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Original Research

Comparison of Safety and Efficacy of Two Different Chemotherapy Dosing Schedules Used in Concurrent Chemoradiation of Head and Neck Cancer: A Retrospective Experience from a Tertiary Cancer Care Institute of Eastern India

Sayoni Bhanja Department of Radiation Oncology, Chittaranjan National Cancer Institute, Kolkata, India.
Debarshi Lahiri Department of Radiation Oncology, Chittaranjan National Cancer Institute, Kolkata, India.
Sanjoy Roy Department of Radiation Oncology, Chittaranjan National Cancer Institute, Kolkata, India.
Tapas Maji Department of Radiation Oncology, Chittaranjan National Cancer Institute, Kolkata, India.
Palas De Department of Radiation Oncology, Chittaranjan National Cancer Institute, Kolkata, India.

Background and objective: Concurrent chemoradiation has demonstrated improvements in local control and survival in various multi-institutional trials and has become the standard of care for locally advanced head and neck cancers. Platinum-based chemotherapy has shown the greatest benefit, with no significant difference observed between mono- or polychemotherapy. Despite a general consensus that platinum-containing regimens are optimal, the optimal dose schedule remains unclear. This study aimed to assess the efficacy and toxicity of concurrent weekly cisplatin with radical radiotherapy and compare two different chemotherapy dosing schedules used in concurrent chemoradiation for head and neck cancer.

Materials and Methods: The records of 62 eligible patients with locally advanced (T3-4a, N1-2) squamous cell carcinoma of the oropharynx, hypopharynx, and larynx registered between 2016 and 2020 at a regional cancer center in India were analyzed from the hospital database after obtaining approval from the Institutional Ethical Committee and informed consent from all eligible patients. One group of patients (Group A) received concurrent chemoradiation with weekly cisplatin (40 mg/m^2) and radiotherapy to a dose of 66 Gy delivered in 33 fractions over six and a half weeks. The other group of patients (Group B) received cisplatin (100 mg/m^2) on a three-weekly schedule (Days 1, 22, and 43) with the same radiation schedule.

Results: There was no significant difference in baseline characteristics between the two groups (p-value ≥ 0.05). Although complete response occurred more frequently in the three-weekly group compared to the weekly cisplatin group at follow-up of 6 weeks (67.7% vs 61.3%), 6 months (80.6% vs. 67.7%), and 12 months from the completion of concurrent chemoradiation (CCRT) (78.9% vs 65%), this difference was not statistically significant (p-value ≥ 0.05). No statistically significant differences were found in terms of both acute toxicities (anemia, leukopenia, mucositis, dermatitis, upper gastrointestinal toxicities, dysphagia) and late toxicities (laryngeal edema, dry mouth, and edema of the skin of the neck) when weekly concurrent chemoradiotherapy was compared to three-weekly

chemoradiotherapy (p-value ≥ 0.05).

Conclusion: The weekly chemotherapy regimen can be delivered safely on a day-care basis and can be helpful in settings with limited logistics and significant patient burden.

Introduction

Squamous cell carcinoma of the head and neck account for about 90% of all head and neck cancers [1] and originate in the mucosal membranes of the upper aerodigestive tract. Head and neck cancer is the seventh most common cancer (excluding skin cancer and Hodgkin and non-Hodgkin lymphoma) in the world. In India, as per GLOBOCAN 2020 cancer estimates [2], lip and oral cavity cancers are the most common cancers occurring in males and 4th most common cancer in females. Overall they are the second most common cancer after breast cancer comprising 1,35,929 cases (10.3%) in our country in both males and females. In combined population of both the sexes, incidence of head and neck cancer (including lip and oral cavity, larynx, hypopharynx, oropharynx, nasopharynx and salivary gland cancer) is the highest among all cancers in India consisting of about 2,33,269 cases. It is also a leading cause of cancer death in India (3rd most common after breast and cervix comprising 5.4% in overall population) [2].

Radiotherapy plays a major role in the treatment of cancers of the head and neck. It has been frequently used in combination with chemotherapy as a curative treatment, mainly for organ preservation for surgically unresectable malignancies. Concurrent chemoradiation has shown improvements in local control and survival in various multi-institutional trials and been the standard of care for non-metastatic and locally advanced head and neck cancers [3-9]. Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) collaborative group showed an absolute survival benefit of 8% at 5 years for concurrent chemoradiotherapy [10,11]. Platinum-based chemotherapy has shown the maximum benefit with no significant difference between mono- or polychemotherapy. The putative mechanisms of synergistic interaction of cisplatin with radiotherapy in HNSCC include radio sensitization; hypoxic cell sensitization; cell cycle perturbation; ability to form deoxyribonucleic acid (DNA) adducts; and inhibition of angiogenesis [12]. Chemoradiation imparts an increase in both early and late toxicities compared with RT alone. In particular, mucositis and long-term gastrostomy tube dependence secondary to dysphagia have emerged as major dose-limiting toxicities for chemoradiation [13].

Despite a general consensus that platinum-containing regimens are optimal, the actual dose schedule and types of agents to add to platinum remain open questions. Single- agent cisplatin (100 mg/m^2 every 3 weeks) appears to be relatively well tolerated and improved overall survival through multiple phase III trials conducted by various academic and community practices. This approach achieves a relatively high systemic dose exposure that may address subclinical micro metastases while still providing some radio sensitization. Concurrent 3-weekly high-dose cisplatin (100 mg/m^2) is the contemporary ‘standard of care’ for loco-regionally advanced HNSCC based on level I evidence [10,14]. A randomized phase III trial that evaluated the weekly administration of 40 mg/m^2 cisplatin plus RT versus RT alone for the treatment of nasopharyngeal cancer also demonstrated favorable outcomes in patients with an advanced T-stage treated by CCRT [15,16]. Few studies have compared weekly and 3-weekly cisplatin CCRT regimens in patients with SCCHN but there is no definite conclusion regarding optimal scheduling of chemotherapy from the results [17-19]. More frequent administration can provide better radio-sensitization to a larger proportion of the administered radiotherapy dose according to a retrospective study [20]. Marcu and colleagues [21] by implementing the kinetics of cisplatin analysed the scheduling of cisplatin with radiotherapy in a previously developed tumour growth model of HNSCC .This study showed that better radio sensitization can be achieved with daily low dose cisplatin prior to radiotherapy

treatment. Low-dose weekly regimens provide more opportunity for tumour radio sensitization, and less toxicity that may be more easily managed through the use of short chemotherapy breaks without RT breaks. Jeremic et al. [22] used cisplatin at a dose of 6 mg/m^2 daily (total, 30 mg/m^2/week) and documented survival benefit as well as surprisingly, a reduction in distant metastases, leading many to favour a weekly dose of 30 mg/m^2. The only randomized study comparing daily (6 mg/m^2), weekly (40 mg/m^2), and three-weekly (100 mg/m^2) schedule of cisplatin with conventionally fractionated radiotherapy [23] did not find any significant difference in response rates and loco-regional control, but reported varying degrees of mucosal, renal and hematologic toxicity between the groups. In a prospective non-randomized study [19] that compared 3-weekly cisplatin (100 mg/m^2) given to younger patients with good KPS (n = 30) with weekly cisplatin (40 mg/m^2) given to patients of older age or poor KPS (n = 20) along with radical radiotherapy, there were no differences in response rate and grade III or IV toxicities between the two groups. Despite the lack of conclusive recommendation of scheduling, it is quite evident from the available data that a cumulative cisplatin dose of 200–250 mg/m^2 given three-weekly, weekly, or daily during radiotherapy gives therapeutic benefit [20]. Our study aimed to assess the efficacy and toxicity of concurrent weekly cisplatin with radical radiotherapy and compare two different chemotherapy dosing schedules used in concurrent chemoradiation of head and neck cancer.

Materials and Methods

This was a retrospective observational study. The records of 62 eligible patients of locally advanced (T3-4a, N1-2) (Stage III and IVA) squamous cell carcinoma of oropharynx, hypopharynx and larynx registered between 2016 to 2020 at a regional cancer centre in Indiawere analysed from the hospital database. All the patients had a baseline ECOG performance Status of 1 or 2, normal renal function, liver function and blood counts, and baseline audiometry limited to mild sensory neural deficits. Due approval of the Institutional Ethical Committee was obtained and informed consent was taken from all the eligible patients.

One group of patients (Group A) had received Concurrent Chemo-radiation with injection Cisplatin 40 mg/m^2 weekly with Radiotherapy to a dose of 66 Gy delivered in 33 fractions for six & half weeks and the patients of the other group (Group B) received injection Cisplatin 100mg/m^2 in three weekly schedule on Days 1, Day 22 & Day 43 along with the same radiation schedule. Conventional Radiotherapy was planned for all patients after appropriate immobilization using a thermoplastic mask and simulation. All thepatients were irradiated with megavoltage beams on a Linear Accelerator, with conventional fractionation (200 cGy per fraction, one fraction per day, and five days per week) with shrinking field technique. The high risk clinical target volume that included thegross tumor volume was treated to a dose of 66 Gy in 33 fractions over 6.5 weeks. Areas of potential microscopic disease were treated at a dose of 54–60 Gy in 27–30 fractions over 5–6 weeks.

Standard premedication according to the institutional protocol was given prior to chemotherapy and the standard guideline for dose reduction of cisplatin was applied by indirectly calculating the glomerular filtration rate based on Cockroft-Gault formula. The weekly regimen was administered on an outpatient basis.

The patients of three weekly cisplatin group received Cisplatin 100 mg/m^2 with adequate pre and post hydration for two days as per institutional protocol and their pre medications and post medications schedule of chemotherapy were same as the other group.

Statistical analysis

Statistical analysis was performed with help of Epi Info (TM) 3.5.3. Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (s.d.). Chi-square (X^2) test was performed to find the associations. Odds ratio with respective confidence interval was calculated to find the risk factors. t-test was used to test the significant difference between means.

$p<0.05$ was taken to be statistically significant.

Results

A total of 62 eligible patients were taken for analyzing data. The most common subsites were base of tongue and larynx. Most of the patients presented with well differentiated squamous cell carcinoma. There was no significant difference in the baseline characteristics between the two groups. Overall, most patients had T3 disease (40.3%) and had nodal disease(N1) at presentation. In both the groups, Stage III was the commonest stage at presentation followed by Stage IV disease (Group A Stage III 54.8% and Stage IV 45.2% vs. Group B Stage III 51.6, Stage IV 48.4%, Overall Stage III 53.2%).

Maximum patients completed the treatment within 7 weeks of the commencement of RT (54.8% in Group A and 64.5% in Group B, overall 59.7%) (p=0.79). Overall 40 out of 62 (64.5%) patients achieved complete clinical response (61.3% in Group Avs 67.7% in Group B whereas partial response occurred in 22 patients (38.7% in Group A vs 32.3% in Group B; overall 35.5%) at the first follow up (after 6 weeks from completion of radiotherapy). Though the complete response occurred more in 3 weekly group (67.7% vs 61.3%) it was not statistically significant (p=0.59). At the follow up of 6 months from the completion of CCRT, 46 out of 62 (74.2%) patients achieved complete clinical response (67.7%in weekly vs 80.6% in 3 weekly group). Rest of the patients achieved partial response (32.3% in Group A vs. 19.4% in Group B, overall 25.8%). Though the complete response occurred more in Group B patients than in Group A (80.6% vs. 67.7%), it was not statistically significant (p=0.24). Due to Covid-19 situation, temporary disruption of all sorts of communication as well as logistic issues many of the patients couldn’t come for long term follow-up. Only 39 out of 62 patients could complete their 12 months follow up within the scheduled period. At the follow up of 12 months from the completion of treatment, 15 (78.9%) patients in Group B achieved complete clinical response in comparison to 13 patients (65%) in Group A. Overall 28 out of 39 patients had complete response (71.8%). Though the complete response occurred more in group B patients than in Group A (78.9% vs. 65%) at 12 month follow up, it was not statistically significant. (p=0.46). The rest of patients (11 out of 39) were SWD (surviving with disease) (p=0.33).

In Group A patients, grade II anaemia occurred most frequently (57.1%) and in Group B patients, grade I anaemia occurred most frequently (65%). In Group A, grade II leukopenia occurred most commonly (48.1%). In Group B, grade I leukopenia was commonest (52.2%). Patients in Group A experienced more severe form of mucositis (grade III 45.2%, grade II 45.2%) than Group B. Grade III dermatitis occurred more frequently in Group A(19.4%) as compared to Group B (6.5%) (p=0.09). Grade II UGI toxicity was more common in both the groups. Upper GI toxicity of Grade III was more common in Group B patients as compared to Group A (12.9% and 9.7% respectively) (p=0.59). The occurrence of dysphagia was also similar in both the groups. The risk of having dryness of mouth was 1.14 times more among the patients of Group A as compared to the patients of Group B. The risk of having oedema of skin of neck was 3.21 times more among the patients of Group B though not significant statistically.

Discussion

Compliance and Treatment duration

Most of the patients completed Radiotherapy (RT) treatment within 45 to 55days. The patient compliance was good in both the groups. In our study, 87% of patients in Group A received 7 cycles of weekly chemotherapy and 90.3% of the patients in Group B received 3 cycles of three weekly chemotherapy.

Ho and colleagues [18] compared the differences in dose intensity, delays, and toxicity between concurrent 3-weekly (80–100 mg/m^2) and weekly (40 mg/m^2) cisplatin-based definitive CCRT in 51

patients with advanced HNSCC. More patients received a higher cumulative dose of at least 240 mg/m^2 in the weekly arm as compared to the 3-weekly arm (p = 0.04). The 3-weekly regimen was associated with more delays (41% vs. 29%) and omissions of chemotherapy (17.4% vs. 5.6%) resulting in lesser patients achieving cumulative doses beyond 200 mg/m^2, potentially lowering dose-intensity. According to Muhammad Shahid Iqbal et al. [24] 68% percent of patients managed to complete all six cycles of chemotherapy while 87% of patients completed at least 5 cycles of weekly cisplatin.

Response to treatment

In the 3 weekly chemotherapy group, the complete response rate after 6 weeks from completion of treatment was 67.7%, which was very promising. The complete response rate was 61.3% after 6 weeks from completion of treatment in the concurrent weekly cisplatin group. Partial response occurred in 22 patients (38.7% in Group B vs 32.3% in Group A; overall 35.5%) after 6 weeks from completion of radiotherapy. At the follow up of 6 months from the completion of CCRT, 46 out of 62 (74.2%) patients achieved complete clinical response (67.7% in Group A vs. 80.6% in Group B). Rest of the patients achieved partial response (32.3% in Group A vs. 19.4% in Group B, overall 25.8%). Only 39 out of 62 patients could complete their 12 months follow up within the scheduled period. At the follow up of 12 months from the completion of treatment, 15 (78.9%) patients in Group B achieved complete clinical response in comparison to 13 patients (65%) in Group A. Overall 28 out of 39 patients had complete response (71.8%). But the difference in complete response rate was not statistically significant in both the arms at any point of time (6weeks, 6 months or 12 months; p value was 0.59, 0.24 and 0.46 respectively). Patients with partial response were re-evaluated at multidisciplinary tumor board and appropriate decisions regarding further management was taken for each patient. A study by Muhammad Shahid Iqbal et al. [24] showed complete response in 75% of patients who received weekly concurrent cisplatin (40mg/m^2) with radiation. In a prospective non-randomized study [19] that compared 3-weekly cisplatin (100 mg/m^2) given to younger patients with good KPS (n = 30) with weekly cisplatin (40 mg/m^2) given to patients of older age or poor KPS (n = 20) along with radical radiotherapy, there were no differences in response rate and grade III or IV toxicities between the two groups. Despite the lack of conclusive recommendation of scheduling, it is quite evident from the available data that a cumulative cisplatin dose of 200–250 mg/m^2 given three-weekly, weekly, or daily during radiotherapy gives therapeutic benefit [20].

In a more recent phase III trial [25] involving 153 stage II-IV oropharyngeal and nasopharyngeal cancer patients, Sharma et al reported improved response rates (79.2% vs. 69.7%, p < 0.05) and 3-year overall survival (62% vs. 42%, p = 0.024) for concurrent weekly cisplatin as compared to radical radiotherapy alone. Our study also resulted in increased complete response in three weekly arm, though it was not statistically significant.

Toxicity

No significant differences in hematological toxicities (anaemia, leukopenia or thrombocytopenia) were seen between the weekly and 3 weekly concurrent chemotherapy groups. Mucositis was found more in weekly group in comparison to 3 weekly group (Grade III mucositis was seen in 45.2% of patients in weekly chemotherapy group and 29% of patients in 3 weekly group), however it was not statistically significant. Though radiation dermatitis was found more in weekly chemotherapy group in comparison to the other group, (Grade III radiation dermatitis was seen in 19.4% of patients in Group A and 6.5% of patients in Group B) it was not statistically significant. No significant difference was also observed in upper GI toxicities or dysphagia between the two groups.

Laryngeal oedema was found in 25% of the patients in weekly group and 5.3% of the patients in 3 weekly group after 12 months from the completion of treatment. In our study, dryness of mouth was found in 40 % of the patients in Group A and 36.8% of the patients in Group B after 12 months

from the completion of treatment. Oedema of skin of neck was found in 10 % of the patients in Group A and 26.3 % of the patients in Group B. Though laryngeal oedema and dryness of mouth were more in Group A and oedema of skin of neck was more in Group B, none of these differences were significant statistically (p value ≥0.05).

Ho et al. reported similar toxicities between the weekly and 3-weekly groups [18]. The patients treated with 3-weekly cisplatin seemed to suffer more grade 3 radiation dermatitis (56% vs. 26%, p value=0.07). Although in our study grade 3 dermatitis was more in weekly chemotherapy group, but was not statistically significant (p value=0.09). Uygun et al. reported that grade 3–4 toxic events were observed in 53.3% of the patients treated with 3-weekly cisplatin and 40% of those treated with weekly cisplatin, but this difference was also not significant [19]. However, Geeta et al. suggested that 3-weekly cisplatin is less toxic than weekly treatment [17]. According to the meta-analysis of weekly cisplatin versus three weekly cisplatin chemotherapy plus concurrent radiotherapy (CRT) for advanced head and neck cancer (HNC) by Jian Guan et al., six studies supplied data of grade≥3 neutropenia among which included 178 patients in the weekly group and 194 patients in the three -weekly group. Patients treated with three weekly cisplatin seemed to be more prone to nausea and/or vomiting than those with weekly cisplatin (RR=0.59, 95%CI 0.34-1.02, p=0.06). Six eligible studies showed that weekly arm appeared to have similar risk of dermatitis compared to three weekly arm, with an RR of 1.23 (95%CI 0.84-1.82, p=0.29). No heterogeneity was observed for dermatitis analysis. Eight articles of 624 patients reported the data of mucosal toxicity. No obvious difference was observed for the risk of grade≥3 mucositis between the two groups. Further analysis was performed based on the disease sites. Subgroup analyses were much interesting which showed patients in weekly group suffered grade ≥ 3 mucositis more easily when the primary disease located in non-nasopharynx (RR=1.72, 95%CI 1.13-2.61, p=0.01) with a nonsignificant heterogeneity of 43% (p=0.13). However, when the disease site arose in nasopharynx, patients of the two groups had similar risk (RR=0.65, 95%CI 0.29-1.45, p=0.29) [26]. According to Tejpal Gupta et al. [27] acute grade 3 or worse mucositis and dermatitis was seen in 77 (29%) and 92 (35%) patients respectively essentially in patients receiving doses ≥66 Gy and 6 or more cycles of chemotherapy. Other toxicities (hematologic, nausea and vomiting) were mild and self-limiting. Though the acute toxicity of this concurrent weekly chemo-radiation regimen was increased to small extent but intensive supportive care was not required routinely.

In our study no statistically significant differences were found in terms of both the acute and late toxicities when weekly concurrent chemoradiotherapy was compared to three weekly chemoradiotherapy. There was no significant difference in treatment compliance in both the arms.

Thus, the results obtained in this present study are consistent with the various published literature comparing toxicity and response to treatment in the weekly and three weekly Cisplatin arm concurrent with radiotherapy in locally advanced head and neck cancer.

Limitations of the study

1) Long term follow-up of majority of patients couldn’t be done due to poor compliance attributable to Covid-19 pandemic situation, lack of patient awareness and lack of proper communication. This limited the analysis of PFS, DFS and OS data in this population.

2) Sample size was too small to achieve statistically significant data for reaching definite conclusion regarding primary and secondary end points.

3) The other confounding factors (smoking, alcohol, oral hygiene, body weight etc.) were also not taken into consideration while interpreting the difference in toxicities.

In conclusion, the present study compared weekly cisplatin with three -weekly cisplatin concurrent with radiotherapy in locally advanced head and neck cancers. Among the two chemoradiation schedules, there was not much difference in response rates and toxicities. There was no significant

difference in treatment compliance in both the arms. So, the weekly chemotherapy regimen can be delivered on a day care basis without the need of longer admissions and can be helpful in a set up with limited logistics and considerable patient burden.

A bigger prospective randomized study, preferably multi-institutional, with greater sample size and longer duration of follow up may be undertaken before confirming the results of the present study and drawing definite conclusions for final recommendations.

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The authors declare no conflict of interest.

Abbreviations

SCCHN, Squamous cell carcinoma of Head and Neck; CCRT, Concurrent Chemo-radiotherapy; PFS, Progression-free survival; DFS, Disease-free survival; OS, Overall survival.

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