75%)	
N stage			
N0	6 (16.7%)	7 (35%)	0.297
N1	8 (22.2%)	3 (15%)	
≥ N2	22 (61.1%)	10 (50%)	

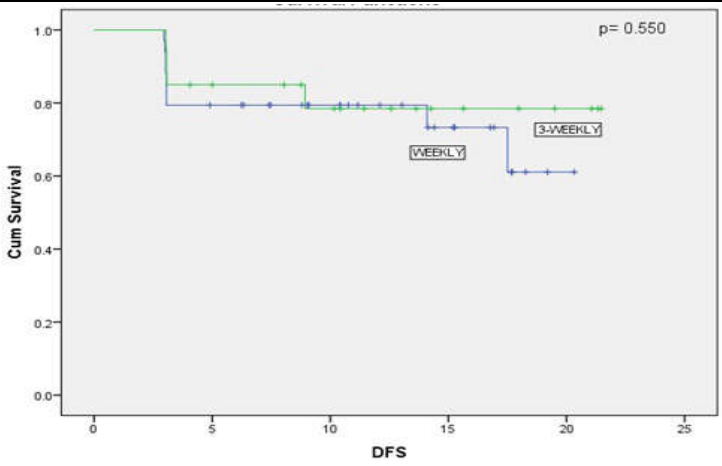

Fig. 1: Disease free survival in months among the weekly and 3-weekly regimens (p=0.55)

Table 2: Comparison of acute toxicities between the weekly and 3-weekly arms

Toxicity	Study arms		P value
	Weekly chemotherapy (n=36)	3-weekly chemotherapy (n=20)	
Maximum hematological toxicity			
≤ Grade I	19 (52.8%)	7 (35%)	0.353
≥ Grade II	17 (48.2%)	13 (65%)	
Decreased Glomerular filtration rate			
< 25% from baseline	7 (19.4%)	3 (15%)	0.871
≥ 25% from baseline	29 (80.6%)	17 (85%)	
Dyselectrolytemia			
≤ Grade I	13 (36.1%)	8 (40%)	0.919
≥ Grade II	23 (63.9%)	12 (60%)	
Nausea and vomiting			
≤ Grade I	33 (91.7%)	10 (50%)	0.003
≥ Grade II	3 (8.3%)	10 (50%)	
Maximum degree of mucositis			
≤ Grade I	6 (16.7%)	5 (25%)	0.450
≥ Grade II	30 (83.3%)	15 (75%)	
Dysphagia at completion			
Grade I	13 (36.1%)	5 (25%)	0.570
≥ Grade II	23 (63.9%)	15 (75%)	
Acute skin reaction			
Grade I	22 (61.1%)	10 (50%)	0.487
≥ Grade II	14 (38.9%)	10 (50%)	
Weight loss			
≤ 10% of baseline weight	11 (30.6%)	10 (50%)	0.192
> 10% of baseline weight	25 (69.4%)	10 (50%)	

Discussion

This study evaluated the acute toxicities and outcomes of concurrent chemotherapy administered on a weekly basis with the accepted standard-of-care 3-weekly cisplatin in patients with locally advanced HNSCC treated with curative CT-RT. As the study was not randomized, with patients receiving either weekly or 3-weekly chemotherapy based on their own preference or at discretion of the treating physician, the weekly cohort was disproportionately larger. Moreover, the weekly group consisted of the older age groups compared to 3-weekly arm, reflecting the tendency of physicians preferring weekly sensitizer regimen among older patients [9]. However, the two arms were comparable with respect to other important variables such as gender, grade of tumor, stage of disease and presence of node metastases.

Considering 85% of planned chemotherapy dose administration as compliant, the compliance was significantly superior in the weekly arm patients when compared to patients receiving 3-weekly chemotherapy regimen. As an assertion to this, the total cisplatin dose received was 240mg/m^2 in the weekly group patients, which was significantly higher than patients on 3-weekly chemotherapy who received an average cumulative dose of 200 mg/m^2. This is attributable to the fact that almost 70% of patients on 3-weekly chemotherapy failed to receive the third course of concurrent chemotherapy. Weekly sensitizer chemotherapy is generally considered to be better tolerated than 3-weekly chemotherapy [10]. For instance, in a retrospective study conducted by Ho et al, weekly arm was more complaint, and none of the patients planned for 3-weekly chemotherapy received the third course of concurrent chemotherapy [11]. As a result, more patients were reportedly able to receive a significantly higher cumulative dose of cisplatin when they received it on a weekly basis.

There was a progressive increase in frequency and severity of acute toxicity with treatment in both the arms. The toxicities were comparable between the two groups, though myelosuppression, especially leucocytopenia, appeared to set in earlier in the 3-weekly group. Considering that both the groups had a similar overall incidence of hematological toxicity, it appears to be of lesser importance in determining the optimum regimen. A similar picture has been reported in other studies comparing the two sensitizer regimens [9,12,13].

Cisplatin induced nephrotoxicity was noted in both the study groups but the drop in creatinine clearance was never below 60 ml/min, and did not lead to withholding chemotherapy or modifying chemotherapy dose in any patient in our study.

Cisplatin is a well-known nephrotoxic agent, with a potential to cause severe, irreversible renal failure. The likelihood of developing cisplatin induced nephrotoxicity is known to increase with higher peak plasma free-platinum concentration [14]. Thus, in theory, a higher dose administration is more nephrotoxic. However, in reported clinical experience, frequency of cisplatin induced nephrotoxicity is similar between the 3-weekly and weekly schedules. In a retrospective study reported by Uygun et al. the incidence of Grade ≥3 renal toxicity, though lower with weekly Cisplatin than with 3-weekly Cisplatin, was not statistically significant [15].

Grade 3 mucositis was 18 % in the weekly arm and 25% in 3-weekly arm but there was no significant difference in severity of mucositis between the arms. There are reports that indicate potentially differing severity of mucotoxicity between the two schedules [12,16]. For instance, in a study by Tsan et al [12], patients receiving weekly cisplatin (40 mg/m^2) suffered significantly higher incidence of severe mucositis than patients receiving 3-weekly cisplatin.

Curative chemoradiotherapy for HNSCC is an intensive treatment, with known significant acute morbidity. Two patients in our study died as a consequence of aspiration pneumonia, a relatively frequent severe toxicity among patients on definitive radiotherapy for HNSCC [17]. Though both of these patients had received weekly cisplatin, since the two regimens were otherwise equivalent in terms of acute toxicity, it is unlikely that the weekly regimen predisposes to a higher incidence of aspiration.

No statistically significant difference noted in response rates or DFS between both the arms in our study. On sub-group analysis, DFS was comparable between the two arms irrespective of site of primary, stage of disease or presence of node metastasis, though the curves appeared to diverge within a few months in favor of the 3-weekly regimen for stage IV disease and node positive patients. There have been differing opinions regarding the efficacy of weekly cisplatin when compared to the standard 3-weekly regimen. While some researchers have reported equivalent outcomes [12,18], others have suggested that outcomes might be inferior with weekly regimen [16,19,20]. A recent metanalysis of 10 studies comparing weekly and 3-weekly regimens also suggests that 3-weekly dosing potentially improves overall survival on a longer follow up beyond five years [21]. More recent approaches have looked into the feasibility of a further reduced dose of cisplatin (6mg/m^2) administered on a daily basis and found it to be comparable, and even favorable in terms of acute toxicity, to the weekly regimen [22-24].

Our study has several limitations. Firstly, it was not a randomized study, though both the arms were comparable in all important variables other than age. Secondly, it involved a small number of patients, unequally distributed between the arms. Additionally, a short follow up prevents detailed outcome measurements and estimation of difference in overall survival between the two schedules, though from recurrence patterns in both arms it is reasonable to foresee an equivalence in survival between them. Despite these shortcomings, the two regimens appear to be comparable to each other in terms of acute toxicity and early outcomes.

Conclusion

Concurrent chemoradiotherapy with cisplatin administered on a weekly basis had a similar frequency and severity of acute hematological and gastrointestinal toxicities when compared to 3-weekly cisplatin, though it was associated with a relatively delayed onset myelosuppression and a substantially lower incidence of nausea and vomiting. Patients receiving weekly sensitizers were also more likely to receive a higher cumulative chemotherapy dose. Response to treatment and DFS were similar between the two concurrent chemotherapy regimens.

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