Original Article

Role of Induction Chemotherapy in Downstaging of Locally Advanced Head-and-Neck Squamous Cell Cancer

Manish Kumar Ahirwar, Veenita Yogi, O. P. Singh, H. U. Ghori, Vivek Tiwari, Bibin Francis

Department of Radiotherapy, Gandhi Medical College, Bhopal, Madhya Pradesh, India

Abstract

Aims and Objectives: To study the effect of induction chemotherapy (CT) in locally advanced head-and-neck squamous cell carcinoma (LAHNSCC) and to compare the two commonly used regimens of CT, including paclitaxel and cisplatin (CDDP) in one arm and CDDP, methotrexate (MTX), and bleomycin in the other arm as induction CT. **Materials and Methods:** It is a retrospective study, including 100 histopathologically proven cases of LAHNSCC who received treatment at a government medical college and hospital in Central India between November 2015 and June 2016. All the patients were randomly divided into two arms: arm A received paclitaxel + cisplatin (TP) and arm B received cisplatin + MTX + bleomycin as induction CT had adequate hematologic, hepatic, and renal functions, and their response to treatment was evaluated clinically after each cycle up to three cycles before external beam radiotherapy. **Results:** The present study showed beneficial effects of induction CT in HNSCC as 82% of the patients showed response or T-downstaging. Among the patients responding to induction CT, 34% showed complete and 48% showed partial response at the primary tumor site according to Response Evaluation Criteria in Solid Tumors. The difference in response between the two arms was statistically significant (P = 0.037). **Conclusion:** The current study shows the beneficial effects of induction CT in LAHNSCC. No statistically significant difference was seen in the response of both regimens of induction CT in terms of overall survival, but significant disease-free survival and progression-free survival were obtained in the TP arm.

Keywords: *Downstaging, head-and-neck squamous cell carcinoma, induction chemotherapy, taxanes*

Introduction

For many years, chemotherapy (CT) has been administered in the adjuvant or neoadjuvant settings and more recently, in concurrent settings with radiotherapy.[1] Concurrent chemoradiotherapy has emerged now as one of the most promising treatment modalities for head-and-neck squamous cell carcinoma (HNSCC). However, the higher response rates with induction CT in untreated patients and the probability of tumor shrinkage have made this approach attractive as well.[2,3] This study is a brief analysis of the use of induction CT as a treatment approach and the emergence of cisplatin (CDDP) with paclitaxel or methotrexate (MTX) and bleomycin, as a standard treatment option.

As taxanes are found to be efficient single-agent CT in the treatment of many solid tumors, investigators started using them as a single agent or with other agents in induction CT regimens. Various trials suggested that the addition of taxanes might enhance the activity of CDDP, docetaxel, and fluorouracil (5FU) (TPF).[4,5] In an analysis, the results of six studies using TPF induction CT (n = 95) were compared with data from five large randomized trials using platinum and 5FU (PF) induction CT (n = 535).[6] This analysis reported that, after adjustment for known prognostic factors, the relative risk of death was higher in the PF group than in the TPF group (relative risk, 1.85; 95% confidence interval (CI), 1.37–2.49), and this corresponded to a significant estimated 20% benefit in the 2-year survival rate (P = 0.0001).

The most successful combinations of CT for head-and-neck cancer are the platinum-based combinations, which, in previously untreated patients, have yielded high response rates. These combinations

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Address for correspondence:
Dr. Veenita Yogi, Department of Radiotherapy, Gandhi Medical College, Bhopal - 462 001, Madhya Pradesh, India.
E-mail: dryogi_vinita@yahoo.co.in

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include platinum and bleomycin; CDDP, bleomycin, and MTX Cisplatin, Bleomycin and Methotrexate (PBM); PBM with one additional drug; CDDP, bleomycin, and a Vinca alkaloid; and CDDP and 5-fluorouracil (5-FU) plus or minus MTX, of which combination CT is employed as induction therapy before definitive surgery and/or radiation therapy remains to be determined in randomized trials. There are suggestions in some trials of increase in the disease-free interval as well as increase in survival time.[7,8] The present study suggests the benefits of induction CT in locally advanced HNSCC (LAHNSCC) and hence can be considered as a useful modality of treatment.

Materials and Methods

This is a retrospective, analytical study. Ethical clearance was obtained from the Institutional Ethical Committee. We have reviewed medical records of 110 patients who were histopathologically proven cases of HNSCC and received treatment at a government medical college of Central India between November 2015 and June 2016. Among these patients, ten patients defaulted treatment at initial stages, so those were excluded from the results. This study included 100 patients, aged between 18 and 70 years with primary HNSCC of T3/T4 stage (as per AJCC cancer manual 7th edition). After informed consent, all patients were randomly divided into two arms, treated with induction CT: arm A: paclitaxel + CDDP (TP) and arm B: CDDP + MTX + bleomycin (PMB) with standard doses in per meter square body surface area. All patients have adequate hematologic, hepatic, and renal functions, and their response to treatment and toxicities were evaluated clinically after each cycle up to three cycles before external beam radiotherapy (EBRT). This study included tumors of the oral cavity, oropharynx, hypopharynx, larynx, and paranasal sinuses. Induction CT regimens used were TP or PMB and each patient received at least three cycles of CT.

Response was evaluated according to Response Evaluation Criteria in Solid Tumors.

Statistical analysis was done by using Microsoft Excel and SPSS software version 22 (IBM Corp., New York, USA). Means were calculated for each of the quantitative values and then comparisons were made using independent *t*-test. Chi-square test was used for the comparison of response between the two arms, and Kaplan–Meier analysis was done for survival analysis, while for the comparison of survival analysis, log-rank hypothesis was used. $P < 0.05$ was taken for statistical significance.

Results

The median age of the patients in this study was 45.6 years (range 18–70 years) among which 67% of patients were male and 33% of patients were female [Tables 1, 2 and Figures 1, 2]. Most of the patients in both arms were of Stage IV disease with 72% (36) in arm A and 56% (28) in arm B [Table 3 and Figure 3]. Fifty-eight percent patients included in this study were of oral cavity cancer, and the rest included hypopharynx, oropharynx, and larynx [Table 4 and Figure 4]. Common toxicities observed were mainly Grade I and Grade II in both the arms [Table 5].

Table 1: Age-wise distribution of patients in arms A and B

Age group (years)	Arm A (*n*=50), *n* (%)	Arm B (*n*=50), *n* (%)
30-40	13 (26)	17 (34)
41-50	16 (32)	16 (32)
51-60	14 (28)	9 (18)
61-70	7 (14)	8 (16)
P	0.63	

Table 2: Sex-wise distribution of patients in arms A and B

Sex	Arm A, *n* (%)	Arm B, *n* (%)
Male	38 (76)	29 (58)
Female	12 (24)	21 (42)
P	0.05	

Table 3: Stage-wise distribution of patients in arms A and B

TNM	Stage	Arm A (*n*=50), *n* (%)	Arm B (*n*=50), *n* (%)
T3, N0, M0	III	0	3 (6)
T2, N1, M0	III	2 (4)	2 (4)
T3, N1, M0	III	5 (10)	13 (26)
T2, N2, M0	IVa	6 (12)	7 (14)
T3, N2, M0	IVa	3 (6)	4 (8)
T4a, N1, M0	IVa	9 (18)	6 (12)
T3, N2, M0	IVa	4 (8)	5 (10)
T4a, N2, M0	IVa	11 (22)	6 (12)
T4a, N3, M0	IVb	3 (6)	0
T4b, N2, M0	IVb	7 (14)	4 (8)
Total		50	50

TNM: Tumor, node, and metastasis

In the current study, we observed beneficial effects of induction CT in HNSCC as most of the patients showed response or T-downstaging in 82% (82). Among the patients who received induction CT, 34% (34) showed complete and 48% (48) showed partial response at the primary tumor site. Eventually, 11% (11) of these patients required salvage surgery and 18% (18) had unresectable or metastatic relapses. Fifty patients were included in each arm with arm A receiving TP and arm B receiving PMB as induction CT. Among all the TP arm patients, 38% (19) showed complete, whereas 52% (26) of the patients showed partial response, while the rest of the 10% (5) had either stable or progressive disease or had defaulted treatment. Among the PMB arm patients, 32% (16) showed complete, whereas 42% (21) showed partial response and the rest (26% [13]) of the patients had either stable disease or progressive disease or had defaulted treatment. The mean number of

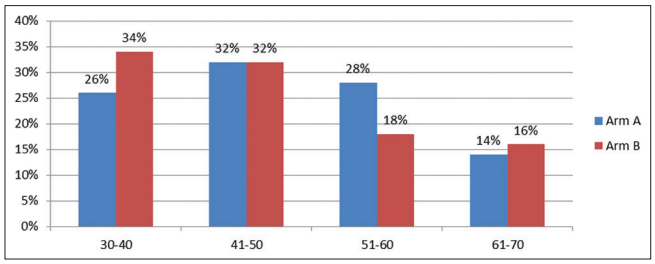

Figure 1: Age-wise distribution of patients in arms A and B

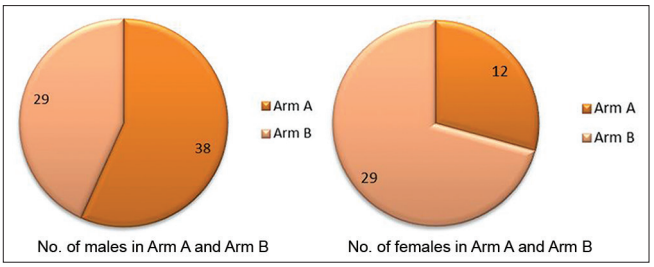

Figure 2: Sex-wise distribution of patients in arms A and B

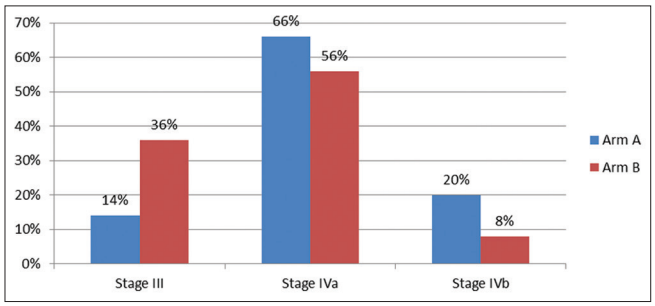

Figure 3: Stage-wise distribution of patients in arms A and B

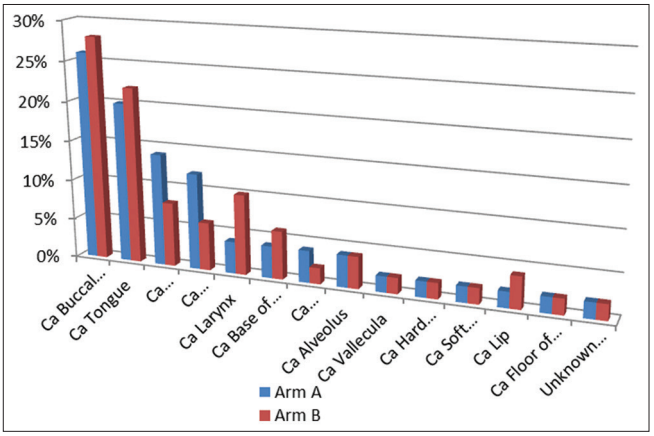

Figure 4: Site-wise distribution of patients in arm A and B

Table 4: Site-wise distribution of patients in arms A and B

Diagnosis	Arm A, *n* (%)	Arm B, *n* (%)	Total, *n* (%)
Carcinoma buccal mucosa	13 (26)	14 (28)	27 (27)
Carcinoma tongue	10 (20)	11 (22)	21 (21)
Carcinoma supraglottis	7 (14)	4 (8)	11 (11)
Carcinoma pyriform fossa	6 (12)	3 (6)	9 (9)
Carcinoma larynx	2 (4)	5 (10)	7 (7)
Carcinoma base of tongue	2 (4)	3 (6)	5 (5)
Carcinoma tonsillar fossa	2 (4)	1 (2)	3 (3)
Carcinoma alveolus	2 (4)	2 (4)	4 (4)
Carcinoma vallecula	1 (2)	1 (2)	2 (2)
Carcinoma hard palate	1 (2)	1 (2)	2 (2)
Carcinoma soft palate	1 (2)	1 (2)	2 (2)
Carcinoma lip	1 (2)	2 (4)	3 (3)
Carcinoma floor of mouth	1 (2)	1 (2)	2 (2)
Unknown primary	1 (2)	1 (2)	2 (2)

patients responded to induction CT was 41 (CI, 35.4–46.7), and the difference between patients responded to CT or not was statistically significant (P = 0.037), which suggests that induction CT downstaged the disease whatsoever regimen was used. Further, it was also noticed that patients who have not responded to induction CT were of relatively older age group (74% of patients not responded to CT were of age group above 50 years) and poor performance status (90% of patients not responded to CT had Karnofsky Performance Status between 70 and 80).

The mean duration of follow-up was 19.5 months. Log-rank test was used for the comparison of survival. For overall survival (OS), P = 0.829 was found with a confidence limit of 95%, which was statistically insignificant showing comparable results in both arms of CT [Figure 5].

While for disease-free survival (DFS), P = 0.008 (95% confidence limit) [Figure 6] and for progression-free survival (PFS), P = 0.003 (95% confidence limit) [Figure 7] were found, suggestive of a significant DFS and PFS. These results suggested that arm A (TP) was superior in terms of DFS and PFS.

Discussion

Earlier in the 1990s, neoadjuvant CT was the most commonly used modality of treatment in LAHNSCC to achieve a better local control of disease, or to improve survival, even though this was not clear from randomized studies. After so many conflicting ideas about the use of CT in HNSCC, various randomized trials were conducted in advanced head-and-neck cancer, while few meta-analyses reviewed its use. These meta-analyses and data publications changed the attitude of physicians toward the use of neoadjuvant CT. In addition, a meta-analysis of trials using PF containing induction regimens demonstrated a significant survival benefit for this approach over locoregional treatment alone in locally advanced disease. More recently, taxanes are now being

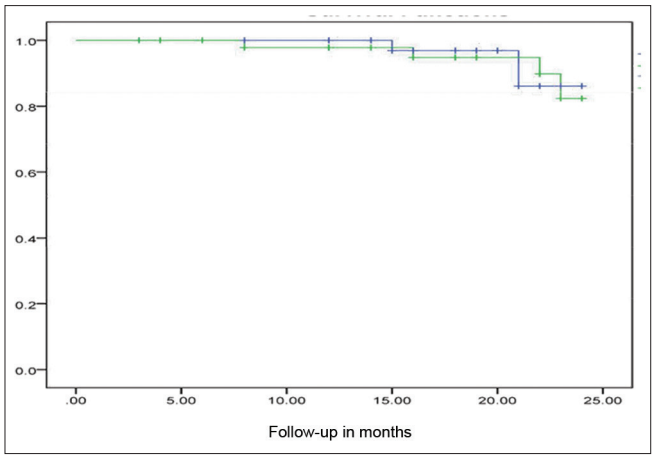

Figure 5: Overall survival (*P* = 0.829) A ___, B___

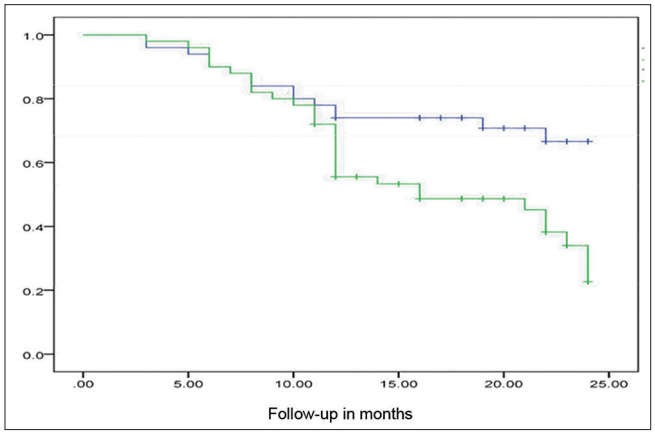

Figure 6: Disease free survival (*P* = 0.008) A ___, B___

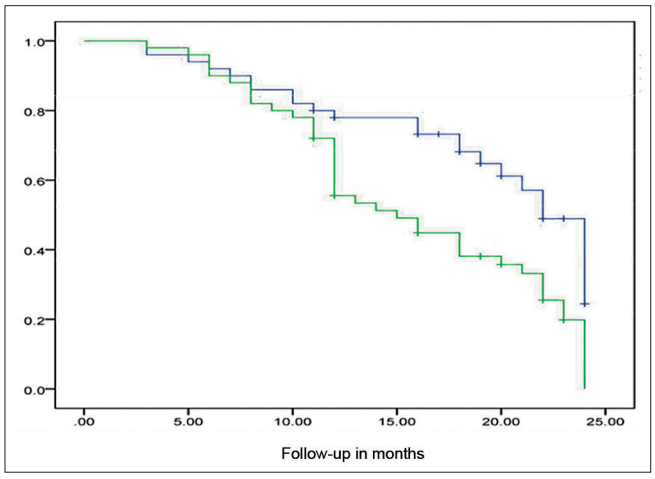

Figure 7: Progression free survival (*P* = 0.003) A ___, B___

introduced as more active regimens of induction CT. The three-drug combination induction regimen of MTX, bleomycin, and CDDP has also been found effective in HNSCC. The present study suggests an extra benefit of the additional induction CT to standard concomitant chemoradiotherapy in comparison to concomitant chemoradiotherapy alone.

Table 5: Treatment-induced toxicities observed in patients of arms A and B at treatment completion

Toxicity	Arm A, *n* (%)		Arm B, *n* (%)	
	Grades I-II	Grades III and IV	Grades I-II	Grades III and IV
Mucositis	38 (76)	12 (24)	43 (86)	7 (14)
Nausea/vomiting	40 (80)	10 (20)	37 (74)	13 (26)
Neuropathy	36 (72)	14 (28)	32 (64)	18 (36)
Renal toxicity	41 (82)	9 (18)	40 (80)	10 (20)
Myelosuppression	42 (84)	8 (16)	41 (82)	9 (18)

CT, prior to radiotherapy or surgery, is a very popular treatment modality for many decades. With the two-drug combination of high-dose platinum and bleomycin infusions in patients with HNSCC subsequently treated with definitive radiotherapy, Hong *et al*. obtained a 76% response rate with a 20% complete remission rate, which is comparable to our study where we found 82% of patients responding to induction CT including 34% of patients showing complete response, while in one other study by Randolph *et al*., the authors reported a 71% response rate.[9,10] However, in a series of previously treated patients, Randolph *et al*. noted that the same combination produced only a 33% response rate. This high frequency of response in previously untreated patients prompted a large multi-institutional National Cancer Institute-sponsored, controlled study of platinum and bleomycin infusion, followed in turn by surgery and radiation therapy in patients with resectable Stages III and IV squamous cancers of the oral cavity, hypopharynx, and larynx.[11] In this study, 462 patients were randomized to one of the following three groups: (1) standard therapy of surgery and postoperative radiation, (2) induction CT (CDDP, 100 mg/m^2, day 1, and bleomycin, 15 units/m^2 bolus, day 3; 15 units/m^2 by 24-h infusion days 3–7) followed by standard therapy, and (3) induction CT and standard therapy followed by maintenance CT (CDDP, 80 mg/m^2 monthly ×6 cycles). The 2-year DFS rate was similar among the groups: 55% for those treated with standard therapy alone and 57% for those with induction CT. Elias *et al*. demonstrated that the three-drug combinations of high-dose platinum, bleomycin infusion, and high-dose MTX with leucovorin rescue as induction therapy in HNSCC produced 68% response.[12] Using more conventional doses of platinum, bleomycin, and MTX in previously treated patients with advanced disease, Vogl and Kaplan obtained significant results in patients treated with induction therapy plus standard therapy and 67% for the third group. In this trial, the low overall response rate of 37% with a complete response rate of 3% of the patients in Group 2 treated with platinum and bleomycin induction CT was considered to be attributed to the minimal CT administered in only a single course of therapy.[13] An improved long-term survival rate probably requires a higher response rate with a greater number of complete responses. This trial indicates that further controlled clinical studies with

more intense induction regimens are needed to determine whether combination CT can improve survival rates in patients with advanced head-and-neck cancer. For assessing the effects of various induction CT regimens as well as the treatment approach itself, in comparison with no induction CT, a meta-analysis of randomized trials was conducted.[14] The objectives of that analysis were to review trials directly comparing OS and PFS with: (a) a TP (F)-based induction CT versus a PF-based induction CT regimen (n = 1154) and (b) a PF induction CT regimen and no induction CT (n = 2785). Treatment subsequent to induction CT was to be the same in both treatment arms. On comparison of survival outcomes, it was found that the risk of death was lower with the use of PF induction CT, compared with no induction CT (relative risk, 0.89; 95% CI, 0.82–0.97), and that taxane-based induction CT was associated with a lower risk for death than PF (relative risk, 0.79; 95% CI, 0.69–0.91).

The combination of paclitaxel and CDDP can be administered in a weekly, biweekly, or three-weekly schedule. The main side effects are neurosensory and neuromotor changes. Hematologic toxicity is acceptable, and doses can be increased after the use of granulocyte colony-stimulating factor.[15] In patients with recurrent and/or metastatic HNSCC, a recent study showed that the combination of paclitaxel and CDDP resulted in an overall response rate of 41.1% (complete responders 6%) and a median OS of 11 months (range 1–53 months) with mild toxicity.[16] In the same patient population, the combination of TP was compared with the standard PF schedule which showed a comparable efficacy (response rate 22% vs. 18%, median survival 8 months vs. 9 months; 1-year survival 41% vs. 30%), with less toxicity.[17] Our study results demonstrated that arm A (TP) was superior in terms of DFS (P = 0.008) and PFS (P = 0.003).

Conclusion

The present study suggests the beneficial effects of induction CT in HNSCC (on clinical response assessment). No statistically significant difference was observed in the response of both regimens of induction CT. Among all the patients who achieved a clinical partial response or tumor downstaging after induction CT, the incidence of requirement for palliative treatment was reduced. Most of the patients who responded well to induction CT also responded well with EBRT, whereas those who showed poor response were treated with alternative protocols.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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