International Journal of Research in Medical Sciences
Vias P et al. Int J Res Med Sci. 2019 Dec;7(12):4543-4547
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20195515

Original Research Article

Concurrent chemoradiation in head and neck cancers with weekly cisplatin: analysing toxicities

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Received: 01 October 2019
Revised: 04 October 2019
Accepted: 01 November 2019

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ABSTRACT

Background: Head and neck cancers constitute 6% of cancers worldwide. The management requires a multidisciplinary approach. Concomitant chemoradiotherapy with cisplatin is the standard approach for locally advanced head and neck cancers. The most commonly used regime uses three weekly cisplatin which is more toxic. Low-dose once-a-week cisplatin is substituted because of perceived lower toxicity and convenience.
Methods: Squamous cell carcinoma of stage III, IVA and IVB of oropharynx, hypopharynx and larynx were studied for one year. 82 patients were studied. Total dose of radiation was 66Gy/33#/6 ½ weeks from Monday to Friday with inj. Cisplatin 40mg/m2 i.v. infusion weekly.
Results: 88% of patients were able to complete five or more weekly chemotherapy cycles with cumulative dose of 200mg/m2. Grade 2 and 3 acute toxicities were seen in weekly cisplatin arm but were conservatively managed.
Conclusions: Weekly cisplatin can be used with concurrent radiotherapy as the acute toxicities are manageable and is well tolerated.

Keywords: Cisplatin, toxicities, Concurrent chemoradiotherapy, Head and Neck cancer, Squamous cell carcinoma

INTRODUCTION

Head and neck cancers are the fifth most common cancers worldwide and the estimated annual global incidence is over half a million.[1] Nearly 60% of this population presents with locally advanced disease. Optimal treatment for locally advanced HNC is challenging, surgery and radiotherapy are the curative therapies and chemotherapy is used as an adjuvant treatment.

Concomitant chemo-radiation represents a more attractive strategy because some chemotherapeutic agents act as radio-sensitizers for tumor cells and also provide additive cytotoxicity. The superiority of this type of nonsurgical strategy relative to RT alone has been demonstrated in randomized trials in squamous cell carcinoma of other anatomic sites including the esophagus and uterine cervix.[2-4]

The most commonly used chemotherapeutic agent is cisplatin. The absolute benefit of adding platinum based chemotherapy to radiation has been estimated as 6.5% at 5 years.[5] The optimal regimen for cisplatin based chemotherapy is yet to be defined and presently there is insufficient data limiting conclusions about tolerability of one regimen over the other. However, the most widely used regimen uses three weekly cisplatin at a dose of 100 mg/m^2 with standard radiotherapy.[6-8] This high dose cisplatin is associated with increased toxicity and affects

patient's compliance. This toxicity also increases hospital stays and interruptions in treatment which may jeopardize the treatment outcome resulting in poorer locoregional control.[6] Alternative protocols, like weekly cisplatin have been used in attempt to reduce toxicities.

Weekly Inj. Cisplatin 40 mg/m^2 is used for concurrent chemoradiotherapy in locally advanced HNC in the institute. Here aim was to review the efficacy of this treatment, evaluate the response, patient compliance and toxicities in a tertiary care center.

METHODS

This prospective study was conducted in the Department of Radiotherapy and Oncology, Regional Cancer Centre, IGMC, Shimla, Himachal Pradesh after approval of Institutional Research and Ethics for a period of two years (from July 2015 to June 2017.)

Inclusion criteria

- Patients with age ≤70 yrs. with squamous cell carcinoma Oropharynx, Hypopharynx, Larynx, Stage III, IV A and IV B (AJCC Cancer Staging Manual 7th edition, 2010) which are previously untreated with normal complete hemogram, renal and liver function tests and performance status >70.

Exclusion criteria

- Age >70 years, histology other than squamous cell carcinoma, previously treated patients, deranged blood investigations and performance status <70.

In this study, patients were subjected to cisplatin based concomitant chemoradiotherapy with Inj. cisplatin 40 mg/m2 (max. 50 mg) iv infusion weekly on day1 of every week for seven doses. Standard anti-emetic protocol was administered, and adequate hydration was done. External beam radiation therapy was given by Theratron® 780e or Equinox™ Cobalt-60 machines using either two parallel and opposed fields or three field technique using Thermoplastic cast for immobilization. Dose of 66Gy were given in 6½ weeks in 33# @ 2Gy per fraction, 5 fractions from Monday to Friday were administered per week.

Outcome and toxicity evaluation

Locoregional response was recorded during first follow up clinically. The response was considered to be complete if there was no visible or palpable disease, partial if there was more than 50% regression, stable if lesion regressed less than 50% in maximal diameter and progressive if lesion increased by 25% or appearance of new lesion or secondary metastatic disease. Toxicities (skin, mucosal, pharyngeal, laryngeal and salivary) (RTOG CRITERIA) were recorded every week during treatment, at the end of treatment and on follow up.

Follow up

First follow-up was done at 6 weeks with complete history and a thorough clinical examination for assessment of disease and toxicity status.

Statistical analysis

Response rate was the primary end point for analysis. The data obtained from both arms were analyzed by student "t"-test and chi-square test.

RESULTS

Over 120 patients were assessed for eligibility and out of them 82 were enrolled in the study. Patient characteristics are shown in (Table 1).

Table 1: Patient characteristics on the basis of A. Age, B. Sex, C. Site, D. Stage, E. number of chemotherapy cycles received and F. Treatment outcome.

Patient characteristics		Number	%age
Age(years)	31-40	2	2.4%
	41-50	9	11.0%
	51-60	36	43.9%
	61-70	35	42.7%
Sex	Male	75	91.5%
	Female	7	8.5%
Site	Hypopharynx	15	18.3%
	Oropharynx	22	26.8%
	Larynx	45	54.9%
Stage	III	39	47.6%
	IVA	42	51.2%
	IVB	1	1.2%
No. of chemotherapy cycles	7	25	30.5%
	6	37	45.1%
	5	10	12.2%
	4	5	6.1%
	<=3	5	6.1%
Treatment outcome	Complete	61	74.5%
	Partial	16	19.5%
	Progression	2	2.4%
	Death	1	1.2%
	Defaulter	2	2.4%

Clinical Outcome: Treatment compliance and acute toxicities

In this study 82 patients of locally advanced HNC were treated with weekly inj. Cisplatin with concurrent radiotherapy. Three-fourth (75.6%) of the patients were able to complete more than or equal to six cycles of chemotherapy. Overall, 87.8% of patients completed five or more cycles, that is, a cumulative dose of 200 mg/m^2 (Table 1). Rest of the patients received 3 or 4 cycles of chemotherapy. Chemotherapy interruptions were seen in 17(20.7%) patients due to toxicities, compliance,

machine outbreak and patient refusal. The incidence of Grade 3 toxicities was: mucositis (25.6%), dermatitis (14.6%), pharyngeal toxicity (7.3%), laryngeal toxicity (3.6%), hematological (6.1%), renal impairment (2.4%) (Table 2). Grade 4 toxicity was seen in none of the patient.

Table 2: Acute toxicities seen in patients.

Toxicity	Grade	Number	%age
Mucositis	G1	6	7.3%
	G2	55	67.1%
	G3	21	25.6%
Dermatitis	G1	16	19.5%
	G2	54	65.9%
	G3	12	14.6%
Pharyngeal toxicity	G1	23	28.1%
	G2	53	64.6%
	G3	6	7.3%
Laryngeal toxicity	G1	40	48.8%
	G2	39	47.6%
	G3	3	3.6%
Salivary toxicity	G1	67	81.7%
	G2	15	18.3%
Hematological toxicity	G0	26	31.7%
	G1	27	32.9%
	G2	24	29.3%
	G3	5	6.1%

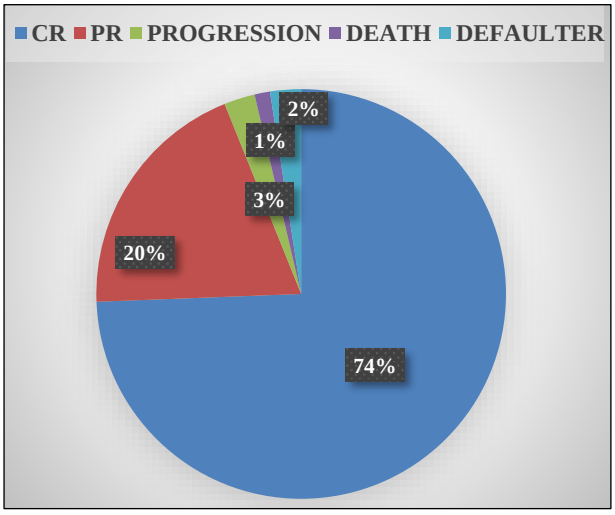

Figure1: Response at first follow ups.

Clinical Outcome: response to the treatment

Response was assessed after 6 weeks of treatment completion. 61(74.5%) patients achieved complete clinical response. Clinical suspicion of residual disease was seen in 16 patients (19.5%).

Progressive disease was seen in 2 patients and 1 patient died. Two patients were lost to follow up (Figure 1).

DISCUSSION

For locally advanced inoperable HNC, definitive chemoradiotherapy remains the standard of treatment. The most common chemotherapeutic agent used in combination with radiotherapy is cisplatin. Cisplatin acts as a radiosensitizer, causes inhibition of repair of potentially lethal damage and sublethal damage. It forms DNA adducts and arrests the cell cycle in G2 phase.[9] The optimal regimen for use of concurrent cisplatin is yet to be defined, although the most robust evidence is use of three weekly cisplatin in dose of 100mg/m^2. But this high dose cisplatin is associated with increased toxicities and thus the completion rate of this regime remains challenging. Also, it increases the unnecessary hospital stay.

The choice of particular regimen varies markedly from 3 weeks (100 mg/m^2) to low dose daily administration (6 mg/m^2). Due to the significant toxicities and suboptimal compliance which is negatively influencing the outcome, there is a trend towards use of low dose weekly cisplatin with radiotherapy.[10] Among the weekly cisplatin schedule, doses as low as 20 mg/m^2 concurrent with RT to 60 mg/m^2 have been tried.[11] But an Intergroup randomized trial (Quon et al), demonstrated no improvement in OS and freedom from failure, suggesting 20 mg/m^2 was too low a dose.[12] Thus, weekly cisplatin became an attractive schedule from the standpoint of delivery, tolerance and compliance and the most common dose used is between 30 to 40 mg/m^2.

A good compliance with any form of treatment is necessary in order to minimize the interruption to oncological treatment. In EORTC 22931, compliance to chemotherapy decreased as the first, second and third cycles were administered to 88%, 66% and 49% of patients respectively.[7] In this study, 88% of the patients received cumulative dose of >200 mg/m^2 by weekly administration of injection cisplatin. Six or more cycles were completed by 75% of the patients resulting in higher total dose than three weekly schedules. In a latest study, only 47% of the patients were able to receive dose >200 mg/m^2 with weekly cisplatin while 76% of patients received this dose with three weekly cisplatin.[13] This could be due to flexibility of decision of chemotherapy which is to be done at only two time points. Also, it can be hypothesized that most of the patients will have recovered from high dose toxicities of chemotherapy. In another study, 94% of patients completed three weekly planned chemoradiation while 88% of patients could complete weekly chemoradiotherapy.[14]

Data wise 75% of the total patients receiving weekly chemotherapy, in this study had complete response. Noronha et al showed 2-year locoregional control was significantly higher with three weekly arms at 73% as compared to 58% in weekly arm.[14] The patients who received dose >200 mg/m^2 also revealed superior locoregional control in tree weekly arm.

Espeli et al, reported higher incidence of grade 2-3 dermatitis for 3 weekly cisplatin as compared to weekly cisplatin (p=0.5).[15] In patients, grade 2 dermatitis was most commonly seen in 65% of total patients. In another study, 59% of the patients had grade 2 dermatitis and 41% of patients had grade 3/4 cutaneous toxicity with weekly cisplatin.[16] Homma et al, stated that the rate of Grade 3 or greater leukopenia and mucositis was 26.4% and 39.6%, respectively with weekly cisplatin which were similar or less than those in Phase III trials of three weekly cisplatin regime.[17] In present study, grade 3 hematological toxicity was seen in 6% of patients and mucositis was seen in 26% of patients. The incidence of grade 3/4 neutropenia was approximately 30% with 3 weekly cisplatin compared with 10-15% with weekly cisplatin8. A Japanese study reported no difference in incidence of grade 3/4 renal toxicity, however, grade2 for which dose reduction or discontinuation of cisplatin must be considered, was 30-32% in 3 weekly arms compared with 2-15% in weekly cisplatin arm.[18]

Ho et al, compared weekly cisplatin with 3 weekly cisplatin with concurrent chemoradiotherapy. Cumulative dose of more than 240mg/m^2 was reached in weekly arm in most of the patients, while none in 3 weekly arms was able to receive all the 3 cycles. Thus, more delays and omission of chemotherapy was seen in 3 weekly arms than in weekly arm.[19] In patients with locally advanced nasopharyngeal cancer weekly cisplatin was associated with improved quality of life without compromising the efficacy and the toxicity profile was similar in both the arms.[20]

Study favors most of the above studies where weekly cisplatin is better tolerated and is more compliant than 3 weekly regimes. According to experience, it is easier to manage weekly cisplatin regime because of close monitoring and easy dose adjustments as well as toxicities can be conservatively managed. However, compliance still remains an issue.

CONCLUSION

Weekly cisplatin with concurrent radiotherapy in locally advanced head and neck cancers can be administered safely with acceptable toxicity which are manageable and without compromising the tolerability of patient. However, prospective randomized trial is needed to compare three weekly cisplatin regimes with weekly cisplatin.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Vias P, Gupta M, Seam RK, Gupta M, Fotedar V, Ahuja R. Concurrent chemoradiation in head and neck cancers with weekly cisplatin: analysing toxicities. Int J Res Med Sci 2019;7:4543-7.