Original Article

Long-term results of low dose daily cisplatin chemotherapy used concurrently with modestly accelerated radiotherapy in locally advanced squamous cell carcinomas of the head neck cancer region

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ABSTRACT

Introduction: Concurrent single agent cisplatin (CDDP) with radiotherapy (RT) improves outcomes in locally advanced squamous cell carcinomas of the head neck (LA-SCCHN). CDDP at 100 mg/m^2 at 3 weekly intervals raise compliance, hospitalization, and supportive care issues. Low dose daily CDDP was delivered with RT to evaluate its compliance, long-term safety and efficacy. **Patients and Methods:** During the period of month between November 2005 and May 2007, 52 patients of stage III/IV LA-SCCHN were given with conventional RT in a phased manner (dose-70 Gy/35 fractions/6 weeks) along with daily CDDP (6 mg/m^2; capped 10 mg-30 cycles) over 6 weeks. No hospitalization or antiemetic cover was planned. Compliance, acute and late toxicity were recorded as per Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer grading system and survival outcomes were evaluated. **Results:** The median follow-up was 63 months. 43 (83%) cases complied with RT schedule and >28 cycles of CDDP was administered in 38 (73%) cases. Confluent mucositis was seen in 65%, Grade III/IV dysphagia in 67%; 77% required enteral feed and hospitalization in 15%. There were four treatment related deaths. At 5 years, the loco-regional control was 25% (median-11 months) and the overall survival was 31% (median-11 months). The 5 years actuarial rates of late Grade III/IV toxicity was 24%. Late swallowing difficulty/aspiration were seen in 17%; xerostomia-40%; ototoxicity-6%; nephrotoxicity-4%; and no second malignancy. **Conclusion:** Low dose cisplatin with moderately accelerated RT schedule appears feasible and logistically suitable "out-patient" option without increasing long-term toxicity in LA-SCCHN cancer region.

Key words: Chemotherapy, low dose cisplatin, radiotherapy

INTRODUCTION

Squamous cell carcinoma of the upper aero digestive tract is the most common malignancy seen in India with an age-adjusted incidence of 20.5-49.2 per 100,000 population.[1] Strategies have been adopted with the aim to enhance the efficacy of radiotherapy by attempting to increase the loco-regional control (LRC) rates and simultaneously to decrease the incidence of distant metastasis. Concurrent chemo-radiotherapy has become the standard of care in head and neck cancers (HNCs) after the publication of various meta analyses.[2-5] MACH-NC meta-analysis reported 8% survival benefit with the addition of concurrent chemotherapy.[5] Cisplatin has been the most extensively studied agent. Various dose schedules have been studied so far, such as 100 mg/m^2 at 3 weekly intervals, 35 mg/m^2 at weekly interval and 6 mg/m^2 daily.[6-9]

Integration of the two approaches i.e., addition of chemotherapy along with altered fractionation radiotherapy (RT) (either concomitant boost schedule or

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hyperfractionation) for any potential therapeutic gain (both in terms of LRC and overall survival [OS]) have been also tested by many workers.[9,10] In most trials, cisplatin has been used singly. These have been attempted with either concomitant boost schedules or hyperfractionation.

Low dose daily cisplatin when administered concurrent with radiotherapy, has been reported to be better tolerated. Jeremic *et al*., in their study have reported superior outcome as a result of radiosensitizion through the inhibition of the repair of potential lethal damage and sublethal damage along with hypoxic cell sensitizer. They found a strong trend favoring hyperfractionated RT (HFRT) with low dose daily cisplatin as compared to concurrent RT with low dose daily cisplatin both in terms of OS and local recurrence-free survival.[9]

Unlike a 3 weekly schedule, low dose daily cisplatin does not merit active hydration and strong antiemetic cover therefore it can be easily administered on an out-patients basis, in case "day care" facilities are lacking in a particular setup. Low dose daily cisplatin coupled with 6 fractions a week RT (Monday to Saturday) being practiced in the department at that point in time was studied prospectively to check out its compliance, efficacy, and long-term safety.

PATIENTS AND METHODS

Untreated, squamous cell carcinoma of the upper aero digestive tract (oral cavity, oropharynx, hypopharynx, or larynx) in stages III and IV locally advanced squamous cell carcinomas of the head neck (LA-SCCHN) (T2N2-3M0, T3-4 any N M0) were inducted in this study. Patients having a second primary neoplasm, recurrent disease, distant metastasis, carcinoma of the nasopharynx and paranasal sinuses, prior radiation or chemotherapy and pregnant woman were excluded.

Treatment protocol

Patients were given 6 fractions a week, nonconformal RT in a phased manner (dose-70 Gy/35 fractions/6 weeks along with daily CDDP (6 mg/m^2; capped at 10 mg) in 500 ml NS solution for a planned 6 weeks in 6 days a week.

Radiotherapy technique

Patients were simulated in supine position in a thermoplastic head and neck immobilization device. RT planning was done in a phased manner. Phase I was planned to include the primary and the draining lymph node regions and to a dose of 44 Gy/22 fractions/4.5 weeks, treated 5 days in a week at 2 Gy/fraction (Monday to Friday). In Phase II off-cord reduction was done and a dose of 16 Gy/8 fractions/1.5 weeks at 2 Gy/fraction, delivered 5 days in a week (Monday to Friday). Phase III was delivered as a boost on Saturday, as limited volume portal including original gross tumor volume alone with a margin of 2 cm and a dose of 10 Gy/5 fractions/over 5 Saturdays at 2 Gy/fraction was delivered. Thus, the total planned dose of 70 Gy/35 fractions/6 weeks was delivered using Telecobalt machine (Theratron 780-C, AECL, Canada). Scheduled overall treatment time was 40 days.

Chemotherapy delivery

All patients received daily dose of CDDP at 6 mg/m^2 (ma × 10 mg). RT was synchronized with CDDP therapy and delivered within an hour of administration of CDDP. Chemotherapy was withheld if the total leukocyte count fell below 4000/cu mm until recovery is observed. All patients were administered chemotherapy on an out-patient basis with the hydration with one pint of normal saline over 120 min; single shot of injection ondencetron was given just before chemotherapy. Cisplatin was delivered bolus in 50 ml NS over 10 min.

No planned hospitalization or round the clock antiemetic cover was given. Compliance, acute and late toxicity were recorded based on the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system and long-term survival outcome were evaluated.

Patients were followed-up regularly during RT after completion of treatment. Acute and late morbidity including cisplatin induced nephro and ototoxicity were recorded as per the RTOG/EORTC guidelines, while hematological indices were scored according to the WHO criteria.

Statistical analysis

OS was measured from the date of registration. LRC was defined as complete disappearance of visible and palpable disease for at least 6 months following initiation of therapy. Loco-regional persistence of the disease was classified as failure on day 1. Loco-regional relapse beyond 6 months was scored as an event for disease-free survival (DFS). Failure at any site including local site was scored as an event for DFS. Death due to any cause was scored as an event for OS. Univariate and multivariate analysis for prognostic factors affecting local disease control and OS were undertaken.

RESULT

During the period of month between November 2005 and May 2007, 52 biopsy proven stage III/IV patients were included in the study. The median follow-up was of 63 months. Demographic characteristic are shown in Table 1. All patients gave history to tobacco ingestion either in the form Paan (betal), Pan masala, bidi, or cigarette smoking.

Human papilloma virus status was not determined since tobacco was a documented etiological factor in these tumors.[11] Most of these computed tomography scan staged patients were either considered inoperable by the referring ENT surgeon/head and neck oncologist or patient had refused surgery.

All patients received chemo-radiotherapy as per protocol. Seven cases received less that the planned RT doses. Of these who received the stipulated 70 Gy, RT protocol compliance (i.e., treatment within 39-44 days) and chemotherapy (28-30 cycles) compliance were seen in 83% (43/52) and 73% (38/52), respectively. The overall compliance was 73% (38/52).

23% (14/52) received 27 cycles or less, principally for reasons of toxicity. This also included those who left treatment midway (due to any reason) or died during therapy. The compliance to the interventions is shown in Table 2.

Acute toxicity was documented as per RTOG/EORTC and is mentioned in Table 3. During treatment, patients lost weight due to mucositis leading to inadequate intake. Antibiotics and growth factors were not used prophylactically. The need for enteral support and weight changes are mentioned in Table 4. Enteral support was started in initial phase of RT All patients with Hb <10 g/dl were transfused whole blood as per the departmental policy. Intravenous hydration was given to patients either as day care or as in-patients, as and when clinical signs and symptoms of dehydration were observed.

15% patient (8/52) required hospitalization for a mean duration of 3 days (range 1-6) during or just after completion of treatment for supportive care or treatment related morbidity. Severe, i.e., Grade III neutropenia was seen in 12% (6/52).

Local recurrence was seen in two patients between 6 and 19 months following treatment and both had to undergo neck dissection following RT. Six patients developed distant metastasis to lung (4) followed by bone (3) and liver (1).

The major late toxicities that were studied, included dryness of mouth present in 21 (40%); subcutaneous fibrosis in

Table 1: Demographic characteristics (*N*=52)

Character	*N* (%)
Age (years)	
Median (range)	55 (29-75)
Gender	
Male	47 (90)
Female	5 (10)
Primary site	
Oral cavity	3 (6)
Oropharynx	29 (55)
Larynx	17 (33)
Hypopharynx	3 (6)
T stage	
T2	2 (4)
T3	25 (48)
T4	25 (48)
N stage	
N0	13 (25)
N1	12 (23)
N2	23 (44)
N3	4 (8)
TNM stage	
III	15 (29)
IV	37 (71)
KPS	
70	5 (10)
80	34 (65)
90	13 (25)
Tobacco	52 (100)
Diabetes mellitus	5 (10)

TNM: Tumor node metastasis, KPS: Karnofsky performance score

Table 2: Treatment compliance; RT and CT (*N*=52)

Variables	*N* (%)
Dose (Gy)	
<70	7 (13)
70	45 (87)
RT duration (days)	
<39	7 (13)
39-44	43 (83)
>44	2 (4)
CT cycles	
<27	14 (23)
28-30	38 (73)

RT: Radiotherapy, CT: Chemotherapy

Table 3: Acute morbidity (RTOG/EORTC scoring criteria) (*N*=52)

Variable	*N* (%)
Mucositis	
Grade I, II	18 (35)
Grade III/IV	34 (65)
Dysphagia (during the treatment)	
Grade I, II	13 (25)
Grade III, IV	35 (67)
Leukopenia	
TLC 3000-<4000	4 (8)
TLC 2000-<3000	7 (13)
TLC 1000-<2000	6 (12)
Anemia	
Hb 11-9.5	8 (15)
Hb<9.5-7.5	3 (6)
Weight loss in kg (median)	5 (9)

RTOG: Radiation therapy oncology group, EORTC: European Organization for Research and Treatment of Cancer, TLC: Total leukocyte count

Table 4: Supportive treatment and intervention during the treatment (*N*=52)

Variable	*N* (%)
Blood transfusion	9 (17)
IV fluids	11 (21)
Nasogastric tube feeding	4 (8)
PEG	36 (69)
Hospitalization	8 (15)

PEG: Percutaneous endoscopic gastrostomy, IV: Intravenous

8 (15%); the swallowing difficulty and or aspiration in 9 (17%); ototoxicity in 3 (6%); deranged renal parameter on follow-up glomerular filtration rate (GFR) estimation were seen in 2 (4%) [Table 5]. However, in spite of deranged GFR, patients were asymptomatic and GFR became normal in 1-2 months.

Regarding mortality, four patients died during or within 1 month after completion of treatment. Two died due to dyselectrolytemia following RT. Of these one died in the hospital and other died at home and informed over telephone. Two deaths occurred due to aspiration; one at 42 Gy plus 15 cycles of cisplatin and other at 44 Gy plus chemotherapy. The second patient developed septicemia as a consequence of aspiration and died. No second malignancy has been reported thus far.

31% (16/52) patients were lost to follow-up at the time of analysis. 5 years LRC was 25% and the 5 years survival rate (OS) was 31% [Figure 1].

DISCUSSION

There is level 1 evidence that concurrent chemo-radiotherapy improves the LRC and survival.[2-5,10] Most series report that cisplatin is the most active agent with nonoverlapping toxicity profile.[9,12] Optimal timing and dose scheduling still needs to be defined. Few studies have studied the role concurrent low dose cisplatin.[9,12-16] Delivering low doses of cisplatin daily was initiated based intuitively on the fact that most profound effect of CTRT would be expected from fractionated administration of both treatment modalities concurrently. With each fraction of radiotherapy cisplatin acts as a radiosensitizer. In addition, pharmacokinetics indicate that increased exposure to active platinum compound is more effective, i.e., continuous exposure (practically low dose CDDP) is superior to bolus administration of chemotherapy.[8,9] This was the theoretical basis for the current study design. The choice of daily cisplatin, instead of weekly schedule (as was the earlier practice in our department) was based on the experience reported by Jeremic *et al*., and Bartelink *et al*.[9,12-14]

In this prospective study, where the patient profile was younger in comparison to Western reports,[13,14] all patients were habituated to tobacco either in the form of Paan (betel) quid or bidi cigarette smoking. These habits are prevalent in these parts of India.[17] Treatment protocol adherence was seen in the three-fourth of cases in the present study. Hematological toxicity was not significantly increased in this group of patients. Special care in the form of enteral support and or hospitalization for supportive care was required in three-fourth cases during treatment. Late sequel, i.e., radiation related swallowing changes and or aspiration rate was similar to RT alone series.[18] Cisplatin-induced transiently deranged renal parameter were picked up on routine GFR estimation in two patients-both of them remained asymptomatic.

Jeremic *et al*., have reported superior outcomes with concurrent use of daily cisplatin as compared to RT alone.[9,13,14] The benefit appeared to be of the order of the benefit reported by 3 weekly schedule.[3,5,6] In addition, the study also highlights on practical benefits of such a protocol-no need for excess hydration.This may especially be relevant from a tropical country's point of view where dehydration is a common occurrence; no requirement for elective hospitalization for chemotherapy delivery; lastly, such a schedule offer more control over delivery/stoppage of chemotherapy, when required. Studies in sites such as nonsmall cell lung cancer have also used low dose cisplatin and have reported better tolerability than conventional regimes.[19] As regards the optimal dose of low dose cisplatin, most studies have used 6 mg/m^2 (max - 10 mg daily).[9,12-15] Homma *et al*., used low dose daily cisplatin at 4 mg/m^2 and compared it with weekly carboplatin and found results to be inferior. This could have been due to use of ineffectively low dose schedule of cisplatin.[16,20]

Alteration of fractionation by either hyperfractionation or acceleration has improved the LRC.[21] One of the most promising accelerated fractionation schedules of current times has been the one followed as standard of care in Denmark. DAHANCA 6 and 7 have attempted to study 2 independent factors of radiation resistance simultaneously, i.e. hypoxia and repopulation. The benefit of acceleration was in addition to the effect achieved by the use of hypoxic modification. Therefore moderately accelerated RT in HNCs with 1 week reduction in OTT was found to be superior to a conventional regime.[22] The applicability of

Table 5: Late toxicity (RTOG/EORTC scoring criteria) (*N*=52)

Variable	*N* (%)
Xerostomia	21 (40)
Dysphagia and aspiration	9 (17)
Subcutaneous fibrosis	8 (15)
Ototoxicity	3 (6)
Nephrotoxicity (>50% fall in GFR)	2 (4)
Second malignancy	-

RTOG: Radiation therapy oncology group, EORTC: European Organization for Research and Treatment of Cancer, GFR: Glomerular filtration rate

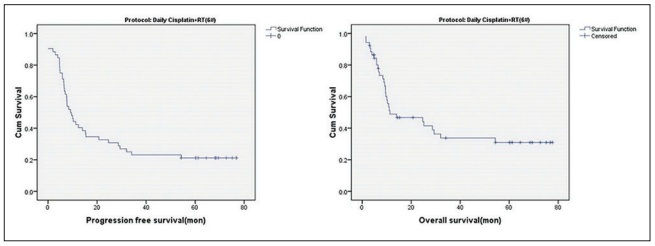

Figure 1: Progression free survival and overall survival in months

this protocol has also been tested by International Atomic Energy Agency (IAEA) in Asian and African countries.[23] This trial had similar patient profile as ours, i.e., advanced presentation. They reported a similar benefit of 10% improvement in local control as the DAHANCA study. In IAEA conducted trial significant proportion of patient were treated by a Telecobalt machine. In the present study, we too adopted 6 fractions a week radiotherapy using Telecobalt machine. This was a pragmatic and useful approach in our set up since it helped in easing the load on the teletherapy machine by reducing the overall treatment time by 1 week. In fact, our radiotherapy practice during that time period reflects radiotherapy scenario of today in majority of centers within India, and many parts of the world, i.e., use of nonintensity-modulated radiation therapy based radiotherapy planning techniques and treatment by Telecobalt unit.

In order to maximize the survival gains further, the two strategies, i.e., altered fractionation and concurrent chemotherapy has been combined and studied by several researchers.[9,13] The question of which radiotherapy schedule benefits more with low dose daily cisplatin has been addressed by Jeremic *et al*., comparing conventional RT with HFRT with or without daily CT.[9,13,14] They reviewed the two randomized trials in advanced HNC population (similar tumor burden/stage as in the present study).[14] The authors carried out a retrospective analysis of the four arms of these two trials. They summarized that a strong trend favored HFRT with daily cisplatin as compared to conventional RT with daily cisplatin. The toxicity was greater in the HFRT + CT arm. Grade III and above acute toxicity profile in the trial was 49%.[24-27] 5 year control rate and survival were superior in HFRT + CT arm. No treatment related deaths was reported by them, but hospitalization was needed to manage toxicity in 9% patients.

Other authors such as Glicksman *et al*., combined low dose cisplatin with late intensification HFRT in stage III, IV cases.[28] 95% of the patients who initiated treatment completed it. The disease-specific survival was impressive and the combination was well-tolerated (78% at 3 years). At the same time, RTOG-9914 conducted a Phase II trial of concomitant boost RT with concurrent CT in HNC patients. A high compliance rate was reported which was attributed to a gastrostomy tube insertion in the most patients before or during treatment or follow-up. This study emphasized the need for proper selection of patients for such intense protocols along with the need for supportive care.[29]

A German study by Staar *et al*., compared concomitant boost with or without CT and reported nonsignificant differences in LRC.[27] This trial suggested that efficiency of AFRT with the addition of chemotherapy might not be as high as in studies with conventional fractionation plus simultaneous chemotherapy. Patients with oropharyngeal carcinomas showed significantly better LRC as compared to hypopharyngeal primaries. Although our cisplatin schedule was different, we observed a similar trend in our study where in terms of LRC, oropharyngeal carcinomas did better than hypopharyngeal and oral cavity cancers. This was possibly a depiction of the biology of disease.

Our early mortality and high lost to follow-up rate are two reasons for inferior survival outcomes as compared to peer studies.[9,13,14,29] Treatment related mortality especially due to aspiration is a well-recognized killer and needs intense supportive care and compliance on the part of patient and his care takers in order to prevent it.[18,30] Patients not reporting in the follow-up clinics after completion of treatment is an issue most series are silent about. This needs to be addressed in detail as it can be rather high, especially in less educated and financially constrained societies such as ours.[31]

In terms of providing support, we probably initiated enteral nutrition later than reported in other studies.[29] This may have reflected in our high hospitalizations and mortality.[9,13,14,29] The initial delay in initiation of enteral nutrition was due to resistance offered by the patients for any intubation. The reason behind resistance was lack of awareness, myths and financial constraints.

Our late radiation related swallowing changes and or aspiration rate was similar to RT alone series.[18] Late ototoxicity (6%) and nephrotoxicity (4%) were similar to studies using weekly or 3 weekly cisplatin.[12,13]

To summarize, extra caution in terms of maintenance of nutrition and hydration needs to be taken before, during and after treatment in such a chemo-radiotherapy protocol. Combined toxicities of cisplatin and accelerated RT were higher and needed attention. Specific toxicities of cispaltin, i.e., hematological and adverse impact on renal functioning were no greater than reported with other schedules.[9,11,12,15,16] A randomized trial of noninferiority design comparing daily schedule with a 3 weekly schedule is likely to provide the answer.

CONCLUSIONS

Low dose cisplatin with moderately accelerated RT schedule appears feasible and logistically suitable "out-patient" option without increasing long-term toxicity, provided extra caution is adopted before and during treatment in LA-SCCHN region. Based on this experience,

we recommend its usage in centers that are overburdened with patients and lack adequate resources i.e., (in door hospital beds and RT machines) provided, they have enough supportive man power in terms of nurses and dietician who can take care and advice regarding nutrition and hydration.

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