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Comparative study on hemato- and nephrotoxicity profile of weekly versus every 3-weekly cisplatin dosage during induction chemotherapy in locally advanced head neck squamous cell carcinoma

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Abstract

Background: Cisplatin is a frontline anticancer drug routinely used as part of concurrent chemoradiation administered at 3-weekly (100 mg/m^2) dose. However, its role as fractionated weekly dose has achieved favorable outcome in patients with locally advanced squamous cell carcinoma of head and neck (LA-SCCHN) during induction chemotherapy (IC). We therefore sought to compare the toxicity outcomes of patients with LA-SCCHN treated with platinum-based IC at a single institution study using split-dose cisplatin chemotherapy. We compared the hematological and renal toxicity profile between the weekly cisplatin (30 mg/m^2) (group A) versus 3-weekly (100 mg/m2) (group B) dosage schedule in this setting.

Results: The median age of the patients in groups A and B were 49.1 years and 48.27 years respectively with male: female ratio of 4:1. Most of the patients were of oropharyngeal cancers. Group A patients showed greater neutropenia (40.2%) than group B (20.6%). There was statistically significant fall in Hb% level in group A (13.9%) than in group B (11.9%). Renal profile showed greater rise in serum urea and serum creatinine (52.7%) in group B than in group A (52.29%) with statistically significant difference.

Conclusions: Since toxicities induced by high-dose cisplatin are irreversible and reduce quality of life in patients, the weekly regimen may be preferred owing to less renal toxicity, lesser hospitalization and more feasible in situations with high patient load and limited resources.

Keywords: Induction chemotherapy, Squamous cell carcinoma of head and neck, Hematotoxicity, nephrotoxicity

Background

Squamous cell carcinoma of head and neck (SCCHN) has a high incidence in North-east India region (54.48%) [1] which is primarily treated with cisplatin-based chemotherapy along with radiotherapy and or surgery. In such patients, cisplatin toxicity is a matter of concern which ranges from mucositis, dermatitis, dysphagia to hematological and renal toxicity being a dose limiting toxicity [2]. These problems are especially more severe in locally advanced squamous cell carcinoma of head and neck (LA-SCCHN) who require extensive surgery with chemoradiation resulting in higher morbidity.

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Therefore, to achieve favourable outcome in such groups of patients, induction chemotherapy (IC) with ciplatin has been advocated [3, 4]. As comparative data on the toxicity profile of weekly versus every 3 weeks platinum-based induction chemotherapy are lacking, we undertook this comparative study to ascertain the haematological and renal toxicity profile between these two induction chemotherapy regimens practiced in our center. This study intended to throw new light towards optimizing drug combinations and reasons for therapeutic non-compliance.

Aims

1) To compare the hematological and renal toxicity profile of weekly versus three weekly ciplatin based IC regimen administered in patients with LA-SCCHN

Methods

This is a 2-month prospective observational study carried out in the Department of Otolaryngology of a teaching hospital on patients diagnosed with LA-SCCHN requiring IC followed by other modality such as radiotherapy and/or surgery but was kept outside our study protocol. A total number of 30 patients meeting the inclusion criteria were selected for the study. One group of patients received weekly cisplatin at 30 mg/m^2 dose (group A) and the other group received cisplatin dose of 100 mg/m^2 at every three weeks interval regimen (group B).

Inclusion criteria

(a) All patients above 18 years of age, (b) histologically proven patients of LA-SCCHN region except nasopharynx, paranasal sinus and ear malignancies, (c) cases diagnosed within last 12 months and requiring IC, and (d) patients with normal hematological and renal function profile before the start of chemotherapy.

Exclusion criteria

(a) Unresponsive patients in terminal stage, (b) postoperative patients and patients receiving adjuvant chemotherapy or concurrent chemoradiation, and (c) any past history of chemotherapy and radiotherapy.

The patients were included in the study only after taking written informed consent from the patients. Besides routine clinical, radiological, and pathological workup for LA-SCCHN patients, fitness for chemotherapy was assessed by thorough systemic examination along with lab tests viz. renal function test, complete blood count and serum electrolyte assay. Five part automated hematology analyzer (800 XI and 1000Xi, Sysmex) were used for these tests. Myelosuppresion was assessed by WBC count, RBC count, Hb levels, hematocrit, ESR, and DLC count. Renal toxicity was assessed from serum urea and serum creatinine levels.

Regimen of group A

(Once weekly dose for 3 consecutive weeks followed by a gap of 21 days and ending the whole cycle by administering once weekly for another 3 consecutive weeks.) Inj. Dexamethasone 1 amp i/v stat + Inj. Prochloreperazine 1 amp i/m stat + Inj. Pantoprazole 1 amp i/v stat. After 30 min➔Inj. Cisplatin (30 mg/m^2) in 2, 500 ml NS over 2 h➔Inj. Ondansetron i/v stat + Infusion Mannitol 1 unit i/v rapidly ➔ Inj 5FU (500 mg/m^2) in 3500 of NS over 3 h➔ Inj Pantoprazole 1 amp i/v stat ➔1500 ml NS.

Regimen of group B

(Every 21 days dose for a total of 6 cycles): Inj. Dexamethasone 1 amp i/v stat + Inj. Prochloreperazine 1 amp i/m stat + Inj. Pantoprazole 1 amp i/v stat. After 30 min➔Inj. Cisplatin (100 mg/m^2) in 2500 ml of NS over 2 h➔ Inj. Ondansetron i/v stat + Infusion Mannitol 1 unit i/v rapidly➔Inj 5 FU (1000 mg/m^2) in 3500 ml of NS over 3 h➔ Pantoprazole 1 amp i/v stat➔1, 500 ml NS.

Systemic chemotherapy is defined as standard-dose chemotherapy and drug dosage is calculated using body surface area [BSA = (weight × .02) + 0.4]. The chemotherapeutic agents used in the two regimes are Inj. Cisplatin and Inj. 5 FU. The rationale for using combination chemotherapy is to achieve higher response rates and increase overall survival and cost effectiveness. The published meta-analysis by Browman GP et al. [5] on cisplatin and 5-FU combination regimens showed it to be most effective regimen in SCCHN. Statistical test using one-way ANOVA and Tukey-Kramer tests were used to find out the p value (< 0.05 for significance) and confidence interval. The approval of the Ethics Committee of the institution was taken before starting the study.

Results

Patient characteristics and dosage

The median age of the patients in group A and group B were 49.1 years and 48.27 years, respectively. There were 12 male and 3 female patients equally in both the groups. The commonest site of lesion for both the groups was oropharyngeal cancer followed by pharyngeal cancer. Majority of the patients belonged to stage III (comprising of 66.6% in group A and 73.3% in group B). In group A weekly regimen, cisplatin dose was administered at 30 mg/m^2 and in group B at 100 mg/m^2 for every 3 weeks. The average cumulative cisplatin dose in weekly cisplatin group was 170 mg/m^2 and in every 3-week group it was 220.32 mg/m^2 (Table 1).

Table 1 Characteristics of LA-SCCHN patients receiving weekly (group A) and every 3-weekly (group B) cisplatin dose

Patient characteristics	Weekly dose cisplatin (mean dose: 30 mg/m^2) (n = 15)	Every 3-week dose cisplatin (mean dose: 100 mg/m^2) (n = 15)
Median age (years)	49.1 ± 5.9	48.3 ± 4.8
Male	12(80%)	12(80%)
Female	3(20%)	3(20%)
Mean BSA	1.6	1.5
Site		
Oral cavity	1(6.7%)	2(13.3%)
Oropharynx	5(33.3%)	6(40%)
Pharynx	3(20%)	4(26.6%)
Larynx	3(20%)	1(6.7%)
Hypopharybx	2(13.3%)	1(6.7%)
Esophagus	1(6.7%)	1(6.7%)
Stage		
Stage I	0	0
Stage II	3(20%)	1(6.7%)
Stage III	10(66.6%)	11(73.3%)
Stage IV	2(13.3%)	3(20%)
Total mean cisplatin dose	170 mg/m^2	220.32 mg/m^2
Total mean 5-FU dose	4672 mg	4620 mg

Effect on haematological parameters

Total leucocyte count and differential count

There is a substantial fall (40.2%) in neutrophil count in group A as compared to group B (20.6%). The fall in total lymphocyte count is found to be similar in both the groups (23.36% and 23.3%, respectively) (Table 2).

Red blood cell count

There is drop in RBC count in both the groups showing greater fall in group A (17.86%) than in group B (12.1%) (Table 2).

Platelet count

A fall of 25.43% in mean platelet count was seen in group A while in group B, it was only 14.8%. The fall in both the groups were found to be statistically extremely significant (Table 2).

Hemoglobin level (Hb%)

We found marginally greater fall in hemoglobin level in group A (13.9%) as compared to group B (11.9%) which was statistically extremely significant (Table 3).

Table 2 Hematological parameters of LA-SCCHN patients in both the groups

Hematological parameters	Weekly dose cisplatin (mean dose: 30 mg/m^2) (n = 15)			Every 3-week dose cisplatin (mean dose: 100 mg/m^2) (n = 15)			Control	ANOVA (p value)
	Pre chemotherapy	Post chemotherapy	Change (%)	Pre chemotherapy	Post chemotherapy	Change (%)		
WBC count	8.6 ± 2.5 ^{a}	6.3 ± 1.6 ^{a}	− 26.6	6.8 ± 1.9	5.7 ± 1.1	− 16.5	5.5 ± 1.6	***
Neutrophil count	5.8 ± 2.4^{a2}	3.5 ± 1.9^{a2}	− 40.2	4.3 ± 1.9	3.48 ± 1.3	− 19.6	3.4 ± 1.2	** (.0018)
Lymphocyte count	2.2 ± 1.1	1.7 ± 0.7	− 21.4	1.5 ± 0.6^{b}	1.2 ± 0.6^{b}	− 23.3	1.8 ± 0.6	* (0.0115)
RBC count	4.8 ± 0.8 ^{a1}	3.91 ± 0.5^{a1}	− 17.9	4.5 ± 0.8	3.9 ± 0.5	− 12.1	4.4 ± 0.5^{x}	** (.0017)
Platelet count	222.6 ± 44.4^{y}	166 ± 44.2^{y,x}	− 25.4	159. ± 24.1	136.1 ± 12.4^{z}	− 14.8	222.6 ± 44.4^{x,z}	***

***p < .001 (extremely significant)
**p < .01(very significant)
*p < .05(significant)
On comparing the different groups by Tukey-Kramer multiple comparisons test, the corresponding letters indicate the significance level between groups as follows:
$^{a, a1, a2}P$ < .01(very significant)
$^{b,x,y,z}p$ < .001(extremely significant). Changes in terms of decrease in levels are indicated in minus sign. *RBC* red blood corpuscles, *WBC* white blood cells

Table 3 Red cell indices of LASCCHN patients in both the groups

Red cell indices	Weekly dose cisplatin (mean dose: 30 mg/m^2) (n = 15)			Every 3-week dose cisplatin (mean dose: 100 mg/m^2) (n = 15)			Control	ANOVA (p value)
	Pre chemotherapy	Post chemotherapy	Change (%)	Pre chemotherapy	Post chemotherapy	Change (%)		
Hb%	11.5 ± 1.2[a2]	9.9 ± 0.8[a2]	− 13.9	11.2 ± 1.5	9.9 ± 0.6		12.1 ± 1.7	***
Hematocrit	37.1 ± 4.9	33.9 ± 3.7	− 8.5	37.8 ± 5.7	34.4 ± 3.7	− 9.1	36.9 ± 5.5	ns
MCV	86.9 ± 9.3	78.9 ± 12.6	− 9.3	81.7 ± 20.3	76.6 ± 9.7	− 6.2	90.6 ± 3.1	* (.0161)
MCH	25.4 ± 3.7	26.7 ± 3.9	5.05	26.1 ± 3.9	26.9 ± 3.4	3.1	27.8 ± 1.3	ns

***p < .001 (extremely significant), *ns*: p < .05 (not significant), *p < .05 (significant)
On comparing the different groups by Tukey-Kramer Multiple comparisons test, the corresponding letters indicate the significance level between groups as follows:
[a2]P < .01 (very significant). Changes in terms of decrease in levels are indicated in minus sign

Hematocrit level

A fall in hematocrit level was seen in both groups but the differences between the groups were not found to be significant (Table 3).

Mean corpuscular volume (MCV)

Post chemotherapy results in both the groups showed a fall in MCV of 9.3% and 6.24%, respectively (Table 3).

Mean corpuscular hemoglobin (MCH)

There was a change in mean MCH of 5.05% and 3.1% between pre-chemotherapy and post-chemotherapy levels in group A and group B, respectively. However, this change was not found to be significant (Table 3).

Effect on renal function

Blood urea level

The rise in blood urea level was greater in group B (33.4%) as compared to group A (23%) and was statistically extremely significant (Fig. 1).

Serum creatinine level

There was increase in serum creatinine level in both the groups with group B showing marginally greater rise (52.7%) than group A (52.29%). This change in the pre- and post-chemotherapy levels were statistically extremely significant (Fig. 2).

Discussion

The present study compared the hemato- and nephrotoxicity of weekly-cisplatin-based chemotherapy with every 3 weeks cisplatin regimen. It was carried out on LA-SCCHN patients in IC setting which was followed by surgery or adjuvant chemoradiation outside the study protocol. These are accepted and preferred multidisciplinary treatment strategies for LA-SCCN [6]. Cisplatin (cis-diaminedichloroplatin) is a frontline chemotherapeutic agent in the treatment of many solid malignant tumours including head and neck cancer. However, it has major toxicities like severe nausea, vomiting, neurotoxicity [7], ototoxicity [8], myelotoxicity, and high incidences of renal dysfunction which is a major dose-limiting factor. Some of the ways to reduce such adverse effects are use of 5HT-receptor antagonists, vigorous hydration [9] and administering cisplatin as a weekly dose which is accepted in international guidelines [10–13]. However, most of these studies are related to concurrent and adjuvant therapies whereas our present study is the first to investigate toxicity in induction chemotherapy setting using weekly cisplatin schedule. The rationale for such low-dose weekly cisplatin (30–40 mg/m) dosage compared to every 3-weekly cisplatin relies on increased treatment compliance [14], better treatment adjustments and discontinuation according to condition of patient [15, 16].

In the present study, LASCCHN was more prevalent in males, mostly presenting in fifth decade of life commonly involving the oropharynx [17, 18, 19]. However, Lu HJ et al. [20] and Mitra et al. [21] reported laryngeal cancer to be commonest. Majority of our patients belonged to stage III which is similar to Sahoo et al. [19] and Mitra et al. [21]. However, several studies reported more cases in stage IV as well [3, 17, 18, 22, 23].

Chemotherapy drug dosage

In the present study, cisplatin dose was administered at 30 mg/m^2 in weekly regimen (group A) providing median cumulative cisplatin dose of 170 mg/m^2 while in the 3-weekly schedule (group B), the cisplatin dosage was 100 mg/m^2 providing the median cumulative cisplatin dose of 220 mg/m^2. In various other studies, similar dosage ranging from 30 to 40 mg/m^2 versus 100 mg/

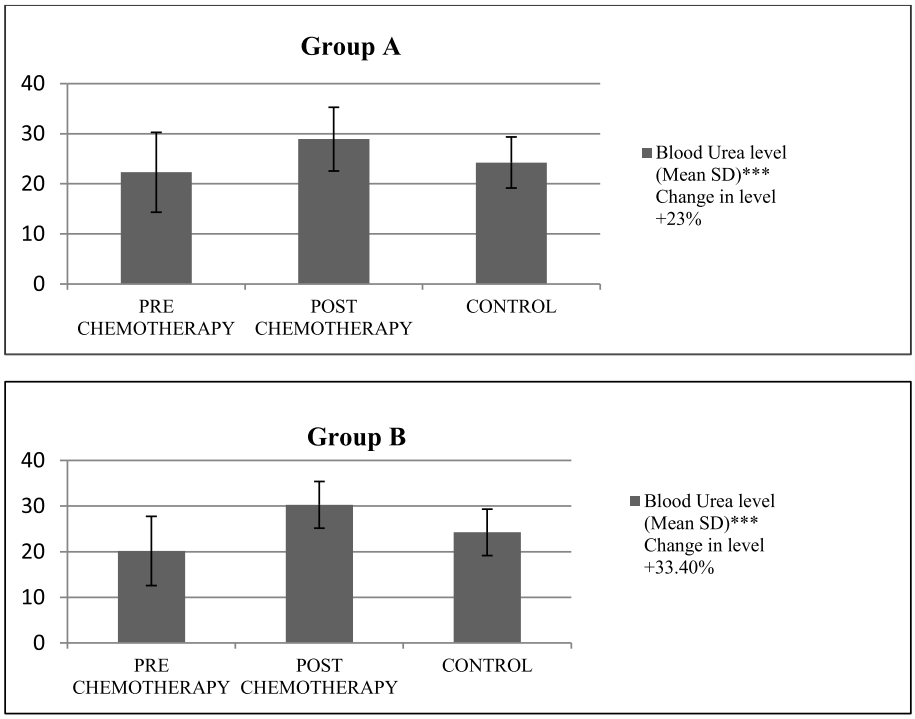

Fig. 1 Changes in blood urea level in both groups. ***$p < .001$ (extremely significant). Change in terms of increase in levels are indicated by plus sign

m^2 was administered in concurrent chemotherapy regimen [18, 19, 21, 23–26]. According to study by Mackewiz J et al. [27], the median total dose of weekly cisplatin group was 160 mg/m^2 and those on 3-weekly regimen was 270 mg/m^2. Moreover, de Jongh FE et al. [28] studied the feasibility of short intensive weekly cisplatin dose with 60 mg/m^2 in LASCCHN. It has been suggested that to achieve better locoregional control and survival benefit, a treatment regime should have a cumulative dose of 200 mg/m^2 [29, 30] which can be fractionated into a weekly cisplatin dose of 30–40 mg/m [31].

Hematological toxicities

Total leucocyte count and differential count

Patients receiving weekly chemotherapy had greater neutropenia than patients in the 3-weekly cisplatin group which was statistically very significant ($p = .0018$) and was similar to studies of Geeta SN et al. [26] and Sahoo TK et al. [19]. This seems to be due to repeated myelosupression by platins and inability to recuperate the loss as leucopenia recovers in 21 days. Kogo M et al. [32] also reported neutropenia in 32.4% cases and showed platelet count and the type of platinum as risk factors for neutropenia. However, higher incidence of neutropenia has also been reported in every 3-weekly concurrent chemoradiotherapy (CRT) group than in weekly group [18, 21, 23, 27, 33]. Several studies have also reported similar high-grade leucopenia and neutropenia in both the groups [25, 34–37]. Lymphopenia was observed in both the groups which was also statistically significant ($P = 0.0115$) and consistent with study of Mackiewicz J et al. [27] who observed higher level of severe lymphopenia in 3-weekly cisplatin (100 mg/m^2) group (88% vs 72.2% $P = .04$).

Red cell count

Anemia is one of the commonest complications in cisplatin chemotherapy [38] in both weekly and 3-weekly groups of patients in concurrent setting [37]. In our study, there was a greater fall of RBC count in weekly cisplatin group as compared to 3-weekly group. This observation was statistically extremely significant and concurs with studies of Sahoo TK et al. [19] and Chen JX et al. [35] who observed this fall before the 4th chemotherapy cycle. The extremely significant anemia in weekly cisplatin group stems from greater myelosuppression which reaches nadir after approximately 10 days. This is accentuated at the weekly dose thereby causing greater fall in RBC. In 3-weekly group, the gap of 21 days before the next dose gives time for proliferating cells to recuperate and offset the fall to a greater extent.

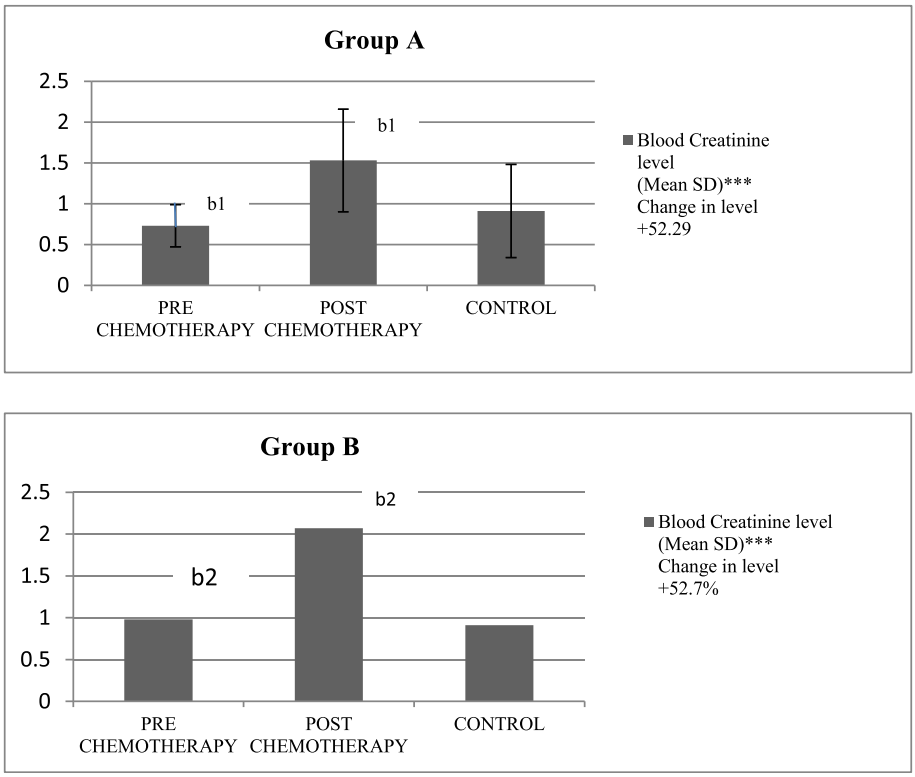

Fig. 2 Changes in serum creatinine level in both groups. ***$p < .001$ (extremely significant). On comparing the pre and post chemotherapy patients in group A by Tukey-Kramer multiple comparisons test, the significance level is indicated by b1, b2:$p < .001$ (extremely significant). Change in terms of increase in levels are indicated by plus sign

However in concurrent chemoradiation setting, anemia was more in the 3-weekly cisplatin group [23]. One of the risk factors for anemia was found to be the performance status of the patient [32]. In LA-SCCHN, the hemoglobin level prior to induction chemotherapy is significantly related to treatment response ($P = 0.01$) and is an independent predictor of overall survival and disease-free survival [39]. Hasan BA et al. [40] also reported that Cisplatin + 5-FU regimen has strong association with anemia onset and severity. We also noted fall in MCV level in both the groups and statistically significant rise in MCH level after chemotherapy. However, some studies pertaining to concurrent CRT have shown no difference in hematological toxicities between weekly and 3-weekly groups [27, 41, 42].

Platelet count

We observed thrombocytopenia in 14.8% cases, showing greater fall in the weekly group as compared to 3-weekly regimen with extremely significant statistical difference. Kogo M, et al. [32] reported thrombocytopenia in 10.2% cases and Yokota T et al. [38] reported in 85% cases receiving IC with docetaxel plus ciplatin and 5FU as combination chemotherapy. In another study, Chen JX et al. [35] reported thrombocytopenia in both the groups ($P < 0.05$, $P < 0.01$) similar to studies by Furqan et al. [37] and Karim et al. [23]. The risk factors for thrombocytopenia were performance status, platelet count and serum creatinine concentration ($p < 0.05$) [32]. Although all these studies were related to patients receiving concurrent chemoradiation, our study throws new light on myelotoxicity level in LA-SCCHN patients in an IC setting. Owing to greater myelotoxicity in LA-SCCHN patients under induction chemotherapy receiving weekly cisplatin (30 mg/m^2), it should be delivered cautiously only prior to full hematological work-up, although the safety and tolerability of this regimen have already been confirmed by previous study [43].

Effect on renal function

There are a number of studies on concurrent CRT regimen which showed higher incidence of nephrotoxicity with 3-weekly cisplatin therapy [17, 44–46]. A multicentric study on 300 SCCHN patients receiving CRT at cisplatin dose of > 200 mg/m^2 reported 33.1% nephrotoxicity in 3-weekly as compared to 20.9% in

weekly cisplatin group [24]. Our results were consistent with these studies in which we showed statistically significant rise in both urea and creatinine levels in both the groups but indicating more renal damage with 3-weekly regimen than weekly cisplatin group. Large meta-analysis study on patients under definitive treatment comparing weekly and 3-weekly cisplatin dosing schedule has also confirmed significantly severe nephrotoxicity in 3-weekly group (p = .0099) [47]. However, Mousavi et al. [48] reported no significant association of cisplatin nephrotoxicity with age (P = 0.1), gender (P = 0.64), and mean dose of cisplatin (P = 0.8). Similarly, Ho KF et al. [25], Mackiewicz J et al. [27] and Espeli V et al. [49] showed no difference in nephrotoxicity in both the groups and reported that in patients receiving CRT, there is no difference in severity and incidence of acute kidney injury between the study groups.

Our study seems to be the first study to report this toxicity profile in an induction chemotherapy setting among two regimens. The prevalence of cisplatin nephrotoxicity was 7.9%. The median time of onset to acute kidney failure in the weekly cisplatin group is reported to be 15.8 days and in 3-weekly group to be 23 days [27]. Study by Melotek et al. [50] have reported that relative changes rather than absolute changes in creatinine level is a better marker for acute kidney injury and found the weekly regimen to cause lesser kidney injury than 3-weekly dosage. Acute kidney injury was commoner in patients ≥ 60 years, whereas leukopenia significantly effected younger patients [51]. Clinical use of cisplatin is limited by renal tubular dysfunction which is dose dependent and causes necrosis, apoptosis, and necroptosis of nephrons [52–55]. The mode of action of cisplatin on cancer cells is attributed to its property of releasing free radicals which, at the same time, has the potential to damage kidney cells. The tissue-specific toxicity of cisplatin causes oxidative stress resulting in biochemical and histological alterations [56].A limitation of our study was that the aspect of treatment response was out of scope of our study but merits further investigation. We suggest future studies through a large multicentric trial comparing the weekly versus 3-weekly cisplatin during induction chemotherapy to validate our results.

Conclusions

To our knowledge, this is the first study on myelotoxicity and nephrotoxicity profile of induction chemotherapy using cisplatin on weekly basis at 30 mg/m^2 dosage in patients of LASCCHN. Patients treated with weekly treatment schedule received lower total cisplatin dose in comparison to those treated with the 3-weekly schedule. It was well tolerated with minimal renal toxicity but incidence of leucopenia, anemia, and thrombocytopenia were higher as compared to the 3-weekly cisplatin dose administered as 100 mg/m^2. Since renal toxicities induced by high-dose cisplatin are irreversible and reduces patients' quality of life, the weekly regimen may be a preferred option which requires fewer hospitalizations and should be more feasible in situations where patient load is high with limited resources.

Abbreviations

LA-SCCHN: Locally advanced squamous cell carcinoma of head and neck; SCCHN: Squamous cell carcinoma of head and neck; IC: Induction chemotherapy; TLC: Total leucocyte count; RBC: Red blood cell; 5 FU: 5 Fluoro uracil; K: Potassium; Na: Sodium; Ca: Calcium; ESR: Erythrocyte sedimentation rate; DLC: Differential leucocyte count; ECG: Electrocardiogram; ANOVA: Analysis of variance; Hb%: Hemoglobin level; Hct: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; CP: Cisplatin; BSA: Body surface area; NS: Normal saline; Amp: Ampoule; CRT: Chemoradiation

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Authors' contributions

AC has contributed to the conception and design of the work and worked on data interpretation, analysis, and manuscript writing. AB has contributed to the conception and design, analyzed and interpreted the patient data of hematological and liver enzymes, and done manuscript editing and reviewed it. AJN contributed to concept of the work, performed literature search, done data acquisition and analysis, and prepared the manuscript. SD contributed to design of the work, performed literature search, took informed consent, and done data acquisition, analysis, and manuscript preparation. AR performed statistical analysis of data, contributed major part in manuscript writing editing and review. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due institutional data protection policy but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Silchar Medical College Hospital with approval number SMC/12994. The patients provided written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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