RESEARCH ARTICLE

Conventional Radiotherapy with Concurrent Weekly Cisplatin in Locally Advanced Head and Neck Cancers of Squamous Cell Origin - a Single Institution Experience

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Abstract

Background: Platinum based concurrent chemo-radiation is the de-facto standard of care in the non-surgical management of locally-advanced head and neck cancer of squamous origin. Three-weekly single agent cisplatin at 100 mg/m^2 concurrent with radical radiotherapy has demonstrated consistent improvement in loco-regional control and survival. This improvement is however at the cost of considerable hematologic toxicity and poor overall compliance. The routine use of this regime is improbable in developing countries with limited resources. We therefore aimed to determine the safety and efficacy of an alternative regime of weekly cisplatin and concurrent radiotherapy in such patients. Materials and Methods: January-05 and April-12, 188 patients of locally-advanced head and neck cancer of squamous origin were treated with concurrent weekly-cisplatin at 35mg/m^2 and conventional radiotherapy 60-66Gy/30-33 fractions/5days per week. Results: Overall, 95% patients received planned doses of RT while 74% completed within the stipulated overall treatment time of <50 days. Eighty-two percent received at-least 5 weekly cycles. Grade-III/IV mucositis was seen in 58%/9% respectively, which resulted in mean weight loss of 9.2% from a pre-treatment mean of 54.5 kg. Grade-III hematologic toxicity-0.5%; grade II nephrotoxicity-2.5% and grade III emesis-3% were also seen. Grade-III/IV subcutaneous toxicity-10%/1% and grade-III/IV xerostomia-10%/0% were observed. Complete responses at the primary site, regional nodes and overall disease were seen in 86%, 89% and 83% patients respectively. The median and 5-years disease-free survival were 26 months and 39.4% respectively, while the median and overall survival were 27 months and 41.8% respectively. Conclusions: Weekly-cisplatin at 35 mg /m2 when delivered concurrently with conventional radical RT (at-least 66y/33 fractions) in locally-advanced head and neck cancer is well tolerated with minimal hematologic and neprologic toxicity and can be routinely delivered on an out-patient basis. It is an effective alternative to the standard 3-weekly cisplatin especially in the context of developing countries.

Keywords: Cisplatin - chemo-radiation - concurrent - head and neck cancer - weekly

Asian Pac J Cancer Prev, **14 (11)**, 6883-6888

Introduction

Platinum based concurrent chemotherapy and conventional radiotherapy (RT) is the gold standard of care in nonsurgical management of squamous cell cancer (SCC) of the head and neck region. This approach is largely based on the updated results of the meta-analysis of the MACH-NC collaborative group, which demonstrated an absolute survival gain of 6.5% at 5 years with concurrent chemo-radiation (CT-RT) (Pignon et al., 2007). Single agent cisplatin (CDDP) was seen to be as effective as and less toxic than in combination with other agents and other non-platinum based CT regimes. A 3-weekly schedule of single agent CDDP at 100 mg/m^2 for planned 3 cycles along with conventional RT has been commonly used in randomised trials with a consistent improvement in loco-regional control and survival (Adelstein et al., 2003; Forastiere et al., 2003; Fountzilas et al., 2004). This regime is however associated with considerable hematologic toxicity and a compliance in about two-thirds (Brizel et al., 2006). Routine use of this regime is improbable in developing countries like India with limited resources, as these patients would often require intensive in-patient care. The situation is further complicated by the fact that the majority hail from the rural belt with co-morbid conditions related to long standing history of tobacco chewing and smoking. CDDP in moderate doses (30-40 mg/m^2) has also been used in a weekly schedule concurrently with RT, mostly on an out-patient basis. Phase II and randomised trials in oesophageal, nasopharyngeal and cervical cancers have shown it to be well tolerated and efficacious (Rose et al., 1999; Chan et al., 2005; Kumar et al., 2007). Taking a

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cue from the available data on this approach and our own experience with regime, we used it for the treatment of LAHNC and present an audit of the same.

Materials and Methods

Study design

The patients were treated in the Department of Radiotherapy at a Government Medical College that primarily catered to population from northern India, mainly from the rural belt. Previously untreated patients, with histological proven SCC of the upper aero digestive tract (excluding naso-pharynx and para-nasal sinuses), in stages III and IV, M0 were treated with this protocol. Surgery was not a part of their planned treatment. Inclusion criteria were age over 18 years, Karnofsky performance status (KPS) >60, normal chest X-ray, normal hematological, liver and kidney functions on routine biochemical examination of blood. All eligible patients were informed about the treatment protocol and consent was obtained.

Radiotherapy

All patients were planned with a thermoplastic head immobilization device and treated either on a 4-MV linear accelerator or a telecobalt unit. A 3-field technique i.e. a parallel opposed pair and an anterior lower neck portal was used in most of the patients. However, missing tissue compensation was not done. In the 1st phase 46 Gy/23-fractions/5 days per week was delivered to the primary and draining lymph node regions by a parallel opposed pair prescribed at mid plane. The lower neck received 50 Gy/25-fractions/5 weeks from an anterior field using a half beam block, normalized at 2-3 cms depth. In the 2nd phase, an off-cord field reduction was carried out to exclude the spinal cord and include the primary tumour and nodal sites with a 2-3 cm margin for a total planned dose of 60 Gy or 66 Gy (at 2 Gy/fraction, 5 fractions per week). Initially, the total dose was kept at 60 Gy with CT-RT due to presumed risk of increased toxicity and poor tolerance in patients. However, the treatment was well tolerated and subsequently the dose was increased to 66 Gy.

Chemotherapy

This consisted of weekly doses of concurrent CDDP at 35 mg/m^2 infused over half an hour, preceded by intravenous hydration and antiemetics and followed by mannitol diuresis and further hydration, usually as an outpatient procedure. On the day of chemotherapy, RT was delivered within one hour of administration of CDDP. Chemotherapy administration was postponed if the total leukocyte count was less than 3500 mm^{-3}, platelet less than 75,000 mm^{-3}, haemoglobin less than 9 gm% and serum creatinine more than 1.6 mg% till recovery was observed. No dose modifications were made.

Evaluation during and following treatment

Patients were evaluated at weekly intervals during RT, every 2 months thereafter for the first 2 years and quarterly subseuently. Acute and late morbidity (beyond 3-months of completion of RT) were recorded as per the RTOG/EORTC guidelines (Cox et al., 1995). Immediate disease control was scored clinically or on a direct laryngoscopy, both for primary and nodal sites at 1 month following completion of all treatment. An overall response rate that included clearance of disease at both the primary and loco-regional nodes was also recorded. The responses were scored as complete response (CR), partial response (PR) and no response/progressive disease (NR/PD).

Statistical analysis

The data was analysed in terms of compliance to treatment, early and late morbidity, disease free survival (DFS), overall survival (OS) and patterns of failure. The survival outcomes were computed from the date of registration. Persistence of disease was scored as a failure from day 0, while loco-regional recurrence was considered as an event for DFS. Death due to any cause was also considered an event when computing DFS and OS. Survival curves were computed using the Kaplan-Meier method. Patients lost to follow-up with persistent or recurrent disease were considered dead and their survival end points were terminated. Patients lost to follow up without evidence of disease at their last visit were censored and their proportion was computed. All P values were two-sided and considered significant at <0.05. Logistic regression was used to ascertain factors of independent significance influencing the response to treatment while multivariate analysis of factors affecting the survival outcomes was performed using the Cox's proportional hazards model.

Results

Between January-05 and April-12, 188 eligible patients were treated by this protocol. Data has been analysed as of April-13. The median follow-up of all patients was 15 months (range 2-100) while for those alive it was 20 months (range 5-100). The baseline characteristics of patients and tumours are shown in Table 1. Male patients predominated (90%) and 99% had a KPS from 70 to 90. The most common primary site was base tongue (32%) followed by tonsil (19%) and arytenoids/AE fold region (16%). Overall, oro-pharynx was the commonest primary region (57%) followed by supraglottic larynx (22%) and hypo-pharynx (14%). Stage III tumours (60%) were more common than stage IV (40%).

Interventions and compliance

This is shown in Table 2. For computation of exact compliance to the protocol, the patients were divided in 2 groups; planned for 60 Gy (n=28) and planned for 66 Gy (n=160). Overall 180 patients (95%) received planned doses of RT. Eight patients did not receive planned doses due to the following reasons: 5 patients did not tolerate RT due to severe mucositis; 1 patient had myocardial infarction and therefore RT was withheld, and in the remaining 2 patients, no reason could be ascertained. Twenty-five (89%) in the 60 Gy group completed RT in the stipulated time of <46 days. Three patients could not complete RT on time; 2 patients due to acute morbidity

and 1 patient for no apparent reason. Likewise, 114 patients (72%) in the 66 Gy group completed RT in the stipulated time of <50 days. Forty-six patients could not complete RT on time due to the following reasons: acute morbidity in 31 patients; machine breakdown in 5 patients and no apparent reason in the remaining 10 patients. The exact compliance to RT (60 Gy/66 Gy in 42-50 days) was therefore observed in 74% (139/188).

One hundred and fifty three patients (81.5%) received at least 5 cycles of CT of which 108 patients (57.5%) received 6 weekly cycles. The remaining 35 patients received <4 cycles due to following reasons; poor treatment tolerance/reduced oral intake in 10 patients, grade 2/3 hematologic toxicity in 8, incomplete RT in 8, grade 2 renal toxicity in 2, grade 3 emesis in 5 and no apparent reason in 2 patients.

Table 1. Patient and Disease Characteristics

Age (years), [mean, SD, range]		50, 9.5, 30-65
Gender, (%)	Male	168 (90)
	Female	20 (10)
KPS (%)	60	2 (1)
	70-80	141 (75)
	90	45 (24)
Pre treatment weight (kg), [mean, SD, range]		54.5, 9.47, 35-85
Duration of symptoms (months), [mean, SD, range]		5, 4.75, 1-45
Baseline haemoglobin (g/dl), [mean, SD, range]		12.6, 1.36, 10-16
Primary site (%)	BOT	61 (32)
	Tonsil	36 (19)
	PFF	26 (14)
	Arytenoids+AE fold	31 (16)
	Valeculla	9 (5)
	Epiglottis	10 (6)
	Anterior tongue	10 (5)
	Buccal mucosa/RMT	3 (2)
	Palate	2 (1)
Primary region (%)	Oral cavity	13 (7)
	Oro-pharynx	108 (57)
	SG larynx	41 (22)
	Hypo-pharynx	26 (14)
Primary T stage (UICC -) (%)	T2	28 (15)
	T3	130 (69)
	T4	30 (16)
Regional N stage (UICC -) (%)	N0	67 (35)
	N1	68 (37)
	N2	49 (26)
	N3	4 (2)
TNM stage (%)	III	114 (60)
	IV	74 (40)

*SD, standard deviation; KPS, Karnofsky Performance Status; BOT, Base of tongue; PFF, Pyriform fossa; AE fold, Ary-epiglottic fold; S-G Larynx, Supraglottic larynx; hypopharynx; RMT, retro-molar trigone; UICC, Union Internationale Contre le Cancer

Table 2. Treatment Compliance

Intervention		Compliance
RT dose (planned 60 Gy/66 Gy)		180/188 (95%)
OTT (days)	60 Gy (n=28) (mean, SD, range)	43.5, 3.98, 38-57
	66 Gy (n=160) (mean, SD, range)	49.3, 7.73, 20-75
OTT (days) compliance	60 Gy (<46 days)	25/28, 89%
	66 Gy (<50 days)	114/159, 72%
CT cycles (n), N (%)	1	1 (0.5)
	2	2 (1)
	3	9 (5)
	4	23 (12)
	5	45 (24)
	6	108 (57.5)

*Gy, Gray; CT, chemotherapy; OTT, overall treatment time

Table 3. Toxicity

Acute toxicity	Grade	Number (%)
Anemia	0	108 (57.5)
	I	60 (32)
	II	19 (10)
	III	1 (0.5)
Leucopenia	0	151 (79.5)
	I	26 (14)
	II	10 (6)
	III	1 (0.5)
Thrombocytopenia	0	167 (89)
	I	18 (9)
	II	3 (2)
Nephrologic	0	167 (88.5)
	I	17 (9)
	II	4 (2.5)
Emesis	I	133 (71)
	II	50 (26)
	III	5 (3)
Mucosal toxicity	I and II	61 (33)
	III	109 (58)
	IV	18 (9)

*Percentage weight loss 9.20%; SD, range (%) 5.3, 0-53

Acute morbidity

This is shown in Table 3. Grade 3 and 4 oral and pharyngeal toxicity was seen in 58% and 9% respectively (total 67%). This had an adverse effect on swallowing and resulted in a mean weight loss of 9.2% (SD 5.3, range 0-53%) during treatment from a pre-treatment mean of 54.5 kg. Hematologic toxicity was as follows: grade II/III anemia-10%/0.5%; grade II/III leukopenia-6%/0.5%; grade II thrombocytopenia-2%. Grade II nephrotoxicity-2.5% and grade II/III emesis-26%/3% were also seen.

Late morbidity

It was recorded for subcutaneous tissue and salivary function. Grade I/II/III/IV subcutaneous toxicities were seen in 17%/72%/10%/1% patients while grade I/II/III xerostomia were seen in 18%/72%/10% patients respectively.

Response

Disease response at the primary site and regional lymph nodes were evaluated at 1 month following CT-RT. The CR/PR/NR at the primary site was seen in 86%/13%/1% and at the regional nodes in 89%/10%/1% patients respectively. This resulted in an overall CR/PR/NR in 83%/16%/1% patients respectively.

On logistic-regression, hypo-pharynx lesions fared significantly worse than other sites (p=0.02, OR 2.9, 95%CI 1.2-7.1), stage IV disease showed a worse response (p=0.04, OR 17.5, 95%CI 2.5-23.7) and doses less than 66Gy resulted in partial response (p=0.05, OR 0.9, 95%CI 0.8-1.0).

Survival

Disease free and overall survivals are shown in figures 1 and 2. Eleven-percent patients (20/188) were LFU without any evidence of disease and were censored for computation of survival outcomes. The median DFS was 26 months (95%CI, 17.1-34.9) with a 39.4% probability of being disease free at 5 years. The median OS was 27 months (95%CI, 19.4-34.6) with a 41.8% probability of

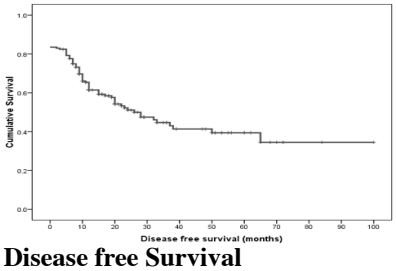

Figure 1. Disease free Survival

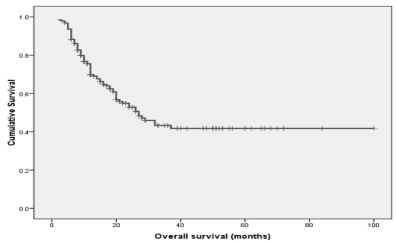

Figure 2. Overall Survival

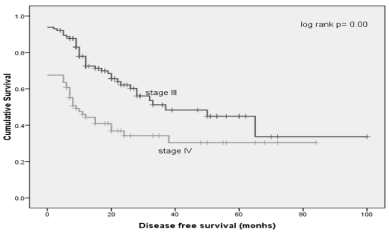

Figure 3. Disease Free Survival (Stage III vs Stage IV)

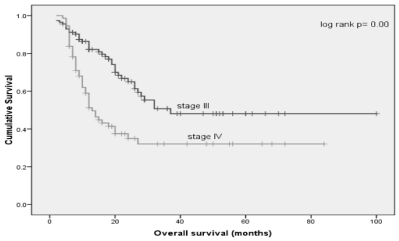

Figure 4. Overall Survival (Stage III vs Stage IV)

being alive at 5 years. We also attempted to establish the influence of overall stage on DFS and OS (figures 3 and 4). The median DFS was 37 months (95%CI, 11.8-62.1) for stage III patients and 9 months (95%CI, 3.6-14.3) for stage IV patients. The estimated 5-years DFS was 45% and 30% for stages III and IV respectively (p value 0.00). Similarly the median OS was 37 months (95%CI, -12.1-62) for stage III and 13 months (95%CI,-9.6-16.4) for stage IV patients. The estimated 5-years OS was 48.1% and 35% for stages III and IV patients respectively (p value 0.00).

Univariate analysis of the following factors likely to influence DFS and OS was undertaken: Age (<54 *vs* >54 years); gender; duration of symptoms (<4 *vs* >4 months); primary site; primary region; KPS; T stage; N stage; overall stage; number of CT cycles (<5 *vs* 5 or more); percentage weight loss (<9% *vs* >9%); RT dose group (<66Gy *vs* 66Gy) and OTT (<48 *vs* >48 days). Lower KPS, higher T stage, higher N stage and higher overall stage for both DFS and OS while RT dose <66Gy for OS only were found to be adverse prognostic factors on univariate analysis. The multivariate model retained T stage (p=0.00, exp (β)=0.34, 95%CI=0.20-0.58), N stage (p=0.05, exp (β)=0.20, 95%CI=0.10-0.61) and RT dose (p=0.00, exp (β)=0.95, 95%CI=0.92-0.98) for DFS while KPS (p=0.05, exp (β)=0.07, 95%CI=0.05-0.15), T stage (p=0.00, exp (β)=0.29, 95%CI=0.17-0.5) and RT dose (p=0.00, exp (β)=0.94, 95%CI=0.91-0.98) were retained for the OS.

Discussion

The principal question we wished to address was whether weekly CDDP concurrent with conventional RT was better tolerated and as efficacious as the standard 3-weekly schedule in LAHNC. The routine use of CDDP based CT-RT in squamous cell head and neck cancer is based essentially on the findings of the meta-analysis of the MACH-NC collaborative group and its subsequent update on the effects of addition of chemotherapy to radiation (Pignon et al., 2000; 2007). The original meta-analysis included a total of 65 trials, of which 26 were on CT-RT. A moderate survival gain of 4% and 8% at 5 years was seen with CT and CT-RT respectively. However, firm conclusions on the benefit of CT-RT could not ascertained due to significant heterogeneity among the trials. This analysis also suggested that multi-agent CT was better than single agent CT and platinum based CT resulted in a non significant increase in deaths (Pignon et al., 2000). An update to this meta-analysis included 24 new trials on CT-RT, which were added to the existing 26 trials. The analysis demonstrated a 6.5% survival gain at 5 years with CT-RT without any significant heterogeneity in the data (HR-0.81, 95%CI 0.78-0.86). It also showed that platinum based regimes were better than their counterparts (HR-0.75 *vs* 0.86) and multi-agent CT added only to toxicity without any appreciable benefit in survival. The analysis however did not comment on the toxicity and efficacy of different schedules of single agent CDDP. The overall toxicity was substantially higher in the concurrent CTRT regimes which led to a detrimental effect in elderly patients (Pignon et al., 2007).

A 3-weekly regime of single agent CDDP at 100 mg/m^2 for 3 planned cycles concurrent with conventional RT is the gold standard in the non-surgical treatment of LAHNC, laryngeal preservation and in the post-operative setting, whenever indicated (Adelstein et al., 2003; Forastiere et al., 2003; Bernier et al., 2004; Cooper et al., 2004; Fountzilas et al., 2004). In the landmark laryngeal preservation 3-arm RCT, 171 patients were treated with 3 cycles of 3-weekly CDDP-100mg/m^2 concurrent with conventional RT. Seventy percent could complete 3 cycles when dose modification was not carried out. Grade III/IV toxicity was as follows: stomatitis/pharyngitis-78%; emesis-20%; hematologic toxicity-47% and nephrotoxicty-4%. The trial demonstrated a significantly higher laryngeal preservation rate of 84% with CT-RT and loco-regional control but not survival (Forastiere et al., 2003). In a 3-arm RCT of CT-RT vs RT alone, 95 patients with unresectable head and neck cancer were treated with the similar protocol. With dose modification permitted in this trial, 85% patients completed 3 cycles. Grade III/IV mucositis-45%; emesis-16%; hematologic toxicity-63% and nephrotoxicity-8% were seen (Adelstein et al., 2003). In a relatively smaller 3-arm RCT, when 45 patients of LAHNC were treated with a similar approach, 91% patients completed planned 3 cycles when CT dose modification was permitted. Grade

III/IV upper gastro-intestinal toxicity-41%; emesis-23% and hematologic toxicity-35% were seen (Fountzilas et al., 2004). In the post-operative setting, 2 large RCT's have shown significant improvement in disease free (Bernier et al., 2004; Cooper et al., 2004) and overall survival (Bernier et al., 2004) using a similar approach of CT-RT in patients with high risk features. The compliance for 3 cycles ranged from 49% to 61%; grade III/IV hematologic toxicity-29% to 61% and mucositis-41% to 55%. In our study, 82% patients received at least 5 cycles of weekly CDDP, without any dose modification. Therefore, the compliance was higher than seen in the laryngeal preservation trial where dose modification was not carried out, and also the post operative trials, where dose modification or delays were considered as deviation from the protocol. It was however considerably lower than seen in the relatively smaller randomised trials, where CT dose modifications were allowed. Grade III/IV oral and pharyngeal toxicity was 67%, which resulted in odynophagia and a mean weight loss of 9.2% (SD-5.3). These patients were managed with oral feeding tubes and intravenous fluids, as out-patients in the day-care facility and admissions were generally not required. Grade III hematologic toxicity at 1%, grade III emesis at 3% and grade III nephrotoxicity in none was however substantially lower than seen in the aforementioned trials. This ensured that patients did not require hospitalization and expensive growth factors and thereby reducing their financial burden. Despite low hematologic and nephro-toxicity, only 82% could receive at least 5 cycles of CT. This was primarily because no chemotherapy dose modification was permitted during the treatment and was postponed in the presence of deranged hematologic and biochemical parameters and/or poor intolerance.

The experimental in vitro studies support the use of lower doses of daily or weekly CDDP concurrent with fractionated RT. Myint and colleagues showed increased radiosensitivity of murine embryonic fibroblasts (MEF) cells at 1μg/mL cisplatin, but when concentrations were increased, instead of observing an increase in radiosensitivity, the data revealed an increasing radioresistance (Myint et al., 2002). In another in vitro experiment with 2 cell lines, a 2-hour post radiation drug exposure resulted in a supra-additive combined effect, whereas a 24-hour preirradiation exposure or protracted postirradiation exposure yielded an additive or slightly subadditive response (Gorodetsky et al., 1998). Mounting evidence from randomized trials in esophageal, nasopharyngeal and uterine cervical cancers in the favour of weekly CDDP based CT-RT has encouraged investigators to use a similar approach in LAHNC (Rose et al., 1999; Chan et al., 2005; Kumar et al., 2007). Most trials have used weekly CDDP either at 40 mg/m^2 (Geeta et al., 2006; Steinmann et al., 2009; Otty et al., 2011; Homma et al., 2011; Pala et al., 2012) or 30 mg/m^2 (Gupta et al., 2009; Watkins et al., 2010; Krstevska et al., 2012) concurrent with 66-70 Gy of conventional external RT. The compliance and toxicity profile has been however better with lower weekly doses. Pala et al treated 148 patients of LAHNC with conventional RT to a dose of 70Gy and concurrent CDDP at 40 mg/m^2. The overall compliance to CT-RT was 64%, grade III/IV mucosal toxicity-32% and osteoradionecrosis of the mandible in 4% (5/148). The survival outcomes were however relatively inferior with 3-years DFS and OS at 29% and 34% (Pala et al., 2012). Similarly, when 62 patients were treated using an identical protocol, it resulted in grade III/IV hematologic toxicity in 19% and a hospital admission rate of 31%. The 3-years DFS and OS at 70.3% and 64.5% respectively was however better than the earlier trial (Otty et al., 2011). In another trial of LAHNC, 53 patients were treated with a similar protocol. The overall compliance to CT-RT was 59%. An early survival analysis showed 2-years DFS and OS of 94% and 88% respectively (Homma et al., 2011). In an Indian trial 83 patients were randomised to receive either 3-weekly CDDP-100 mg/m^2 for 3 cycles (group A, 51 patients) or weekly CDDP-40 mg/m^2 (group B, 32 patients) for 6 cycles concurrent with RT. Treatment compliance was similar at 64% and 66% in groups A and B respectively, however, grade III/IV hematologic toxicity (24% *vs* 14%), treatment interruptions (41% *vs* 22%) and weight loss of >10% (34% *vs* 18%) was significantly higher in the weekly arm. The trial was designed to assess toxicity only and therefore did not comment on survival outcomes (Geeta et al., 2006). To summarise, weekly CDDP-40 mg/m^2 based CT-RT has an overall compliance of around 65%, significant hematologic toxicity of around 20% and treatment related hospital admissions around 30%. The estimated 3-years DFS and OS were around 24-70% and 34-65% respectively.

Watkins et al analysed outcome of 96 LAHNC patients treated with concurrent CT-RT using CDDP-30 mg/m^2 weekly. The overall compliance was 87% and with grade III mucositis and neutropenia in 61% and 8% patients respectively. The estimated 4-years DFS and OS were 48% and 58% respectively (Watkins et al., 2010). A large single institutional retrospective audit from India included 264 patients of LAHNC treated with weekly CDDP-30 mg/m^2 concurrent with conventional RT. Dose modification was allowed. The overall compliance was 65%, with an unusually low incidence of grade III/IV mucositis (29%). While grade III/IV emesis and leukopenia were seen in 3.5% and 6% patients respectively, none had nephrotoxicity or thrombocytopenia. The estimated 5 years LRC and DFS were 46% and 43% respectively, while the OS was not computed (Gupta et al., 2009). In another study, 65 patients were treated with weekly CDDP at 30 mg/m^2 concurrent with 3-D conformal RT. The compliance was nearly 100% and the complete response, 2-years DFS and OS were 72%, 33% and 50% respectively (Krstevska et al., 2012). To summarise, this dose schedule had an overall compliance of around 65-100%, significant hematologic toxicity of around 6-8% and estimated 5-years DFS and OS of around 40-45%.

An intermediate dose schedule of weekly CDDP at 35 mg/m^2 and concurrent external RT of 66 Gy in our study resulted in a toxicity/efficacy profile similar to the CDDP-30 mg/m^2 schedule. Ninety-five percent patients received planned doses of RT; 74% received within the stipulated OTT and 82% received at-least 5 cycles of concurrent CT. Although Grade III/IV mucosal toxicity was seen in 67%, significant hematologic toxicity and emesis were seen in

1% and 3% respectively. The estimated 5-years DFS and OS were 39.4% and 41.8% respectively. This suggests that our schedule was better than the weekly CDDP-40 mg/m^2 schedule in terms of compliance and hematologic toxicity and comparable in terms of survival outcomes. We have previously reported our experience with weekly CDDP at 35 mg/m^2 concurrent with concomitant boost RT in head and neck cancer (Kumar et al., 2005) and with conventional RT in oesophageal cancer (Kumar et al., 2002) and have achieved a favourable outcome.

This protocol was reasonably efficacious as the complete response at primary and lymph nodes were seen in 86% and 89% patients respectively. The median DFS and OS were 26 months and 27 months respectively and the estimated 5-years DFS and OS were 39.4% and 41.8% respectively. Attempts were made to contact all patients who did not turn up for follow up after a point in time. Eleven percent patients were disease free when last seen and could not be traced thereafter (LFU). This is a common problem in our country as many of them hail from far flung and rural areas with limited means to travel or communicate. We censored them for computation of survival mainly to compare our results with the contemporary literature since most studies used this methodology.

In conclusion, LAHNC can be effectively treated with weekly CDDP at 30-35 mg/m^2 administered concurrently with RT, as it is well tolerated with minimal toxicity and delivered on an out-patient basis. It may be preferred over 3-weekly regime in developing countries as the latter has substantial hematologic toxicity which requires intensive in-patient management. This is generally impractical in the developing world due resource constraints.

References

Adelstein DJ, Li Y, Adams GL, et al (2003). An Intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemo-radiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*, **21**, 92-8.

Bernier J, Domenge C, Ozsahin M, et al (2004). Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*, **350**, 1945-52.

Brizel DM, Esclamado R (2006). Concurrent chemoradiotherapy for locally advanced, nonmetastatic, squamous carcinoma of the head and neck: consensus, controversy, and conundrum. *J Clin Oncol*, **24**, 2612-17.

Chan AT, Leung SF, Ngan RK, et al (2005). Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in loco-regionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst*, **6**, 536-9.

Cooper JS, Pajak TF, Forastiere AA, et al (2004). Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous cell carcinoma of the head and neck. *N Engl J Med*, **350**, 1937-44.

Cox JD, Stetz J, Pajak TF (1995). Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys*, **31**, 1341-6.

Forastiere AA, Goepfert H, Maor M, et al (2003). Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*, **349**, 2091-98.

Fountzilas G, Ciuleanu E, Dafni U, et al (2004). Concomitant radio-chemotherapy vs radiotherapy alone in patients with head and neck cancer. *Med Oncol*, **21**, 95-107.

Geeta SN, Padmanabhan TK, Samuel J, et al (2006). Comparison of acute toxicities of two chemotherapy schedules for head and neck cancers. *J Cancer Res Ther*, **2**, 100-4.

Gorodetsky R, Levy-Agababa F, Mou X, Vexler A (1998). Combination of cisplatin and radiation in cell culture: effect of duration of exposure to drug and timing of irradiation. *Int J Cancer*, **75**, 635-42.

Gupta T, Agarwal JP, Laskar SG, et al (2009). Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: a single-institution experience. *Head Neck Oncol*, **1**, 17.

Homma A, Inamura N, Oridate N, et al (2011). Concomitant weekly cisplatin and radiotherapy for head and neck cancer. *Jpn J Clin Oncol*, **41**, 980-6

Krstevska V, Stojkovski I, Zafirova-Ivanovska B (2012). Concurrent radiochemotherapy in locally-regionally advanced oropharyngeal squamous cell carcinoma: analysis of treatment results and prognostic factors. *Radiat Oncol*, **7**, 78

Kumar S, Dimri K, Datta NR, et al (2002). Safety and efficacy of concurrent cisplatin and radiotherapy in inoperable or metastatic squamous cell esophageal cancer. *Acta Oncologica*, **41**, 457-62.

Kumar S, Dimri K, Khurana R, et al (2007). A randomised trial of radiotherapy compared with cisplatin chemo-radiotherapy in patients with unresectable squamous cell cancer of the esophagus. *Radiother Oncol*, **83**, 139-47.

Kumar S, Pandey M, Lal P, et al (2005). Concomitant boost radiotherapy with concurrent weekly cisplatin in advanced head and neck cancers: a phase II trial. *Radiother Oncol*, **75**, 186-92.

Myint WK, Ng C, Raaphorst GP (2002). Examining the non-homologous repair process following cisplatin and radiation treatments. *Int J Radiat oncol Biol*, **78**, 417-24.

Otty Z, Skinner MB, Dass J, et al (2011). Efficacy and tolerability of weekly low-dose cisplatin concurrent with radiotherapy in head and neck cancer patients. *Asia Pac J Clin Oncol*, **7**, 287-92.

Pala M, Odrazka K, Holeckova P, et al (2012). Definitive radiochemotherapy with weekly cisplatin in patients with head and neck cancer; single institution outcome analysis. *J BUON*, **17**, 471-7.

Pignon JP, Bourhis J, Domenge C, Designé L (2000). Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. *Lancet*, **355**, 949-55.

Pignon JP, Maitre AL, Bourhis J (2007). Meta-analyses of chemotherapy in head and neck cancer (MACH-NC): An update. *Int J Radiat Oncol Biol Phys*, **69**, 112-4.

Rose PG, Bundy BN, Watkins EB, et al (1999). Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*, **15**, 1144-53.

Steinmann D, Cerny B, Karstens JH, Bremer M (2009). Chemoradiotherapy with weekly cisplatin 40 mg/m^2 in 103 head-and-neck cancer patients: a cumulative dose-effect analysis. *Strahlenther Onkol*, **185**, 682-8.

Watkins JM, Zauls AJ, Wahlquist AH, et al (2010). Low-dose weekly platinum-based chemoradiation for advanced head and neck cancer. *Laryngoscope*, **120**, 236-42.