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Research Article

A COMPARATIVE STUDY OF WEEKLY CETUXIMAB VERSUS CISPLATIN WITH CONCURRENT RADIOTHERAPY IN ELDERLY PATIENTS OF LOCOREGIONALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK

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A B S T R A C T

Purpose: The standard of care for Locoregionally Advanced Squamous Cell Carcinoma of Head and Neck (LASCCHN) is concurrent chemoradiation. The most common chemotherapeutic agent used is cisplatin (CDDP) given three weekly or weekly. Cetuximab (CTX) is the alternative agent for patients clinically unfit for CDDP. The present study was carried out to compare toxicity, tolerability, locoregional control (LRC) and overall survival (OS) in patients receiving CDDP versus CTX.

Materials and methods: The present retrospective study was carried out at department of Radiotherapy, SMS Medical College, Jaipur; during July 2015 to June 2016 on patients with LASCCHN of oral cavity, oropharynx, hypopharynx and laryngopharynx treated with definitive radiotherapy (70 Gy in 35 fractions) concurrently with either CDDP (40 mg/m2 IV every week) or CTX (400 mg/m2 followed by 250 mg/m2 every week). A total of 64 patients were found eligible, 43 patients in CDDP arm and 21 patients in CTX arm.

Results: Treatment interruptions, requirement of parenteral nutrition and feeding naso-gastric tube insertion were significantly higher in CTX arm compared to CDDP arm (P = 0.005, 0.04, & 0.003, respectively). CTX arm demonstrated significantly more grade II or higher acute dermatitis (P = 0.03) and infusion reactions (P = 0.003); whereas leucopenia and vomiting was significantly higher in CDDP arm (P = 0.04 and <0.001, respectively). At last follow up, there was no significant difference in LRC rate & OS of CDDP arm (86% & 86%) and CTX arm (82.6% & 71.4%), respectively.

Conclusion: Treatment interruptions, requirement of parenteral nutrition & nasogastric feeding, acute dermatitis, and infusion reactions were significantly higher in CTX arm; whereas leucopenia and vomiting was significantly higher in CDDP arm. No difference was noted in LRC and OS between the two groups.

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INTRODUCTION

Head & neck cancer is one of the leading cancers among Indian population, with estimated incidence of about 14.3% (23.3% in males and 6.3% in females) and estimated mortality of about 15.4% (22.8% in males and 7.3% in females) for all cancer cases. [1, 2] At our center, head and neck malignancies constitute approximately 25% of all cancers. Most of the diagnosed head and neck cancers are histologically squamous cell carcinomas (90-95%). More than two third cases require radiotherapy (RT), either as definitive or as adjuvant mode. The standard of care for Locoregionally Advanced Squamous Cell Carcinoma of Head and Neck (LASCCHN) is Concurrent Chemo-Radio-Therapy (CCRT). [3, 4] The most common chemotherapeutic (CT) agent used for CCRT is cisplatin (CDDP, cis-diamminedichloridoplatinum). [5] The optimal regimen of CDDP is still unknown.

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The most widely accepted schedule of CDDP found in literature is 100 mg/m^2 given intravenously (IV) every three weeks. However, this has been associated with higher toxicities leading to undesired treatment interruptions. Alternatively, weekly schedule of CDDP has also been mentioned in literature, using various dose of CDDP; CCRT with CDDP at least 40 mg/m^2 per week remains standard weekly schedule for LASCCHN. [6-8]Given the peculiar toxicity profile of CDDP like nephrotoxicity, ototoxicity, vomiting etc., many other chemotherapeutic agents have been tested for patients clinically unfit for CDDP. Cetuximab (CTX) is the most popular agent among them. [9, 10] CTX is an epidermal growth factor receptor inhibitor, given at a loading dose of 400 mg/m^2 IV one week before start of RT followed by 250 mg/m^2 IV every week for the duration of RT. [11]

MATERIALS AND METHODS

The present study is retrospective in nature carried out at department of Radiotherapy, SMS Medical College, Jaipur; during July 2015 to June 2016 on patients with LASCCHN of

oral cavity, oropharynx, hypopharynx and laryngopharynx treated with definitive radiotherapy with curative intent either with three dimensional conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT) over linear accelerator, concurrently with either CDDP or CTX. Patients with age < 60 years, early stage, previous history of surgery, other than squamous histology, location of primary other than cited above, previous history of radiotherapy, treatment with palliative intent, contraindication to either chemotherapy, distant metastases or second malignancy were excluded from the study. 3 patients who were planned for CTX developed adverse reaction at the first infusion, so further CTX was withheld and they were shifted on CDDP. So, a total of 64 patients were found eligible, 43 patients in CDDP arm and 21 patients in CTX arm.

All patients had undergone basic laboratory investigations prior to administration of every CT cycle; and baseline clinical examination, radiological evaluation (either a contrast enhanced computed tomography or a magnetic resonance imaging) of head and neck region, laryngoscopic evaluation and metastatic work-up prior to RT.

All patients were treated on Seimens Oncor Expression dual energy linear accelerator machine with 6 megavoltage energy photon beam with immobilization in supine position using a thermoplastic device. Patients received 70 Gy in 35 fractions with 2 Gy per fraction to the tumor and involved lymph nodes, and 50 Gy to uninvolved nodes; for 5 fractions per week in both groups. Planning computerized tomography (CT) scan of the area of interest was done followed by delineation of Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Planning Target Volume (PTV) and organs at risk (OAR) volumes as per the RTOG atlas. Patients in CDDP arm received injection cisplatin at 40 mg/m^2 given intravenously concurrently with radiotherapy every week; while patients in CTX arm received loading dose of injection cetuximab at 400 mg/m^2 followed by 250 mg/m^2 every week. The aim was to prescribe 7 cycles of either CT.

All patients had undergone weekly assessment while CCRT was going on for development of any acute toxicity. Toxicities like mucositis, dermatitis, nephrotoxicity and gastrointestinal toxicity were assessed according to Radiation Therapy Oncology Group (RTOG) Acute and Late Radiation Morbidity Scoring Criteria; whereas haematological toxicities like leucopenia, anemia and thrombocytopenia; nausea and vomiting were assessed as per the National Cancer Institute's Common Terminology Criteria for Adverse Events (v4.03). In all toxicities, the worst grade was reported. Patients underwent evaluation at six weeks post CCRT both clinically and radiologically, which was followed by three monthly evaluation till the last follow up.

Response was assessed as per the WHO Criteria. A complete response (CR) was defined as no evidence of disease 3 months after the completion of CCRT, evaluated by clinical and radiological examinations; persistence or progression of disease at that time was determined as non-CR. Disease after achieving of CR was defined as recurrence. A diagnosis of residual disease, progression or recurrence was based on clinical or radiological examinations or pathological confirmation. Locoregional control (LRC) was defined as no reappearance of disease at local or regional site after a complete response (CR) was achieved. Overall survival (OS) was defined as the time between randomisation and either systemic progression, death from any cause or the last follow-up date.

For statistical analysis, all data were prepared and processed on Microsoft Excel 2007 using XLSTAT software version 2017 for windows (Addinsoft, New York, USA). Chi-square was used for all categorical data. *P*-value reports were two tailed and an alpha level of 0.05 was used to assess statistical significance. Survival curves were calculated using the Kaplan-Meier method.

RESULTS

Table 1 Baseline patient & tumour characteristics

Characteristics		CDDP arm, n (%)	CTX arm, n (%)	*P*-value
Age	(median, range)	67.5 (60-75)	68.5 (60-77)	0.94
Gender	Male	43 (100)	21 (100)	-
	Female	0	0	
ECOG PS	0	8 (18.6)	5 (23.8)	0.63
	1	35 (81.4)	16 (76.2)	
Smoking	Yes, present	2 (4.7)	1 (4.8)	0.98
	Yes, quit	41 (95.3)	20 (95.2)	
	No	0	0	
Site	Oral cavity	2 (4.7)	1 (4.8)	0.74
	Oropharynx	23 (53.4)	9 (42.8)	
	Hypopharynx	7 (16.3)	6 (28.6)	
	Laryngopharynx	11 (25.6)	5 (23.8)	
AJCC Stage	III	12 (27.9)	6 (28.6)	0.88
	IV A	25 (58.1)	13 (61.9)	
	IV B	6 (14)	2 (9.5)	
T stage	T1	6 (14)	3 (14.3)	0.95
	T2	22 (51.2)	10 (47.6)	
	T3	8 (18.6)	4 (19)	
	T4a	4 (9.3)	3 (14.3)	
	T4b	3 (6.9)	1 (4.8)	
N stage	N0	2 (4.7)	1 (4.8)	0.96
	N1	14 (32.6)	6 (28.6)	
	N2	24 (55.8)	13 (61.8)	
	N3	3 (6.9)	1 (4.8)	
Grade	I	5 (11.6)	2 (9.5)	0.84
	II	32 (74.4)	17 (81)	
	III	6 (14)	2 (9.5)	

AJCC: American Joint Committee on Cancer, CDDP: Cisplatin, CTX: Cetuximab, ECOG: Eastern Cooperative Oncology Group, N: Nodal, PS: Performance status, T: Tumor

Table 2 Treatment characteristics

Parameters		CDDP arm, n (%)	CTX arm, n (%)	*P*-value
RT technique	3 DCRT	27 (62.8)	9 (42.9)	0.13
	IMRT	16 (37.2)	12 (57.1)	
Treatment interruptions	Nil	26 (60.5)	5 (23.8)	0.005
	<1 week	14 (32.6)	9 (42.9)	
	>1 week	3 (6.9)	7 (33.3)	
Compliance to	RT	42 (97.8)	17 (81)	0.89
	CT	35 (81.4)	15 (71.4)	
Parenteral support required at least once during CCRT	Yes	29 (67.4)	19 (90.5)	0.04
	No	14 (32.6)	2 (9.5)	
Nasgastric tube feeding	Yes	14 (32.6)	15 (71.4)	0.003
	No	29 (67.4)	6 (28.6)	

3DCRT: 3 Dimensional Conformal Radiation Therapy, CCRT: Concurrent chemoradiation, CDDP: Cisplatin, CT: Chemotherapy, CTX: Cetuximab, IMRT: Intensity Modulated Radiation Therapy, RT: Radiotherapy

The baseline patient and tumor characteristics are shown in Table 1. No statistically significant difference was found in patient and tumor characteristics between the two arms. Treatment related parameters are shown in Table 2. Treatment interruptions for more than a week, requirement of parenteral

Table 3 Acute toxicities

Toxicity	Grade	CDDP arm, n (%)	CTX arm, n (%)	*P*-value
Acute dermatitis	< Grade II	20 (46.5)	4 (19)	0.03
	≥ Grade II	23 (53.5)	17 (81)	
Acute mucositis	< Grade II	16 (37.2)	7 (33.3)	0.76
	≥ Grade II	27 (62.8)	14 (66.7)	
Leucopenia	< Grade II	29 (67.4)	19 (90.5)	0.04
	≥ Grade II	14 (32.6)	2 (9.5)	
Anemia	< Grade II	38 (88.4)	21 (100)	0.10
	≥ Grade II	5 (11.6)	0	
Thrombocytopenia	< Grade II	39 (90.7)	20 (95.2)	0.52
	≥ Grade II	4 (9.3)	1 (4.8)	
Infusion reaction	< Grade II	43 (100)	17 (81)	0.003
	≥ Grade II	0	4 (19)	
Vomiting	< Grade II	18 (41.9)	19(90.5)	<0.001
	≥ Grade II	25 (58.1)	2 (9.5)	
Acute nephrotoxicity	< Grade I	37 (86)	21 (100)	0.07
	≥ Grade I	6 (14)	0	
Acute gastro intestinal toxicity	< Grade II	40 (93)	21 (100)	0.22
	≥ Grade II	3 (7)	0	

CDDP: Cisplatin, CTX: Cetuximab

nutrition and feeding naso-gastric tube insertion were significantly higher in CTX arm compared to CDDP arm (P = 0.005, 0.04, & 0.003, respectively). Compliance to RT was seen in 97.7% patients in CDDP arm and 81% patients in CTX arm. 81.4% of patients in CDDP arm and 65.2% of patients in CTX arm completed all the 7 cycles of CT. The treatment related acute toxicities are shown in Table 3. The CTX arm demonstrated significantly more grade II or higher acute dermatitis (P = 0.03) and infusion reactions (P = 0.003); whereas leucopenia and vomiting was significantly higher in CDDP arm (P = 0.04 and <0.001, respectively). Acute nephrotoxicity and gastrointestinal toxicity was exclusively seen in CDDP arm, but the difference was not statistically significant. The median follow-up was 23 months (range, 16 to 27 months). At last follow up, LRC rate of entire cohort was 85% (86% in CDDP arm and 82.6% in CTX arm). Distant metastases were seen in 10.9% patients and deaths were reported in 7.8% of patients; therefore OS in entire cohort was 81.3% (86% in CDDP arm and 71.4% in CTX arm). The Kaplan Meier plot for LRC and OS is shown in Figure 1. No significance difference was noted in LRC and OS between the two arms. However, early deaths were noted exclusively in CTX arm.

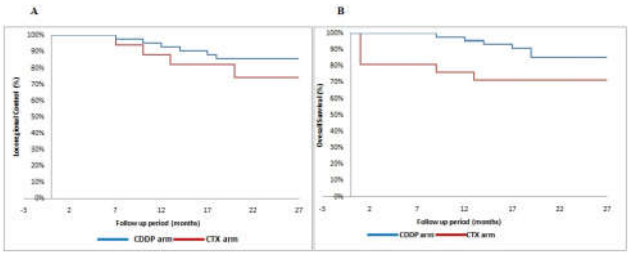

Figure 1 Comparison of (A) Locoregional control and (B) Overall survival functions between cisplatin (CDDP) arm & cetuximab (CTX) arm

DISCUSSION

The role of CCRT in LAHNSCC has been studied in MACH-NC Collaborative Group Meta-Analysis. [12, 13] The main meta-analysis of 63 trials (10,741 patients) of locoregional treatment with or without chemotherapy yielded a pooled hazard ratio of death of 0.90 (95% CI 0.85-0.94, P < 0.001), corresponding to an absolute survival benefit of 4% at 2 and 5 years in favour of chemotherapy. There was no significant benefit associated with adjuvant or neoadjuvant chemotherapy. Chemotherapy given concomitantly to radiotherapy gave significant benefits, but heterogeneity of the results prohibits firm conclusions. Later on, the updated meta-analysis included trials comparing loco-regional treatment alone to loco-regional treatment along with chemotherapy in HNSCC patients conducted between 1965 and 2000. Twenty-four new trials, most of them of concomitant chemotherapy, were included with a total of 87 trials and 16,485 patients. The hazard ratio of death was 0.88 (P < 0.001) with an absolute benefit for chemotherapy of 4.5% at 5 years, and a significant interaction (P < 0.001) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Both direct (6 trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the hazard ratio was 0.81 (P < 0.001) and the absolute benefit 6.5% at 5 years.

Bonner *et al*. conducted a multinational, randomized study to compare radiotherapy alone (213 patients) with radiotherapy plus cetuximab (211 patients) in the treatment of LASCCHN. [11] They found that the median duration of locoregional control and overall survival was 24.4 months and 49 months among patients treated with CTX plus radiotherapy and 14.9 months and 29.3 months among those given radiotherapy alone, respectively (P = 0.005 and 0.03, respectively). Radiotherapy plus cetuximab significantly prolonged progression-free survival (P = 0.006). With the exception of acneiform rash and infusion reactions, the incidence of grade III or greater toxic effects did not differ significantly between the two groups.

Magrini *et al*. claimed their study to be the first randomized study conducted to directly compare RT with concurrent CDDP versus concomitant CTX as first-line treatment of LASCCHN.. [14] Their study was discontinued early because of slow accrual after the enrollment of 70 patients. RT discontinuation for more than 10 days occurred in 13% of patients given CTX and 0% of those given CDDP (P = 0.05). Toxicity profiles differed between the two arms, with hematologic, renal, and GI toxicities more frequent in the CDDP arm, and cutaneous toxicity and the need for nutritional support more frequent in the CTX arm. Serious adverse events related to treatment were higher in the CTX arm (19% v 3%, P = 0.044). LRC, patterns of failure, and survivals were similar between the two arms. Nien *et al*. retrospectively compared concurrent platins (CDDP/carboplatin) with CTX in 339 human papilloma virus (HPV) associated oropharyngeal cancer treated with definitive radiation and found no significant differences in survival or disease control when analyzed by systemic agent. [15] Platin-treated patients had greater hematologic toxicity, and required more intravenous hydration; whereas the incidence of confluent mucositis was highest among patients treated with CTX. Two studies have been reported regarding the incidence of CTX related infusion reactions in oncology patients treated at University of North Carolina Cancer Hospital. The earlier study reported by O'Neil *et al*. concluded much higher incidence of hypersensitivity reactions in patients from North Carolina and Tennessee treated with CTX than are reported nationally and internationally. [16] However, the later study by Keating and his colleagues reported similar incidence of hypersensitivity reaction in the same area to the other areas of the south-eastern United States. Overall, 24.8% of patients experienced an infusion reaction of any grade. [17]Caudell *et al*. have also reported no statistically significant difference among

3 year LRC, distant metastasis-free survival, disease-specific survival, and OS among patients treated with concurrent CDDP or CTX in LASCCHN. [18] Strom *et al*. compared 3 weekly CDDP with weekly CTX given concurrently with radiotherapy for LASCCHN. [19] The 2 year actuarial LRC, distant metastasis and OS of CDDP and CTX were 91% & 90% (p = 0.74), 8% & 12% (p = 0.55) and 87% and 89% (p = 0.47) respectively. On the other hand, Riaz *et al*. have reported inferior outcomes for 174 LASCCHN treated with definitive RT concurrent with CTX compared to CDDP. [20] At median follow-up of 47 months, the 3-year loco-regional failure, disease-free survival, and OS for CDDP versus CTX were 5.7% versus 40.2% (P < 0.001), 85.1% versus 35.4% (P < 0.001), and 90.0% versus 56.6% (P < 0.001), respectively. Ley *et al*. retrospectively compared the outcomes of concurrent CDDP (18 patients) versus CTX (29 patients) to RT in LASCCHN patients. [21] Disease-specific survival at 3 years was 83% in the cisplatin group and 31% in the cetuximab group (hazard ratio 0.15, confidence interval 0.033, 0.66; P = 0.012) whereas disease recurrence was more common in the CTX group compared with the CDDP group. Levy *et al*. also compared three weekly CDDP versus weekly CTX given concurrently with RT in 265 patients of LAHNSCC retrospectively. [22] The 2-year actuarial LRC and distant control (DC) rates were 73 and 79%, respectively. They concluded significantly better LRC in patients treated by CDDP-based CCRT than CTX -based CCRT.

CONCLUSION

CTX and CDDP have different mechanism of actions that may lead to different profiles of toxicity and tolerability. Treatment interruptions, requirement of parenteral support & nasogastric feeding, acute dermatitis, and infusion reactions were significantly higher in CTX arm; whereas leucopenia and vomiting was significantly higher in CDDP arm. Acute nephrotoxicity and gastrointestinal toxicity was exclusively seen in CDDP arm, but the difference was not statistically significant. Similarly, no difference was noted in LRC and OS between the two groups. The limitations of present study include retrospective nature, small cohort size, short follow up and inclusion of elder patients only. A large prospective randomized comparative study is required to address these issues.

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