Original Article

Comparison of Weekly versus Three-Weekly Cisplatin with Concurrent Radiotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma: A Prospective Observational Study from Kashmir Valley.

Rabiya Khanam , Fir Afroz, M Ashraf Teli , Malik Tariq Rasool, Mushtaq Ahmad Sofi, Shahzad Ahmad Khan, Mansoora Akhter

Abstract

Background:

Concurrent chemoradiotherapy (CCRT) with cisplatin is standard care for locally advanced head and neck squamous cell carcinoma (LAHNSCC). Cisplatin is commonly administered either weekly (40 mg/m²) or every three weeks (100 mg/m²). This study compares efficacy and toxicity profiles of both regimens.

Methods:

Sixty patients with histologically proven LAHNSCC were enrolled in a prospective observational study. Arm A received weekly cisplatin and Arm B received three-weekly cisplatin, both concurrently with radiotherapy (66–70 Gy in 35 fractions). Toxicities were graded using CTCAE v4.03 and response evaluated as per RECIST 1.1.

Results:

Median follow-up was 8 months. Baseline characteristics were comparable between arms. Complete response was 73.3% in weekly and 85.7% in three-weekly arms. Grade ≥3 mucositis was more frequent in weekly arm (P=0.037), while grade ≥3 hematologic toxicities were comparable. Hospitalization for toxicity was higher in three-weekly arm.

Conclusion:

Both cisplatin schedules are effective for LAHNSCC. Weekly cisplatin is associated with reduced acute toxicity and hospital admissions, while three-weekly cisplatin may provide slightly better locoregional control. Treatment should be individualized based on patient tolerance and **comorbidities.**

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Keywords

Locally Advanced Head and Neck Squamous Cell Carcinoma, Concurrent Chemoradiotherapy, Cisplatin Treatment Toxicity, Loco-regional Control

Introduction

Head and neck cancers encompass malignancies arising in anatomically complex regions critical for function, aesthetics, and social interaction. These cancers significantly impact quality of life due to functional impairment and treatment-related morbidities. Head and neck squamous cell carcinoma (HNSCC) accounts for over 90% of head and neck malignancies and represents the sixth most common cancer worldwide, with approximately 650,000 new cases annually[1–6]. In India, HNSCC is the most common malignancy in males and a major contributor to cancer morbidity in females[7–10].

Concurrent chemoradiotherapy (CCRT) with cisplatin is the standard approach for locally advanced disease. Cisplatin acts as a radiosensitizer, enhancing the cytotoxic effect of radiotherapy through DNA cross-linking and inhibition of DNA repair[11-14]. Traditional high-dose cisplatin administered every three weeks (100 mg/m²) is associated with significant acute toxicity, including mucositis, nephrotoxicity, and hematologic complications[15-16]. Weekly cisplatin (30–40 mg/m²) has emerged as a feasible alternative, potentially improving compliance while maintaining efficacy[17-21]. However, evidence comparing weekly versus three-weekly cisplatin in LAHNSCC remains mixed. This study evaluates and compares the response and toxicity profiles of these two regimens in a prospective observational cohort.

Materials and Methods

Study Design:This was a Prospective observational study conducted at the Department of Radiation Oncology, SKIMS, Srinagar, from June 2016 to June 2018. Ethical approval was obtained from the institutional ethics committee.

Participants: Patients aged 18–65 years with histologically confirmed locally advanced HNSCC (oral cavity, nasopharynx, oropharynx, hypopharynx, larynx), ECOG performance ≤1, and no distant metastasis

were included. Patients with uncontrolled comorbidities, ECOG ≥2, or who refused consent were Interventions:

- Arm A: Weekly cisplatin 40 mg/m² IV concurrent with radiotherapy.
- Arm B: Three-weekly cisplatin 100 mg/m² IV concurrent with radiotherapy

Radiotherapy Protocol: 66–70 Gy in 35 fractions (2 Gy/fraction, 5 fractions/week) delivered to the primary tumor and regional nodes, with a 46 Gy base and 20–24 Gy boost.

Evaluation:

- Toxicity: Monitored weekly using NCI-CTCAE v4.03 for mucositis, dermatitis, hematologic toxicity, renal toxicity, and treatment interruptions.
- Response: Assessed 6–8 weeks post-treatment via physical examination, imaging (CT/MRI), and biopsy if required.

Statistical Analysis: Data were analyzed using SPSS v20. Continuous variables were expressed as mean ± SD and compared using t-tests. Categorical variables were summarized as percentages and analyzed using chi-square or Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

A total of 60 patients having non-metastatic locally advanced head and neck cancers were enrolled in this study. Of the 60 patients ,30 patients (Arm A) received weekly 40mg/m2 cisplatin on days 1,8,15,22,29,36 and 30 patients (Arm B) received three weekly 100mg/m2 cisplatin on days 1,22,43 during standard dose of RT. One patient in the arm A died because of medical cause unrelated to treatment (MI). The treatment arms were reasonably comparable in terms of baseline characteristics including age, gender, primary site and tumor stage. Median follow up was 8 months (range 4-12 months).In Arm A 93.3% of the patients were male and 6.7% of the patients were female. In Arm B 86.7% of the patients were male and 13.3% patients were female. The difference in gender didn't change the decision of the oncologist to select the patients in any arm. The mean age in Arm A was 51.7±15.52 years and mean age in Arm B was 53.4± 9.36 years. Patients were relatively uniformly distributed in both the arms as far as age was concerned. These were the patient reported comorbidities, we didn't screen patients for comorbidities. Although all patients were subjected to cardiology before start of chemotherapy. Hypertension was the predominant comorbidity in both the arms, 30.0% in Arm A and 20.0% in Arm B. Overall comorbidities were more common in arm A as compared to Arm B. Presence or absence of comorbidities didn't change the decision of oncologist to select the patients in either arm.Most prevailing primary tumor site in arm A was Larynx 33.3% and Arm B was nasopharynx 43.3%. The tendency to select the patients for three weekly regimen in nasopharyngeal carcinoma predominated.

At presentation most common stage in both the arms was stage III followed by stage IV. In Arm A 50.0% of the patients and Arm B 46.7% of the patients had stage III. Further in Arm A (33.3%) and in Arm B (26.7%) of the patients had stage IV disease. The difference in stage of the tumor in two arms didn't change the decision of physician to select the patients in either arm. The mean of baseline hepatological parameters in both the arms. The decision of selecting the patient in any arm by oncologist was not changed by baseline hepatological parameters. Mean creatinine clearance before treatment in Arm A was 78.7ml/min and 85.7ml/min in arm B. The difference in two arms was not statistically significant.

Most of the patients (53.3%) in Arm A received 6 cycles of chemotherapy. Most of the patients (43.3%) in Arm B received three cycles of chemotherapy followed by 2 cycles by 33.3% and 1 cycle by 23.3% of the patients.

The mean cumulative dose of cisplatin in Arm A was 218.7(80-280) mg/m2 and in Arm B was 220.0(100-300)mg/m2. The difference in both the arms was not statistically significant.

Vomiting was more common in arm B as compared to arm A, 26.7% in arm B and 16.7% in Arm A. The difference was not statistically significant (p=0.347).

≥ Grade III Anemia was more common in Arm A as compared to Arm B, 30.0% of the patients in Arm A and 6.7% of the patients in Arm B had ≥ Grade III Anemia. The difference between two arms was statistically significant (p= 0.045).

≥Grade III leucopenia was more common in Arms B (36.7%) as compared to Arm A (6.7%). The difference between two arms was statistically significant (p=0.012).

≥ Grade III neutropenia was more common Arm B as compared to arm A. 43.3% of the patients in Arm B and 10.0% of the patients in Arm A had ≥ Grade III neutropenia. The difference between two arms was statistically significant (p=0.009).

≥ Grade III Thrombocytopenia was more common in arm A (13.3%) as compared to Arm B (6.7%). The difference was not statistically significant.

≥ Grade III renal toxicity was more common in Arm B as compared to Arm A, 26.7% of the patients in Arm B and 3.3% of the patients in Arm A had ≥ Grade III renal toxicity. The difference was statistically significant (p=0.031).

≥ Grade III mucositis was more common in Arm A as compared to Arm B. 70.0% in arm A and 43.3% in Arm B .The difference was statistically significant (p=0.037).

In both the arms < grade III dermatitis was more common than ≥ Grade III. ≥ Grade III dermatitis was more common in Arm A (13.3%) as compared to Arm B(6.7%). The difference was not statistically significant.

Six to eight weeks post treatment, 28 out of 30 patients in Arm A and 29 out of 30 patients in Arm B were assessed for treatment response. Majority of the patients had complete response in both the arms 57.1% of the patients in Arm A and 53.6% in Arm B followed by partial response 39.3% of the patients in Arm A and 42.9% in Arm B. There was no statistically significant difference between the two arms. 1 patient in each arm died from treatment related toxicity.

Discussion

Locally advanced head and neck squamous cell carcinoma (LAHNSCC) poses a significant therapeutic challenge, particularly in developing countries where the majority of patients present with advanced-stage disease due to delayed diagnosis and limited healthcare access[22]. Concurrent chemoradiotherapy (CCRT) with cisplatin remains the standard of care, as it enhances the radiosensitivity of tumor cells and improves locoregional control compared to radiotherapy alone[11,23]. Cisplatin exerts its radiosensitizing effects primarily through the formation of DNA cross-links, inhibition of DNA synthesis, and suppression of sublethal damage repair, resulting in enhanced tumor cytotoxicity when administered with fractionated radiotherapy[13,14].The optimal dosing schedule of cisplatin for CCRT has been debated. Traditional high-dose cisplatin (100 mg/m² every three weeks) is associated with higher rates of severe acute toxicities, including mucositis, neutropenia, renal impairment, and treatment interruptions[15,16]. In contrast, weekly low-dose cisplatin (30–40 mg/m²) aims to reduce toxicity while maintaining cumulative dose intensity and treatment compliance[17-21].In the present study, both arms achieved comparable overall response rates (weekly arm: 96.4%, three-weekly arm: 93.1%), suggesting equivalent short-term efficacy. This aligns with observations from So Yeon Lee et al. (2018), who reported similar objective response rates between weekly and three-weekly cisplatin in LAHNSCC patients undergoing CCRT[21]. Likewise, Dong-Fang et al. (2018) found no statistically significant differences in 5-year overall survival (OS) and disease-free survival (DFS) between the two regimens in nasopharyngeal carcinoma, supporting the clinical feasibility of weekly cisplatin as a less toxic alternative[20].

In our cohort, ≥Grade III mucositis was significantly higher in the weekly arm (70%) compared to the three-weekly arm (43.3%), which may reflect cumulative mucosal exposure to repeated cisplatin doses during radiotherapy. Similar findings were reported by Tsan et al. (2012), who observed increased mucositis in patients receiving fractionated low-dose cisplatin[24]. Conversely, hematologic toxicities such as leucopenia and neutropenia were significantly higher in the three-weekly arm, consistent with observations by Rades et al. (2016), highlighting the myelosuppressive impact of high-dose intermittent cisplatin[25]. Renal toxicity was also more frequent in the three-weekly arm (26.7% vs 3.3%; p=0.031), reflecting the well-documented nephrotoxic potential of high-dose cisplatin[26-27].Treatment adherence is critical for achieving optimal outcomes. In this study, a higher proportion of patients in the weekly arm completed all planned chemotherapy cycles and experienced fewer radiotherapy interruptions, underscoring the tolerability advantage of weekly cisplatin. This observation is consistent with the study by S. Rawat et al. (2016), which reported better compliance with weekly regimens due to reduced need for hospitalization and supportive care[22]. In resource-limited settings, this reduced demand for inpatient care is particularly valuable.The distribution of primary tumor sites and patient demographics in our study mirrored regional patterns. Laryngeal and nasopharyngeal carcinomas predominated, reflecting local tobacco and dietary habits, unlike Western populations where oropharyngeal and tongue cancers are more common[21]. Male predominance (90%) was consistent with known risk factor prevalence, including tobacco use and alcohol consumption in men .Several previous studies have evaluated the weekly versus triweekly cisplatin question. Vanita N. et al. (2018) reported superior locoregional control with three-weekly cisplatin but at the cost of higher acute toxicity, hospitalization, and supportive care needs[28]. Fayette et al. (2015) observed improved 5-year OS with three-weekly cisplatin (62.3% vs 52.6% for weekly), although multivariate analyses suggested that patient comorbidities and treatment interruptions may modulate this effect[26]. Conversely, Lee SY et al. (2018) and Dong-Fang et al. (2018) concluded that weekly cisplatin achieved comparable efficacy with lower toxicity, suggesting that cumulative dose and dose intensity rather than schedule alone determine treatment outcomes[20,21].

The findings from this study reinforce the concept that weekly cisplatin is a practical, less toxic alternative, particularly in settings where inpatient resources are limited and patient comorbidities preclude high-dose chemotherapy. Nevertheless, for nasopharyngeal carcinoma or patients who can tolerate higher doses, three-weekly cisplatin may confer modest improvements in locoregional control, as supported by prior meta-analyses and randomized trials[26,28,29].

Limitations:

This study was a prospective observational study rather than a randomized controlled trial. Patient allocation to weekly or three-weekly arms was at the discretion of treating oncologists, introducing potential selection bias. Furthermore, the follow-up duration (median 8 months) was insufficient to assess long-term survival, late toxicities, or second primary malignancies. Future randomized trials with larger sample sizes and extended follow-up are warranted to definitively guide cisplatin scheduling in LAHNSCC.

Summary

In conclusion, both Cisplatin regimens are effective for concurrent chemoradiotherapy in LAHNSCC. Weekly cisplatin provides an acceptable alternative with lower acute toxicity and better treatment adherence, whereas three-weekly cisplatin may offer slightly improved locoregional control at the expense of higher toxicity. Treatment individualization based on patient tolerance, tumor site, and institutional resources remains critical.

Conflict of interest Nil

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