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Original Research

Three Weekly Versus Weekly Cisplatin: Comparison of two Different Chemotherapy Protocols with Concurrent Radiotherapy in Locally Advanced Head and Neck Cancer

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Introduction: Chemoradiotherapy (CRT) with concurrent cisplatin-based chemotherapy is the treatment of choice of locally advanced head and neck cancers (LAHNC), but the optimal regimen of cisplatin remains contentious. Though 3-weekly cisplatin is the recommended schedule, it is associated with severe adverse reactions. A lower dose weekly schedule is generally accepted to be more tolerable and is widely used in our country.
Methodology: Our study retrospectively compares the 3-weekly and the weekly concurrent cisplatin schedules in patients of LAHNC treated with CRT. Patients were selected for either schedule based on the treating physician’s preference. The two schedules were compared for treatment-related toxicities, radiotherapy interruptions, cumulative cisplatin doses delivered and overall survival (OS) as well as disease-free survival (DFS) at 2 years.
Results: In our study, 43 patients received the 3-weekly schedule while 40 received the weekly schedule. Age, gender, disease stage or site did not affect selection for either regimen, except cancers of the nasopharynx and salivary glands, who almost exclusively received the 3-weekly schedule (90.1%). Patients who received adjuvant CRT after radical surgery were more likely to receive the weekly schedule (66.7%) while patients treated with up-front CRT were more often given the 3-weekly schedule (57.6%). Overall, the 3-weekly arm was associated with more toxicities and treatment breaks, but was more successful in delivering an adequate cumulative dose of cisplatin and had a better OS and DFS at 2 years follow up compared to the weekly arm. It also appeared that treating physicians were more likely to withhold one or more of the weekly cycles to manage treatment toxicity which lead to inadequate cumulative dosing in a high (45%) percentage of patients.
Conclusion: Our study reiterates that the 3-weekly cisplatin arm has a better outcome profile than the weekly cisplatin arm at the price of increased toxicity. Weekly schedules have lower toxicities but may not achieve outcomes equivalent to 3-weekly unless adequate cumulative doses are achieved. As our study is retrospective and non-randomized, selection bias may have affected our results.

Introduction

Head and neck cancers (HNCs) are the sixth most common cancer worldwide with an incidence of 6,33,000 cases and 3,55,000 deaths annually [1]. In developing countries approximately 80% of cases present with locally advanced head and neck cancer (LAHNC) [2]. It constitutes about 30% of

all cancers occurring in India and the majority of the cases occur in males [3]. LAHNC can often be unresectable and are managed with radiotherapy (RT) or chemoradiotherapy (CRT). The addition of concurrent chemotherapy to RT in LAHNC has been proven to be superior to RT alone. It is presently the standard of care in the treatment of LAHNC, either in the role of definitive treatment, for cases in which disease is not amenable to surgical resection, or as adjuvant therapy after surgical resection reveals adverse pathological features [4,5].

For concurrent CRT, the chemotherapeutic agent of choice is cisplatin. Concurrent cisplatin regimens were established as the most effective with single-agent activity, synergistic interaction and non-overlapping toxicity. It is has a wide-ranged dosage delivery schedule ranging from a high-dose [100 mg/m2] every three weeks for three cycles, to a low-dose (6 mg/m2) daily administration [6]. Most randomized controlled trials done on the subject have accepted cisplatin in a dose of 100 mg/m2 given every 3-weeks concurrently with RT as a standard reference regimen in the definitive and adjuvant settings [4,6,7]. The logical reasoning for high dose chemotherapy are a greater tumour-cell kill and the address of micrometastasis at presentation while a lower dose chemotherapy schedule can be argued for based on providing adequate radiosensitization with lower toxicities causing fewer treatment breaks and more optimal RT delivery. Uncertainties exist regarding appropriate CRT regimens because of significant heterogeneity in published data concerning patient selection, chemotherapy dose schedules used and RT techniques and fractionation employed [8,9].

Apart from the above-mentioned reasons, 3-weekly CRT remains a major challenge to deliver in a real-world setting with limited resources due to the associated acute toxicities, poor tolerance and increased inpatient admissions. To overcome these challenges, splitting the 3-weekly cisplatin into a weekly schedule with a dosage ranging from 20 to 40 mg/m2 has been attempted and is widely practised in India. Investigative studies on the subject have shown some promising results such as achieving equivalent or even better antitumor efficacy, fewer side effects, and lower cost and hospitalization rates compared to the 3-weekly schedule [10,11].

Considering the discordant nature of the available research regarding the optimal scheduling of cisplatin- based concurrent CRT in LAHNC, we undertook this study to compare the use of a standard 3-weekly regimen to the more popular weekly cisplatin schedule.

Materials and Methods

Our study aimed to compare the efficacy of the two concurrent cisplatin schedules, in terms of overall survival (OS) and disease-free survival (DFS), as well as their toxicities. Both 3-weekly and weekly concurrent cisplatin schedules are used at our centre for CRT in HNSCC. Whether the patient receives one or the other schedule is a matter of the personal preference of the oncologist attending to the patient as different treating physicians prefer different schedules. The dose prescription is 100 mg/m2 every three weeks for 3 cycles in the 3-weekly protocol and a dose of 40 mg/m2 every week for 6 cycles in the weekly protocol. All patients received radiotherapy on a Theratron 780E telecobalt machine using 2D treatment planning.

Data was collected retrospectively from treatment records of all patients treated with CRT for HNSCC between 2015 to 2016. All patients identified were followed up prospectively up to two years from treatment completion. Telephonic communication and interviews were used to confirm the survival status of patients defaulting on physical follow up.

Demographic variables such as age, gender, history of tobacco use of the patient and site and stage (AJCC 7th edition, 2010) of the disease were recorded. Treatment-related data collected included the concurrent cisplatin schedule that was prescribed and whether the CRT delivered was upfront definitive in intent or adjuvant following radical surgery. Information was also recorded on any significant treatment breaks in the CRT (≥ 7 days), whether the patient was able to receive the

planned radiation dose, whether he/she could receive all the planned chemotherapy cycles (3 or 6 respectively) or an adequate cumulative dose of cisplatin (≥200 mg). Outcomes recorded were OS and DFS at 2 years from treatment completion. Toxicities in the form of dermatitis and oropharyngeal mucositis were recorded as per the CTCAE version 4.03. Myelosuppression was recorded as any patient with a Total Leucocyte Count (TLC) falling below 1500 during the course of CRT while derangement of renal function was recorded if any patient had a rise in serum creatinine levels ≥ 1.2 mg/dl. It was also recorded if the patient required a nasogastric (NG) tube placement during the CRT due to nutritional difficulties.

All statistical analysis was carried out using Statistical Package for social sciences (SPSS) version 21 (International Business Machines Corporation (IBM), Armonk, New York, U.S.). Crosstabulation with Pearson's Chi-squared test was used to study the association between the study variables. The Mann-Whitney test was used to compare the distribution of the study outcomes in the two treatment arms. All tests were two-tailed with a p-value <0.05 considered as statistically significant. The Kaplan– Meier method was used to estimate mean OS and DFS. The survival difference between patients who received 3-weekly or weekly schedules was tested through the log-rank test.

Results

Table 1 shows the frequency distribution of variables in the study population and the two treatment schedules.

	(%)	3 Weekly (%)	Weekly (%)	p-value
Age				
Range	20 - 74	20 - 68	34 - 74	
Mean	56	55	57	
< 60 years	45 (54.2)	25 (58.1)	20 (50)	0.513
≥ 60 years	38 (45.8)	18 (41.9)	20 (50)	
Sex				
Male	67 (80.7)	37 (86)	30 (75)	0.268
Female	16 (19.3)	6 (14)	10 (25)	
Tobacco Use				
Yes	58 (69.9)	28 (65.1)	30 (75)	0.35
No	25 (30.1)	15 (34.9)	10 (25)	
Site				
Oral Cavity	38 (45.8)	19 (44.2)	19 (47.5)	0.235
Oropharynx	17 (20.5)	8 (18.6)	9 (22.5)	
Larynx	11 (13.3)	4 (9.3)	7 (17.5)	
Hypopharynx	6 (7.2)	2 (4.7)	4 (10)	
Nasopharynx	5 (6)	4 (9.3)	1 (2.5)	
Others (PNS & Salivary gland)	6 (7.2)	6 (14)	0 (0)	
Stage				
I	2 (2.4)	1 (2.3)	1 (2.5)	0.606
II	9 (10.8)	3 (7)	6 (15)	
III	34 (41)	17 (39.5)	17 (42.5)	
IV	38 (45.8)	22 (51.2)	16 (40)	
Treatment Modality				
Radical Surgery & Adjuvant CCRT	24 (28.9)	8 (18.6)	16 (40)	0.032
Definitive CCRT	59 (71.1)	35 (81.4)	24 (60)	
Total	83	43	40	

Table 1. Frequency Distribution of Study Variables in the Patient Cohorts.

The mean age of the study population was 56 years with more than 80% of the population being males and 70% giving a positive history of tobacco use. The oral cavity was by far the commonest subsite (46%) and 87% of cases were locally advanced (stage III or IV). 71% of patients received upfront, definitive CRT while 29% underwent radical surgery followed by adjuvant CRT. There was no statistically significant difference in the distribution of variables in the two arms.

Figure 1 shows a bar chart comparing the difference in treatment interruptions, compliance to planned radiotherapy and chemotherapy in the two treatment schedules.

Figure 1. Effect of Chemotherapy Regimen on Planned Treatment Course and Adequacy.

Figure 2 shows the frequency of measured toxicities in the two treatment arms.

Figure 2. Treatment-related Toxicity Observed in the Two Treatment Schedules.

The 3-weekly arm had significantly more radiation dermatitis (p=0.000) and oropharyngeal mucositis (p=0.000) compared to the weekly arm. The patients in the 3-weekly arm also had a higher incidence of NG tube placement (p=0.238), myelosuppression (p=0.32) and renal function derangement (p=0.35) during the course of treatment though this was not statistically significant.

Figure 3 shows the overall survival of the two treatment groups on a Kaplan-Meier plot.

Figure 3. Comparison of Overall Survival at 24 Months between Patients in the Two Arms.

The 3-weekly group (Median OS = 18.33 months) appears to have a distinctly better overall survival at 2 years than the weekly group (Median OS = 17.23 months) though this difference is not statistically significant (p= 0.221). At the end of 24 months of follow up, the 3-weekly arm had 65.17% of patients alive while 53.59% of patients were disease-free compared to 52.5% alive and 42.5% disease-free in the weekly arm.

Discussion

Concurrent chemoradiation has been widely adopted as the standard of care for LA-HNC after the publication of a large and most comprehensive meta-analysis based on individual patient data of 10,741 patients in 63 randomized trials. This meta-analysis also confirmed an absolute survival benefit of 8% at two years and five years by the addition of chemotherapy to radiotherapy [5].

The debate between three weekly and weekly cisplatin in head and neck cancer continues to be relevant. Oncologists are always divided in their opinion regarding the better compliance of weekly cisplatin and better local regional control offered by 3-weekly cisplatin regimen. In a country like India with limited health care resources and a disproportionately large oncological burden, the better compliance and ease of administration of weekly cisplatin on an OPD basis is very convenient and is the treatment of choice followed in many oncology centres across the country. As mentioned before a wide range of weekly cisplatin ranging between 20 mg/m² to 100 mg/m² has been tried in clinical practice. An Intergroup randomized trial of 307 eligible patients comparing 20 mg/m2 of cisplatin with RT to the same RT alone demonstrated no improvement in overall survival (OS) or freedom from failure, suggesting that 20 mg/m2 (weekly) was too low a dose. But the study also

revealed an increased risk of late laryngeal and oesophagal toxicities [10]. In the face of recognized toxicity, institutional practices favouring a weekly schedule have typically favoured doses of ≥ 30 mg/m2. Asif et al subjected 30 patients to Cisplatin at an intermediate dose of 30 mg/m2 intravenously once a week with RT compared to RT alone group [11]. This was a relatively well-tolerated schedule and has been also employed with altered fractionation regimens with satisfactory outcomes. According to one of the largest meta-analyses regarding chemoradiotherapy in head and neck cancers by Szturz et al, high-dose cisplatin was defined by a dose of 100 mg/m2 given once every 3–4 weeks for a total of three doses if combined with conventional radiotherapy or two doses if combined with altered fractionation radiotherapy. Low-dose cisplatin was defined by a dose not exceeding 50 mg/m2 given at weekly intervals for a total of at least six applications in the case of conventional radiotherapy or at least four applications if combined with altered fractionation radiotherapy in the definitive and adjuvant setting [12]. This meta-analysis also highlighted that a cumulative dose of 200 mg/m2 ensures adequate survival benefit compared to radiotherapy alone but was not clear about the benefit of dose escalation on overall survival. Keeping the above data in mind our institute follows a weekly schedule of 40 mg/m2 and a 3-weekly schedule of 100mg/m2. In our study, we have used conventional fractionation in all patients with concurrent chemotherapy with a dose of 100mg/m2 for the 3-weekly schedule and 40 mg/m2 for the weekly schedule in both definitive and adjuvant settings. All patients in our study were planned to receive a cumulative dose of 200mg/m2.

All the study variables were equally divided in the two studies, the difference in performance status of patients in the two arms could not be compared as it had not been recorded. The performance status of the individual patient may have played a role in a selection bias towards one or either regimen.

29% of patients got adjuvant radiotherapy in our study and 71% were treated with definitive intent. There was no significant post-op complication encountered in the operated arm with all patients starting their adjuvant treatment within six weeks of surgery.

In the comparative study by Tsan et al [13], in definitive conventional chemoradiation, the three-weekly protocol clearly showed higher haematotoxicity, nausea and/or vomiting, and nephrotoxicity, thus typically cisplatin-related adverse events. As described in the literature, in our study too, the toxicity seen in the 3-weekly arm was significantly more than the weekly arm, with statistically higher levels of dermatitis and mucositis. A higher proportion of patients also needed enteral nutritional support that was represented by more patients requiring NG tube placement in the 3-weekly arm (18/43 – 42%), than the weekly arm (5/40 – 12.5%). Similarly, myelosuppression and renal dysfunction were more frequently seen in the patients in the 3-weekly arm than the weekly arm though these findings were transient and not statistically significant. No patient progressed to chronic kidney disease or was dialysis-dependent.

Compliance with the planned treatment was the most important challenge faced by many researchers for completion of the 3 weekly schedules. The higher toxicity in the 3-weekly arms often results in poorer compliance due to multiple treatment interruptions and sometimes abandonment mid-way through the planned course. What was interesting in our study was that while the increased toxicity did lead to a greater number of treatment breaks in the 3-weekly arm compared to the weekly arm, the number of patients who were able to complete the planned radiotherapy dose (60 to 70 Gy in 30 to 35 fractions subject to clinical scenario) and the number of patients who were able to complete the planned chemotherapy cycles (3 in the 3-weekly and 6 in the weekly arm) were significantly lower in the weekly arm compared to the 3-weekly arm.

Thus, the rates of treatment completion were higher in the 3-weekly group than the weekly group. One possible reason for this result could be that the difference in performance status (PS) in patients in the two arms have not been accounted for and probably acted as a confounder. It is possible that the treating oncologist preferred to place patients with good PS in the 3-weekly arm and poorer PS patients in the weekly arm considering the known poor tolerance of the former.

Another reason could be that while the weekly cycles were delivered as an OPD procedure, the patients receiving the 3-weekly regimen were admitted to the hospital for at least 24 hours during and after the delivery of the chemotherapy drug. It is likely that they were more closely monitored during inpatient admission for hydration and symptomatic relief. Nevertheless, it was reassuring that there was no compromise in treatment completion in the 3-weekly arm despite a more demanding regimen. What was of concern was the high proportion of patients in the weekly arm who did not receive the planned number of chemotherapy cycles. The authors suggest that this may be due to the poorer PS in the weekly arm patients and a lower tolerance amongst treating doctors to “skip” a cycle of chemotherapy in the weekly arm, whenever toxicities appear, considering there are 5 more cycles. Doctors are probably less likely to skip a cycle in the 3-weekly arm considering there are a total of three cycles with each cycle contributing 1/3rd of the total chemotherapy dose.

Similarly, it was also of concern that a significantly greater fraction of patients in the weekly arm (22.5%) did not receive an adequate cisplatin dose than the 3-weekly arm (2.3%). While receiving only 2 of the 3 planned cycles in the 3-weekly arm was sufficient to achieve the “adequate” cumulative dose of cisplatin in most patients, in the weekly arm, at least 5 of the 6 cycles were required to accumulate the required dose in the majority of the patients. Thus, even missing 2 of the cycles would mean that the required cisplatin dose was not received by many patients and the anti-tumour and radiosensitizing effects of cisplatin were not achieved as planned and were below par. The reasons for the discrepancy of cumulative dose achieved in the two regimens are similar to what has been described above for the number of chemotherapy cycles.

In our study, the locoregional control seen was 53.59% in the 3-weekly arm versus 42.5% in the weekly arm while median OS at 2 years was 19.37 months and 17.23 months in the 3-weekly and weekly arms respectively. There are very few trials available in the literature that focus on the endpoint of survival. A large single institutional retrospective audit from Tata Memorial Hospital included 264 patients of LA-HNC treated with weekly cisplatin 30 mg/m2 concurrently with conventional RT. The estimated 5-years loco-regional control (LRC) and disease-free survival (DFS) were 46% and 43% respectively, while the OS was not computed (14). Weekly cisplatin (40 mg/m2) with concurrent RT reported an impressive 2-year OS and local progression-free rates (PFR) of 93.7% and 88.0%, respectively with complete response in the primary site in 98.1% of patients in another single-arm study [15]. In one of the few comparative studies published, Tsan et al in 2012 reported the results of a small phase III trial randomly assigning 55 patients to one or the other concurrent cisplatin regimens. Both groups received the same mean doses of chemotherapy and radiotherapy, but significantly more patients could tolerate cumulative doses of at least 200 mg/m2 cisplatin in the high-dose arm [13]. Similar in design to the above study, in a phase III trial, comparison was made of three weekly cisplatin to weekly cisplatin (30 mg/m2) in both adjuvant and definitive settings (with around 90% of the patients in the former group). After a median follow-up of 22 months, the primary endpoint, estimated cumulative 2-year locoregional control, was improved by 14.6% in the three-weekly cohort. The resulting gains in median progression-free survival and overall survival fell short of statistical significance [16]. In our study too, though there was a clear trend towards improved survival at 2 years in the 3-weekly arm compared to the weekly arm, it was not statistically significant. While the higher cisplatin dose leading to greater anti-tumour and radio-sensitizing effects were the primary reasons for the improved locoregional control and survival in the 3-weekly arm, the poorer treatment compliance and possibly poorer PS in the weekly arm are likely to have contributed to the poorer survival in the weekly arm as well. Our study was possibly insufficiently powered to detect the difference in survival with statistical significance.

In conclusion, the findings of our study highlight the significantly superior locoregional control seen in the 3-weekly arm. But any survival benefit has to be weighed against the higher toxicity profile of the 3-weekly arm. Compliance was better in the 3-weekly arm in our study despite higher toxicities which was possibly a result of appropriate patient selection and more intensive patient care in the 3-weekly arm. Inpatient care and monitoring was an integral part of our 3-weekly arm and we recommend that all institutes that can give such care to their patients try to follow the 3-weekly

schedule. Nevertheless, despite consensus regarding superior survival outcomes of the 3-weekly protocol, the weekly protocol remains an important treatment option for patients deemed unfit for the 3-weekly schedule. We recommend a minimum of 5 to 6 cycles delivered concurrently with radiotherapy whenever the weekly schedule is used.

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