RESEARCH ARTICLE

Concurrent Chemoradiation with Weekly Cisplatin for the Treatment of Head and Neck Cancers: an Institutional Study on Acute Toxicity and Response to Treatment

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Abstract

Background: Concurrent chemoradiation with three weekly high dose cisplatin is the non-surgical standard of care for the treatment of locally advanced head and neck cancers. Although this treatment regime is efficacious, it has high acute toxicity, which leads not only to increased treatment cost, but also to increased overall treatment time. Hence, the current study was undertaken to evaluate the acute toxicity and tumor response in head and neck cancer patients treated with concurrent chemoradiation using 40 mg/m^2 weekly cisplatin, which has been our institutional practice. Materials and Methods: This single institution retrospective study included data for 287 head and neck cancer patients treated with concurrent chemoradiation from 2012 to 2014. Results: The mean age of the patients was 48.8 years. The most common site of involvement was oral cavity. Most of the study patients presented with advanced stage disease. The mean overall treatment time was 56.9 days. Some 67.2% had overall complete response to treatment as documented till 90 days from the start of treatment. According to the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria, mucositis was seen in 95.1% of the patients. Dermatitis and emesis were observed in 81.9% and 98.6%, respectively. Regarding haematological toxicity, 48.8% and 29.6% suffered from anaemia and leukopenia, respectively, during treatment. Acute kidney injury was assessed using the Common Terminology Criteria for Adverse Events (CTCAE), and was found in 18.8% of the patients. Conclusions: Concurrent chemoradiotherapy with weekly cisplatin is an effective treatment regime for head and neck cancers with reasonable toxicity which can be used in developing countries, where cost of treatment is so important.

Keywords: Cobcurrent chemoradiation - RTOG - CTCAE - developing countries - efficacy

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Introduction

Overall 57.5% of the head and neck cancers (excluding oesophageal cancers) worldwide occur in Asia, especially in India (Chaturvedi, 2009). The reflected burden of head and neck cancers (HNCA) in India is actually much less than the actual burden, and has been compared to the tip of the iceberg (Mishra et al., 2014). Majority of the patients with HNCA present in Stage IV disease in India (Pandey et al., 2014).

Organ preservation approach with chemoradiotherapy is currently the standard of care for the management of HNCA (Lasrado et al., 2014). Based on the meta-analysis of the MACH-NC collaborative group, which demonstrated a 6.5% absolute survival advantage at 5 years in HNCA with concurrent chemoradiation, platinum based concurrent chemoradiation has become the non-surgical standard of care in the treatment of HNCA (Pignon et al., 2007). Although 3 weekly high dose cisplatin is the current chemotherapy of choice while given concurrently with radiation (Pignon et al., 2000, 2005, 2007), there is still no uniform consensus on it due to the wide variation in various study designs and due to the different ways of combining chemotherapy with radiation (Browman et al., 2001; Baykara et al., 2013). Further, the 3 weekly high dose cisplatin based chemoradiation regime has been shown to have considerable haematological toxicity and is non-compliant in one-third of the patients (Brizel et al., 2006). The situation is further complex in developing countries like India, where there are limited resources and the patients need intensive inpatient care. Hence, moderate doses of weekly cisplatin has been advocated as concurrent chemoradiation (Dimri et al., 2013).

The current study aims at finding out the efficacy and acute toxicity of concurrent chemoradiation with moderate dose cisplatin in Indian setting.

Materials and Methods

Study design

This is a single institutional retrospective study done with the data available from the computer and clinical

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case sheets of the patients with squamous cell carcinoma of the head and neck who were treated in the Department of Radiotherapy in a South Indian institute from January 2012 to December 2014. Previously untreated patients with non-metastatic HNCA (excluding cancers of the esophagus, nasopharynx and paranasal sinuses) who were treated with 40 mg/m^2 cisplatin based concurrent chemoradiation were only included in the study. Patients treated with neoadjuvant or adjuvant chemotherapy were excluded from the study. Patients treated with any other chemotherapeutic agents or with any other dosage regime of cisplatin were also excluded from the study. All patients who completed their treatment were only included in the present study. A total of 287 patients were found to be satisfying the inclusion criteria of the study.

Radiotherapy

All patients were treated with conventional radiotherapy with 6 MV photons with a linear accelerator after immobilization with thermoplastic mask. All patients were treated with conventional fractionation. The gross tumor volume was treated to a dose of 66 or 70 Gy in 33- 35 fractions. The first phase 46 Gy was delivered in 23 fractions to the mid-plane with pair opposing lateral fields. The lower neck whenever indicated, was treated with a matched low anterior neck field upto a dose of 50 Gy in 25 fractions using a half beam block, normalized at 2-3 cms of depth. In the second phase, shrinking field off-cord technique was used to deliver the radiation dose to the primary tumor site along with the nodal sites with a 2-3 cms margin upto a dose of 66 or 70 Gy.

Chemotherapy

40 mg/m^2 weekly cisplatin was administered intravenously during the course of radiation. Pre-chemotherapy hydration was given with 1000 ml normal saline and 500 ml of dextrose normal saline. Antiemetic premedication was given with 8 mg of dexamethasone and 8 mg of ondansetron. Cisplatin was delivered along with 500 ml of normal saline over 3 hours. Post-chemotherapy hydration was given with 1000 ml of normal saline and 500 ml of ringer lactate along with 10 ml of magnesium sulphate. Also 100 ml of 20% mannitol is given post-chemotherapy to ensure forced diuresis. On the day of the chemotherapy, radiation was delivered within an hour of cisplatin administration. Post-chemotherapy antiemetic prophylaxis was given with pantoprazole, domperidone and ondansetron for the next five days. Chemotherapy administration was postponed if the haemoglobin level was less than 9 gm/dl or total leukocyte count was less than 2500 mm-3 or platelet count was less than 75,000 mm-3 or serum creatinine was more than 1.5 mg%, till recovery. Dose modifications were not done in any patient.

Patient evaluation

All the study patients were evaluated weekly during the course of chemoradiotherapy for assessing the toxicity of the treatment. After completion of chemoradiation, all patients were followed up after every 4 weeks for the next two months to assess the acute toxicity till the day 90 from the commencement of treatment and also to assess the response to the treatment. All acute toxicities were recorded according to the Radiation Therapy Oncology Group (RTOG) guidelines (Cox et al., 1995) apart from the acute kidney injury, which was recorded according to the Common Toxicity Criteria grading system. Disease control was assessed clinically or with direct laryngoscopy whenever indicated till two months from the completion of treatment. The response to treatment were graded as complete response (CR) or partial response (PR) and no response (NR). Response was evaluated for the primary tumor site and the loco-regional lymph nodal sites. An overall response rate was also assessed which included both primary tumor site response as well as regional nodal response.

Statistical analysis

All data were tabulated in Microsoft Excel and analysed with SPSS (Statistical Package for Social Sciences) software version 20. The response to treatment was correlated with various prognostic variables by using the Chi-square test. p-value less than 0.05 was taken to be statistically significant.

Results

During the study period, 287 patients of HNCA satisfied our study criteria. The baseline characteristics of patients, tumors and the treatment variables are depicted in Table 1. 58.2% of the patients were of age less than or equal to 50 years. 65.9% of the study patients were males. Cancers of the oral cavity were the most commonly found primary tumors accounting for 36.9% of the patients, while 31% of the study patients had primary oropharyngeal cancers. According to the AJCC 7th edition staging, 51.6% of the patients presented with T3 primary tumors and 39.4% patients had N2 nodal disease. Majority of the patients presented with Stage IV disease. There were no patients with Stage I disease and only 7.3% study patients presented with Stage II disease. A total radiation dose of 66 Gy was delivered in 68.3% of the study patients, while the rest were administered a dose of 70 Gy. Most of the patients treated in 2014, were treated upto 70 Gy due to the better tolerance of concurrent chemoradiation over the years. 83.6% of the study patients received more than 4 cycles of concurrent weekly cisplatin. The mean overall treatment time was 57 days. Only 57.1% patients completed their overall treatment within 57 days. This prolonged overall treatment time was mostly due to the reluctance of the patients (most of whom were rural) and some due to non-compliance to treatment. 110 patients of the 123 who had overall treatment time more than 57 days, were reluctant to come for daily treatment, while treatment time was prolonged due to treatment non-compliance in only 13 of these 123 patients.

Response rates

Response to treatment was assessed till two months after the completion of treatment. Complete response in primary tumor site, regional nodal site and overall was seen after treatment completion in 81.2%, 77% and 67.2% patients respectively. Partial response to treatment

in primary site of the tumor, regional nodal site and overall was observed in 17.1%, 20.9% and 28.9% patients respectively. No overall response was seen in 11 patients

Table 1. Patient, Disease and Treatment Variables in the Study

	Number of patients (n = 287)	Percentage of patients
Age		
≤ 50 years	167	58.2
> 50 years	120	41.8
Sex		
Male	189	65.9
Female	98	34.1
Primary tumor site		
Oral cavity	106	36.9
Oropharynx	89	31
Hypopharynx	47	16.4
Larynx	45	15.7
Histopathological Grade		
Well Differentiated	88	30.7
Moderately Differentiated	165	57.5
Poorly Differentiated	34	11.8
T Stage		
T 1	20	7
T 2	73	25.4
T 3	148	51.6
T 4	46	16
N Stage		
N 0	64	22.3
N 1	67	23.3
N 2	113	39.4
N 3	43	15
AJCC Stage		
Stage II	21	7.3
Stage III	99	34.5
Stage IV	167	59.4
RT dose delievered		
66 Gy	196	68.3
70 Gy	91	31.7
Number of cycles of Chemotherapy		
≤ 4	47	16.4
> 4	240	83.6
Overall treatment time		
≤ 57 Days	164	57.1
> 57 Days	123	42.9

Table 2. Response rates to treatment

Types of Response to treatment	Number of patients	Percentage of patients
Primary tumor response		
CR	233	81.2
PR	49	17.1
NR	5	1.7
Regional nodal response		
CR	221	77
PR	60	20.9
NR	6	2.1
Overall response		
CR	193	67.2
PR	83	28.9
NR	11	3.8

CR = Complete response, PR = Partial response, NR = No response

Table 3. Acute Toxicity in the Study Patients

Acute toxicities	Grades of toxicity	Number of patients	Percentage of patients
Mucositis	0	14	4.9
	I	32	11.1
	II	104	36.2
	III	97	33.8
	IV	40	13.9
Dermatitis	0	52	18.1
	I	35	12.2
	II	97	33.8
	III	72	25.1
	IV	31	10.8
Emesis	0	4	1.4
	I	192	66.9
	II	72	25.1
	III	19	6.6
Anemia	0	147	51.2
	I	91	31.7
	II	45	15.7
	III	4	1.4
Leucopenia	0	202	70.4
	I	36	12.5
	II	32	11.1
	III	13	4.5
	IV	4	1.4
Thrombocytopenia	0	269	93.7
	I	15	5.2
	II	3	1.1
Acute kidney injury (CTCAE)	0	233	81.2
	I	49	17.1
	II	5	1.7

CTCAE = Common Toxicity Criteria for Adverse Events

(Table 2). On applying Chi-square test, site of primary tumor (p-value <0.001), stage of disease (p-value <0.001), total radiation dose delivered (p-value <0.001) and overall treatment time (p-value 0.023) demonstrated statistically significant correlation with the overall tumor response to treatment.

Acute toxicity

Acute toxicities in the study patients have been depicted in Table 3. Grade II, III and IV mucositis was present in 36.2%, 33.8% and 13.9% patients respectively. RTOG Grade II, III and IV skin toxicity was seen in 33.8%, 25.1% and 10.8% of the study patients respectively. Apart from four patients, all the study patients had vomiting episodes inspite of the administration of the antiemetics. 51.2%, 70.4% and 93.7% of the study patients did not have any anemia, leukopenia and thrombocytopenia respectively. In terms of acute kidney injury as graded according to the CTCAE Version 4, 17.1% and 1.7% patients had Grade I and Grade II toxicity respectively. Majority of the toxicities occurred in between the 3rd week and 7th week of treatment initiation.

Discussion

The present study reports one of the largest single-institutional experience of concurrent weekly cisplatin based chemoradiation in the non-surgical management of HNCA in South India. The aim of this study was to

address the patient and tumor characteristics in South Indian setting and the post-treatment tumor response rates and acute morbidity associated with concurrent weekly cisplatin based chemoradiotherapy.

The mean age of presentation with HNCA in our study was 48.8 years. This is quite low when compared to western literature (Fan et al., 2012). But similar mean age of presentation has been reported in Indian studies (Gupta et al., 2009; Dimri et al., 2013). The earlier age of presentation in the current study may be attributed to the rampant use of chewable tobacco, smoking and also reverse smoking. There was a relatively higher rate of HNCA in females in the current study when compared to other Indian studies (Dimri et al., 2013), which can be attributed to the higher incidence of reverse smoking and smoking in the study population. The most commonly encountered primary tumors were that of oral cavity (hard palate mostly), which can be again attributed to the practice of reverse smoking in this part of the country and also the habit of chewing tobacco and betelnut. Similar to some other Indian studies (Lasrado et al., 2014), more than 50% tumors were moderately differentiated. Alike other Indian studies (Gupta et al., 2009; Dimri et al., 2013), T3 tumors were the most common primary tumors. Majority of the study patients presented with AJCC Stage III or IV tumors, which is in concordance with data from other developing countries (Pruegsanusak et al., 2012). Similar to other regional studies (Dimri et al., 2013), 83.6% patients received more than 4 cycles of weekly cisplatin with concurrent radiation. The mean overall treatment time was higher in the current study when compared to other literature, because most of the present study patients were illiterate and came from rural background, hence were many a times reluctant to come for treatment even after repeated counselling. Very few patients were actually delayed treatment due to non-compliance.

A meta-analysis (Pignon et al., 2009) with a total of 87 trials and 16,485 patients demonstrated a 4.5% absolute benefit of chemotherapy at 5 years. Also, both direct and indirect comparisons demonstrated a more pronounced benefit with concurrent chemotherapy when compared to induction chemotherapy. The absolute benefit was 6.5% at 5 years. Cisplatin acts synergistically with radiation in the treatment of HNCA in the following ways- as a radiosensitizer by inhibiting potentially lethal and sublethal damage repair, as a hypoxic cell sensitizer, as a cell cycle inhibitor, by forming deoxyribonucleic acid adducts and as an inhibitor of angiogenesis (Marcu et al., 2003). The use of 3 weekly cisplatin at 100 mg/m^2 concurrently with radiation is recommended now in the non-surgical management of locally advanced HNCA for organ preservation (Adelstein et al., 2003; Forastiere et al., 2003; Pignon et al., 2007). But only 60% of the patients actually remain fit enough to receive the desired 3 cycles of chemotherapy due to higher systemic and mucosal toxicities (Brizel et al., 2006). The non-compliance is even more in developing countries due to the limited resources (Dimri et al., 2013). Few studies have demonstrated comparable efficacy of weekly moderate dose cisplatin based chemoradiotherapy with less toxicity and better patient compliance, especially in developing countries with limited resources (Gupta et al., 2009; Dimri et al., 2013). The post-treatment response rates of tumors to concurrent chemoradiation with weekly cisplatin based regime was found to be similar to that reported in literature (Dimri et al., 2013). They found 86% and 89% complete response in primary tumor site and lymph nodes respectively.

In the laryngeal preservation trial by Forastiere et al. (Forastiere et al., 2003), only 70% patients received the desired 3 cycles of high dose cisplatin during radiation. Also Grade III or IV pharyngitis, haematological toxicity, emesis and nephrotoxicity were seen in 78%, 47%, 20% and 4% of the study patients respectively. Whereas, a HNCA study (Dimri et al., 2013) from India with weekly 35 mg/m^2 cisplatin based chemoradiation demonstrated acute Grade III or IV mucositis, emesis, anemia and leukopenia in 67%, 3%, 0.5% and 0.5% patients respectively. Another study (Gupta et al., 2009) demonstrated acute Grade III or IV mucositis and dermatitis in only 29% and 35% of the study patients respectively. Similarly, in the present study acute Grade III or IV mucositis, dermatitis, emesis, anemia and leukopenia were seen in 47.7%, 35.9%, 6.6%, 1.4% and 5.9% study patients respectively. Even though most of the patients were from rural background and lacked proper nutrition, the high grade toxicities were quite comparable to other regional studies. Another study (Geeta et al., 2006) with 40 mg/m^2 cisplatin based chemoradiotherapy demonstrated an overall treatment compliance of 65%, significant hematologic toxicity of around 20% and treatment related hospital admissions of approximately 30%.

In conclusion, the treatment of HNCA with 40 mg/m^2 weekly cisplatin based chemoradiation is an effective and less toxic regime. It can be especially used in developing nations with limited resources, where intensive in-patient nursing care throughout the period of chemoradiation is not possible. The patient compliance also improves, thereby curtailing treatment breaks and improving tumor control. A long-term follow up randomized controlled trial should be undertaken in our setting to further estimate the efficacy of this regime when compared to the 3 weekly cisplatin based chemoradiation.

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