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Weekly versus Three–Weekly Cisplatin–based Concurrent Chemoradiotherapy as definitive treatment in Head and Neck Cancer – Where do we stand?


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Abstract

Purpose

To compare toxicity, compliance, and early response of weekly and 3–weekly cisplatin administration concurrent with radiotherapy as definitive treatment in locally advanced squamous cell carcinoma head and neck.

Materials and Methods

Patients with histologically proven stage III – IV B head and neck carcinoma presenting from June 2013 to March 2014 were randomly assigned to weekly (35 mg/m², 6 cycles; arm A) and 3 weekly (100 mg/m², 3 cycles; arm B) cisplatin with concurrent radiotherapy.

Results

60 patients were randomly assigned to treatment, 30 in each arm. Median follow-up was 8 months (range 4–13). There was no significant difference in grade 3 mucositis between the two arms (75.9% vs 70%, p = 0.20). Grade 3 neutropenia was more frequent in arm B (55.2% vs 26.7%, p = 0.01). Hypomagnesemia was the commonest electrolyte imbalance and it was significantly higher in arm B (60% vs 20%, p = 0.001). Completion rate of scheduled chemotherapy cycles was higher for patients receiving weekly regimen. Response at 3 months was similar for all the patients (Complete Response (66.7% vs 62.1%), p = 0.200). Our data suggested that there is a reduced need of hospitalization and supportive care measures for patients receiving weekly cisplatin with RT (p = 0.05).

Conclusions

Weekly cisplatin 35 mg/m² chemotherapy concurrent with radiotherapy is equally effective and less toxic in terms of neutropenia, hypomagnesemia and need for supportive measures than the conventional 3 weekly cisplatin 100 mg/m² regimen.

Keywords

Squamous cell carcinoma, Cisplatin, Head and Neck neoplasm, Mucositis, Neutropenia

Introduction

Globally, head and neck cancers (HNC) are amongst the commonest malignancy. (1) Approximately 50–60% of patients present with locally advanced HNC which poses a therapeutic challenge. Concurrent chemoradiation has emerged as standard of care for these patients. (2)

The Meta–Analysis of Chemotherapy in Head and Neck Cancer (MACH–NC) update suggested that the magnitude of benefit was higher for platinum based chemoradiotherapy compared with concomitant therapy with other cytotoxic agents. (3) Cisplatin is the most widely used agent in combination with radiotherapy (RT). The dose and delivery schedules of cisplatin have ranged from intermittent higher dose (100 mg/m²) every 3 weeks to low dose (6 mg/m²) daily administration. (4) The best available evidence of the chemoradiotherapy related clinical benefit for the treatment of locally advanced HNC is based on cisplatin administration at 100 mg/m² every 3 weeks, in combination with standard RT. (5) However, various studies have shown that 3–weekly regimen was associated with significant increase in acute toxicities.

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such as mucositis, hematological complications and renal complications. As a result of these acute toxicities, only 74% to 85% of patients were able to complete all the three planned doses of three-weekly cisplatin\textsuperscript{(5,6,7)} Therefore, at present a great emphasis has been on the potential activity of alternative platinum based chemoradiation approaches that might decrease toxicities and increase compliance while maintaining dose intensity. The most popular schedule of concurrent cisplatin outside the context of clinical trials is not the three-weekly regimen but a weekly schedule\textsuperscript{(8)} of cisplatin in the dose range of 30–40 mg/m\textsuperscript{2}. Data suggest that weekly regimen has also been found to be feasible\textsuperscript{(9,10,11)} in terms of toxicities, less frequent treatment interruptions and more patients achieving cumulative doses beyond 200 mg/m\textsuperscript{2}, potentially increasing the dose intensity and thus suggests that weekly cisplatin is becoming the regimen of choice for use in concurrent chemoradiotherapy in locally advanced HNC.

After doing thorough research of the literature we found that there is insufficient data, variability of results and no uniformly accepted optimal chemotherapy schedule along with radiotherapy as definitive treatment for locally advanced HNC, compelling a need of additional research in this field. Keeping this in mind, we compared the weekly schedule versus 3-weekly schedule of cisplatin as definitive chemoradiotherapy for locally advanced HNC with respect to acute local and systemic toxicities as well as tumour response.

Materials and Methods

This prospective randomized study was approved by the Scientific Committee and Institutional Review Board. Patient data consisted of those with locally advanced squamous cell carcinoma head and neck receiving definitive chemoradiotherapy in our department from June 2013 to March 2014. A total of 60 patients fulfilling the specified inclusion and exclusion criteria were recruited for the study.

Inclusion criteria:

- Age 18 – 65 years.
- Histologically proven squamous cell carcinoma.
- Locally advanced (stage III – IV B) disease.
- Oral cavity, oropharynx, hypopharynx and larynx primary tumours.
- Normal haemogram, renal and liver function tests.
- Written informed consent.

Exclusion criteria:

- Previously treated head and neck malignancy.
- Evidence of distant metastasis.

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Pre-treatment evaluation:

All patients were evaluated including history and physical examination, complete blood count, renal function and liver function tests. Preventive dentistry and biopsy of the primary tumour was mandatory for all patients. Radiological investigations included magnetic resonance imaging (MRI) of the face and neck, chest radiography, ultrasound abdomen. All the patients were staged according to TNM staging system (AJCC 7th edition).

Randomization:

After pre-treatment evaluation and staging, patients were randomized into two arms by sequential randomization according to their first visit in the RT department (Fig. 1).

Radiotherapy planning:

Radiotherapy planning was done on conventional simulator. All the patients were treated with a 6MV photon linear accelerator treatment unit using standard three-field technique i.e. two parallel opposed lateral fields and a low anterior neck field. The daily dose was 200 cGy per fraction, a dose of 46 Gy in 23 fractions to the primary tumour, involved lymph nodes and possible subclinical disease, followed by a boost to the primary tumour and metastatic nodes to a dose of 24 Gy in 12 fractions, resulting in a total dose of 70 Gy in 35 fractions.

Chemotherapy protocol:

Concurrent chemotherapy regimen was given by medical oncologist using cisplatin 35 mg/m\textsuperscript{2} intravenously weekly (days 1, 8, 15, 22, 29, and 36) or 100 mg/m\textsuperscript{2}
intravenously every 3 weeks (days 1, 22, and 43 during RT). In the 3–weekly arm, the patient was admitted one day before and cisplatin was given intravenously over 2 days in equal divided dose in 500 ml of normal saline with adequate hydration, anti–emetic prophylaxis, and mannitol infusion while weekly cisplatin was given on OPD basis in day care ward with the similar hydration and other measures. Supportive treatment like hospitalization, administration of colony stimulating factor and insertion of Ryle’s tube feeding was done as and when indicated. Complete blood profile and renal parameters were checked before starting every chemotherapy. Total dose of cisplatin, number of chemotherapy cycles received and details of RT were documented. Any delay causing treatment interruption was noted.

**Evaluation of Toxicities:**

All patients were reviewed once weekly in OPD to assess treatment–induced toxicity. These included acute in–field toxicity (mucositis), acute systemic toxicity (vomiting, significant weight loss and acute renal toxicity), hematological toxicity (haemoglobin, total leucocyte count, and platelet count) and electrolyte imbalances (hyponatremia and hypomagnesemia). Toxicity was graded according to the NCI – CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 4.03. Acute toxicity was defined as toxicity that was noted during RT.

**Response evaluation:**

Response evaluation was performed three months after completion of chemoradiotherapy by physical examination, direct laryngoscopy, and magnetic resonance imaging (MRI) face and neck. Additional investigations were performed whenever necessary. Biopsy was performed if there was residual or recurrent disease. Clinical and radiological responses were evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

**Statistical analysis:**

Statistical analysis was conducted using SPSS version 20.0. The qualitative data was compared by applying chi–square test or Fisher’s exact test, as appropriate. The quantitative data was compared by applying student T–test. A p–value less than 0.05 was considered significant.

**Results**

**Patient and tumor parameters**

Sixty patients having non–metastatic locally advanced HNC were validated for inclusion in the analysis. Of the 60 patients, 30 patients were randomly assigned to receive weekly 35 mg/m² cisplatin, and 30 patients were randomly assigned to receive 3–weekly 100 mg/m² cisplatin concurrently with standard dose of RT. One patient in arm B died during treatment because of medical cause unrelated to the treatment (Dengue). Median follow–up was 8 months (range: 4 – 13 months). The treatment arms were reasonably comparable in terms of baseline characteristics including age, primary site, and tumour differentiation (Table 1). However, the weekly arm had more advanced stage patients as compared to 3–weekly arm.

**Treatment characteristics**

Mean RT dose received by patients in both the arms was similar (69.86 Gy ± 0.73 vs 69.22 Gy ± 4.38). However, a higher mean cisplatin dose was received by arm B patients (438.27 mg ± 65.03) as compared to arm A patients (291.66 mg ± 23.05) during RT. Five patients in arm A and 10 patients in arm B had RT interruption due to various reasons like mucositis, hematological toxicity and non–compliance. Although not statistically significant, 10% and 20.7% of arm A and arm B patients respectively did not complete the planned course of CT (p = 0.15).

**Treatment toxicities**

The main treatment toxicities are summarized in Table 2. There was no statistically significant difference between the two arms in terms of grade 3 or higher mucositis (70% vs 75.9%, p = 0.20), however there was statistically significant difference between the two arms in terms of systemic toxicity in the form of vomiting in 20% and 34.5% of patients in arm A and arm B patients respectively (p = 0.03). Weight loss ≥ 10% during the course of treatment occurred in 23.3% patients in arm A and in 41.4% patients in arm B (p = 0.08). Frequency of acute renal failure in the form of deranged serum creatinine was similar for both the arms and was of mild grade only. Among the haematological toxicities, neutropenia (p = 0.02) was significantly more frequent in the 3–weekly arm, whereas the difference for anemia and thrombocytopenia was insignificant. Incidence of hypomagnesemia was found to be higher in 3–weekly arm as compared to weekly arm (60% vs 20%, p = 0.001).

**Response to treatment**

The analysis of data showed that 3 months after completion of treatment, complete response (66.7% vs 62.1%) as well as partial response (33.3% vs 37.9%) were similar in both the arms, with no statistically significant difference between both the arms (p = 0.20).
Need for supportive treatment

Supportive treatment in the form of feeding procedure (such as percutaneous endoscopic gastrostomy or Ryle’s tube) \((p = 0.05)\), use of colony-stimulating factors \((p = 0.05)\) and hospitalization for supportive care during CRT were more for 3-weekly arm patients as compared to weekly arm \((p = 0.05)\) (Fig. 2).

Discussion

Locally advanced HNC accounts for a considerable portion of all head and neck cancers, particularly in developing countries. Chemoradiotherapy has been demonstrated to be the standard of care in the management of these patients. Benefits of using combined modality therapy for the treatment of locally advanced HNC comes at the cost of markedly increased acute toxicity. Therefore, using various schedules of concurrent cisplatin with RT has become an area of interest to overcome the problem of increased acute toxicity. We compared weekly 35 mg/m² cisplatin with 3-weekly 100 mg/m² cisplatin concurrent with RT in definitive setting for locally advanced HNC.

Among the in-field toxicity, we found mucositis as the commonest toxicity in both the arms. Incidence of grade 3 mucositis was found to be slightly higher in 3-weekly arm compared to weekly arm \((75.9\% \text{ vs } 70\%, \ p = 0.20)\) although it was not statistically significant. None of our patients had grade 4 mucositis. The study carried out by Azony et al \((12)\), showed that 40% patients developed grade I mucositis, 55% patients grade II and 5% grade III in 3–weekly arm patients. While in weekly arm, grade I mucositis was observed in 60%, grade II in 30% and 10% developed grade III mucositis with no significant statistical difference between both the arms \((p = 0.27)\).

Our study showed that weekly cisplatin significantly reduced the incidence of neutropenia as compared with 3–weekly cisplatin. There was no significant difference in the incidence of anemia and thrombocytopenia in both the arms. A retrospective study by Mitra et al \((13)\) reported neutropenia to be the dose limiting toxicity. Grade 3 neutropenia was found in 33% of weekly arm and in 43% of 3–weekly arm, but it was not statistically significant.

No statistically significant differences were observed between the two arms regarding renal toxicity \((26.7\% \text{ vs } 31\%, \ p = 0.21)\). However, the patients receiving 3–weekly cisplatin have a higher incidence of grade III vomiting as compared to weekly cisplatin \((p = 0.03)\). A possible explanation for this finding could be the use of high dose cisplatin per cycle in the 3–weekly regimen. Azony et al \((12)\) reported that 15% patients developed grade III vomiting in 3–weekly group as compared to 5% in weekly group \((p = 0.23)\). Further, 3–weekly arm patients have significant weight loss during treatment \((41.4\% \text{ vs } 23.3\%, \ p = 0.08)\) and this could be due to an increased incidence of mucositis and vomiting leading to reduced appetite in these patients.

Among the electrolyte imbalances caused by cisplatin, hypomagnesemia was the most frequent complication
seen in patients receiving 3-weekly CT (60% vs 20%, p = 0.001). Mashhadi et al. (14) conducted a study on patients with various malignancies receiving cisplatin 50 mg/m² to 100 mg/m². They reported incidence of hypomagnesemia to be 18% without any other electrolyte abnormalities.

Compliance has always been an important issue with the combined modality therapy. Our study showed that the patients in the weekly arm have high completion rate of scheduled CT cycles, thus having better compliance than 3-weekly arm. In our study, 90% patients completed all 6 cycles of planned weekly CT in comparison to 79.3% patients in the 3-weekly CT. In addition, 3-weekly arm patients required higher CT dose reduction as compared to patients receiving weekly CT. Interruption in the RT treatment were also found to be more for 3-weekly arm patients as compared to weekly arm patients (p = 0.07). As per Institutional policy, we preferred to continue RT and defer CT until the patient recovered from hematological or mucosal toxicities. Similar findings have been reported by Cooper et al. (7) that 61% of their patients completed all 3 planned cycles of cisplatin, 23% received 2 cycles, 13% received 1 cycle, and 2% received no CT.

A striking finding from our study was that weekly cisplatin patients have reduced requirement of feeding tube placement, colony stimulating factors, and hospitalization for supportive care over the treatment period as compared to 3-weekly patients and it almost reached statistically significant level (p = 0.05). In the setting of financial constraints in developing countries, this finding is very important so as to reduce the cost of treatment by use of minimum additional supportive care.

There is no difference in response (complete as well as partial) between the two arms. Our study showed that weekly cisplatin CT arm experienced the same response as the 3-weekly CT arm but with less toxicity. After thorough search of the literature, we found that our study is among one of the few studies addressing the comparison between weekly 35 mg/m² concurrent cisplatin with 3-weekly cisplatin as definitive treatment for locally advanced squamous cell HNC (Table 3). Weekly 35 mg/m² cisplatin concurrent with RT is feasible and has equivalent response rate compared with 100 mg/m² 3-weekly, which is currently considered the standard regimen in definitive treatment of locally advanced squamous cell HNC. The current study had some limitations in terms of small sample size and shorter follow-up. Further evaluation with larger number of patients and longer follow-up is suggested for the confirmation of these results.

‘Cisplatin is like an energizing food but it doesn’t mean that one can take plateful of it’. This saying is true for three-weekly cisplatin as it has been proven to be a potent radio sensitizer, but we should not forget that increase in the dose leads to more toxicity as well. Thus, we conclude that this randomized comparison

![Figure 2: Comparison of Supportive care needed in both the arms](image)

Table 3: Literature review: Comparative studies between weekly versus 3-weekly cisplatin concurrent with radiotherapy for locally advanced squamous cell carcinoma head and neck
suggests that weekly cisplatin schedule is more effective in reducing acute local and systemic toxicities, better compliance to treatment with an equivalent tumour response as standard 3-weekly cisplatin–based chemoradiation. Our study highlights the reduced utilization of resources such as supportive measures and hospitalization for supportive care with weekly schedule as the most attractive feature in developing countries where financial constraints are barriers to treatment. This study on optimal dosing schedule of cisplatin as definitive concurrent chemoradiotherapy in locally advanced HNC can serve as a benchmark for directing future studies on larger number of patients with longer follow-up.

References


