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Original Article

Oncology Section

Feasibility and Response of Concurrent Weekly Docetaxel with Radical Radiotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Objective: (1) To study the feasibility, adverse effects and response of concurrent weekly Docetaxel with radical radiotherapy in inoperable locally advanced head and neck squamous cell carcinoma. (2) To assess the compliance and tolerance of weekly Docetaxel with radiotherapy.

Material and Methods: Twenty one patients with stage III and IV head and neck squamous cell carcinoma satisfying inclusion criteria were selected and treated with conventional external radiotherapy of 70Gy in 35 fractions with weekly concurrent Docetaxel (15mg/sqm), administered one hour before radiotherapy. Assessment of toxicities and evaluationof response was carried out.

Results: Majority of patients had stage IV diseaseand 17/21 (81%) received the planned radiotherapydose of 70Gy and ≥4 cycles of weekly chemotherapy. Duration of treatment ranged from 7.1to 11.2 weeks. The toxicities noted were Grade III mucositis in 57% and grade III skin reaction in 23%, grade III dysphagia in 38% and grade II weight loss in 23% of patients. Systemic toxicities associated with chemotherapy were minimal and there was no dose limiting toxicities. The overall locoregional response at first follow up was 85%, with complete response of 70% and partial response of 15%.

Conclusion: Concurrent Docetaxel is a feasible and suitable alternate to Cisplatin and 5-Fluorouracil chemotherapy with good patient compliance. The late toxicities and survival need to be followed up.

Keywords: Chemoirradiation, Cisplatin, Head and neck cancer

INTRODUCTION

Head and neck cancers, is among the ten most frequent cancers in the world and is common in regions with high prevalence of tobacco and alcohol habits. They account for one-fourth of male and one-tenth of female cancers in India [1]. Standard treatment of locoregionally advanced, inoperable squamous cell head and neck cancer (in patients who are not considered for palliative treatment) is a combined modality approach with radiotherapy and chemotherapy as majority of the patients following single modality develop locoregional recurrence. The addition of chemotherapy to radiotherapy results in significant improvement in locoregional control and survival [2-5].

Natural history of head and neck malignancy mainly intent the need for loco regional control and systemic control need to be addressed secondly. An aggressive treatment for locoregional control of disease has to be evolved. Concomitant chemoirradiation is a strong support for the above theory [2].There are enough clinical studies and meta – analysis of those studies emphasis the importance of concomitant chemoirradiation as a better treatment modality in locally advanced head and neck malignancy [3-5]. Thus, the outcome with combined modality approaches with chemo radiotherapy seems to be superior to radical radiotherapy alone or sequential therapy.

Chemotherapeutic drugs that have shown activity in the treatment of squamous cell carcinoma of head and neck when combined with radiation include Methotrexate, Bleomycin, Mitomycin C, 5-fluorouracil, Carboplatin and Cisplatin. Meta-analysis of the studies of concurrent chemoirradiation has shown five year survival advantage of 8% in head and neck cancer [4,5]. Cisplatin is the most commonly used agent in majority of the studies, but is associated with several toxicities, especially renal and vestibulocochlear complications [6]. This often results in limitation in administration of essential cycles of concurrent Cisplatin with radiation and also cannot be administered to patients with poor renal function and defective hearing.

Taxanes are one of the newer chemotherapeutic agents that have shown good response rate in locally advanced and metastatic head and neck cancer in initial trials [7]. Docetaxel is a novel semisynthetic agent that acts by enhancing tubulin polymerization and inhibiting microtubule depolymerisation. The radiation sensitizing effect of Docetaxel has been confirmed in vitro and is probably related to cell synchronization effect [8]. This leads to cell cycle arrest in G2/M phase, which is known to be 2.5 times more sensitive to radiation than G1/S phase [8]. The affinity of Docetaxel for the tubulin binding site is 1.9 times greater than that of Paclitaxel and in vitro studies have demonstrated that the intracellular half-life of Docetaxel is three times that of Paclitaxel, leading to higher intracellular levels of Docetaxel in the steady state [9]. The maximum tolerated dose of Docetaxel is 100mg/sqm every 21 days and short-lasting neutropenia is the dose-limiting toxicity [10]. Other significant toxicities include alopecia, mucositis, fatigue, sensory neuropathy, fluid retention, and rash and hypersensitivity reactions. Phase II studies of Docetaxel as a single agent in patients with squamous cell carcinoma of the head and neck (SCCHN) has documented response rates of 27% to 43% [11]. Since chemoirradiation showed definite advantage in reducing mortality of head and neck cancer [12] and low dose weekly chemotherapy during radiotherapy had shown equal benefits with other multi drug regimens [13], a combination of weekly docetaxel with radiation was attempted.

Several phase I and phase II studies showed that conventional radiotherapy can be combined with weekly Docetaxel (doses between 10mg/sqmand 20mg/sqm) with acceptable toxicity and activity [14-16]. Therefore, this would be a good alternate to Cisplatin in patients with poor renal function and defective hearing.

A prospective single arm study of radiotherapy and concurrent weekly Docetaxel (15mg/sqm) for locally advanced head and neck cancer was conducted to assess the feasibility and response.

MATERIALS AND METHODS

A prospective single arm study of radiotherapy and concurrent weekly Docetaxel for locally advanced inoperable head and neck cancer was conducted after obtaining Institutional Research Committee and Ethics Committee approval. All patients with locoregionally advanced squamous cell carcinoma of oral cavity, oropharynx, hypopharynx and larynx (stage 3 and 4), seen fromSeptember 2006 to August 2007 who fulfilled the inclusion and exclusion criteria were included in the study. All patients were informed about the treatment protocol and written informed consent was obtained to participate in the study.

Pre treatment evaluation

Detailed history and physical examination was done in all patients. Flexible nasopharyngo laryngoscopy (NPL scopy) was done for assessment of extent of primary disease and staging before starting the treatment. Biopsy of the primary tumor site or fine needle aspiration of clinically significant nodes was done. Necessary blood investigations (haemoglobin, blood counts, hepatic and renal function) and radiological evaluation like chest x-ray, soft tissue of neck, barium swallow and orthopantomogram were done in selected cases. ECG and ECHO were done prior to administration of chemotherapy. CT scan or MRI scan of head and neck were done in relevant situations only. All patients had pre-RT dental check up and dental clearance was obtained before starting radiotherapy.

Inclusion criteria

Patients with histologically proven inoperable squamous cell carcinoma of larynx, laryngophaynx, oropharynx and oral cavity of stages III and IV (T3-4 and N0-3, T1 N2-3 and N2-3 and T2 N1-3) with ECOG of 0,1 or 2 with normal liver, renal and bone marrow function were included in the study.

Exclusion criteria

Patients with metastatic disease, previous history of treatment with radiotherapy, chemotherapy or surgery, more than one site of malignancy, chronic medical illness which would compromise treatment and any co-existing medical problems with contraindication for Docetaxel were excluded from the study.

Treatment Radiotherapy

Technique: Radiotherapy was delivered with Cobalt-60 or 6MV photons using parallel opposed lateral fields to encompass the primary tumor and the upper neck nodes to midplane. The lower neck was treated by direct anterior field prescribed to 3cm depth for telecobalt or dmax for 6 MV photons.

Dose: The primary and the clinically/radiologically significant neck nodes were planned for a radical dose of 70Gy in 35 fractions over seven weeks, with prophylactic dose of 50Gy in 25 fractions for microscopic disease, delivering 200cGy per fraction, to midplane, 5 fractions per week. Spine shielding was done at 40Gy and 10 to 30Gy equivalent dose were delivered to posterior neck using 9MeV electrons. Lower neck was treated to 46Gy in 23 fractions.

Chemotherapy

Docetaxel was administered at 15mg/sqm, one hour infusion before radiotherapy on weekly basis starting from day 1 of radiotherapy and repeated on D 8, 15, 22, 29, 36 and 43.

Evaluation during treatment

All patients were evaluated weekly during treatment clinically and blood investigations (haemoglobin, blood counts, hepatic and renal functions) were done prior to each cycle of chemotherapy. Docetaxel was not administered if the serum bilirubin was greater than the upper limit of normal (ULN). Dose of Docetaxel was reduced by 20% in patients who developed grade 3 or 4 diarrhea, liver enzymes greater than five times the ULN, and grade 2 palmar-plantar toxicity.

Chemotherapy was not administered if any focal signs of infection, total blood counts <3000/cubicmm, absolute neutrophil count < 1500/cubicmm, platelet count< 100000/cubicmm. Chemotherapy administration was delayed or omitted and radiotherapy was interrupted / stopped when patients developed grade III mucositis or skin reactions. Minor side effects were managed symptomatically.

Weekly assessment

All patients were monitored weekly and assessment was done according to common toxicity criteria (Cancer Therapy Evaluation Program Common Toxicity Criteria, Version 2.0DCTD, NCI, NIH, DHHS April 1999).

Response assessment and Follow up

Response assessment was done by clinical evaluation and NPL scopy. In suspicious cases CT scan was done for confirmation of the response (Response Evaluation Criteria for Solid Tumours, RECIST version 1.0). All patients were advised to come for follow up six weeks after treatment and every three months in the first year, every six months in the second year, and every year thereafter. During follow up visits patients had clinical assessment and endoscopies to assess locoregional disease and also assessment for late radiation toxicities.

Data analysis

The data was entered in excel spread sheet and analysed using the epi info software (supplied by the Centre for Diseases Control, Atlanta, USA).

RESULTS

Patient characteristics

A total of 21 patients were enrolled in the study from September 2006 to August 2007. All patients received chemoirradiation as per study protocol. Data collected from all the patients was assessed and evaluated during follow up visits, at six weeks and subsequent visits after completion of the treatment. Baseline characteristics are described in [Table/Fig-1]. Twenty one eligible patients were studied which included 19 males and 2 females. The age ranged from 38-75y, with majority of the patients in the age group 50 to 60 years (42.9%). All patients had a performance status of ECOG 0-1 and majority of patients had stage IV disease (IV A -52.4% and IV B - 4.8% disease).

Treatment characteristics

Among the 21 study patients, 17(81%) tolerated 70Gy of radiation and of the remaining 4 patients, one (4.8%) received 64Gy and 3 patients (14.3%) tolerated <60Gy. Nineteen patients received radiation by conventional technique using Cobalt-60 and remaining 2 with conformal technique using 6MV photons on Linear Accelerator. Median duration of treatment was 8.2 wk (range 7.1- 11.2 wk). 17 out of 21 patients (81%) completed the planned radiotherapy (70Gy) treatment, 19 out of 21 patients (90%) tolerated four or more cycles of concurrent chemotherapy and remaining two patients had three cycles of chemotherapy.

Toxicity

Breaks in external radiotherapy and total duration of treatment along with reason for breaks in treatment were analysed in detail. Majority of our patients (94%) completed treatment within 9 wk. Five patients

	Total no of subjects=21	
Characteristics	**Median**	**Range**
Age, years	55	38-75
Performance status	Total	%
ECOG 0	8	38.10%
ECOG 1	13	61.90%
Site of Primary		
Oral cavity	1	4.80%
Oropharynx	9	42.90%
Hypopharynx	6	28.60%
Larynx	5	23.60%
Stage group		
Stage III	9	42.90%
Stage IV A	11	52.40%
Stage IVB	1	4.80%
Histology		
Well diff sq cell carcinoma	1	4.80%
Mod. diff sq cell carcinoma	13	61.90%
Poorly diff sq cell carcinoma	7	33.30%
	Median	**Range**
Base line haemoglobin (gm%)	11.7	8.9-15.2

[Table/Fig-1]: Baseline characteristics
Abbreviations: ECOG = Eastern Co operative Oncology Group

(29%) completed treatment without any breaks. There were only < 2 breaks in all except one patient, with an average of eight days break during the treatment period.

Locoregional toxicity: Mucositis and skin reaction were the major toxicities observed. Grade III mucositis was noticed in 57% of patients during 5th, 6th and 7th week of radiotherapy. Skin reaction developed from 3rd week onwards and grade III skin reaction was seen in 23%. Treatment related dysphagia was experienced after 3rd week of treatment. Grade III dysphagia developed in 8 patients (38%) and required nasogastric tube feeding, the remaining were managed conservatively with analgesics. Grade II weight loss was experienced in 5 patients (23%).

Systemic toxicities: Frequency of systemic toxicities and infections observed during treatment are described in [Table/Fig-2,3]. Grade III thrombocytopenia was observed in 1 patient and 2 had drop in haemoglobin of <8gm%during treatment. Grade III neutropenia and febrile neutropenia were not seen in our study. One patient experienced prolonged constipation and developed intestinal obstruction. He presented with features of acute abdomen and fever and expired in casualty. Subsequent postmortem analysis showed features of duodenal ulcer with perforation.

Response of treatment

The median follow-up period was eighteen months [Range 6 to 36 months]. Among the 21 patients, 20 patients were available for first follow up (at 6 wk) evaluation. Fourteen patients (70%) had complete response,three (15%) had only partial response and remaining three(15%) did not show any significant response. So, over all response rate for the regime was 85%.One patient expired during study period and so not counted for evaluation. All the patients who had a complete response had received ≥4 cycles of concurrent chemotherapy. The complete responders were undergone regular follow ups as per the protocol. Palliative chemotherapy with Cisplatin and 5-Fluorouracil was administered for partial responders and those who had residual/recurrence at follow-up. Three patients recurred during 2nd year and two lost to follow up after 3rd year.

Toxicities	Grade 0	Grade I	Grade II	Grade III	Grade IV and V
Anaemia	8(38%)	8(38%)	3(14%)	2(9.5%)	
Neutropenia	18(85.6)	2(9.6%)	1(4.8%)	(0%)	
Thrombocytopenia	18(85.6%)	2(9.6%)		1(4.8%)	
Renal					
S. Creatinine	20(95.2%)	0%	1(4.8%)		
Liver					
SGOT	15(72%)	3(14%)	3(14%)		
SGPT	7(33.8%)	9(43.2%)	5(23%)		
ALP	18(85.6%)	3(14%)			
Peripheral edema	19(90.4%)	0%	2(9.6%)		
Alopecia		0%			
Vomiting		0%	1(4.8%)		
Diarrhea		1(4.8%)			
Constipation	18(85.6%)	2(9.6%)			1(4.8%)
Weight Loss	5(23%)	11(52%)	5(23%)		

[Table/Fig-2]: Systemic toxicities

Systemic infection	
1. Respiratory infection	4(19%)
2.Skin abscess	4(19%)
3.Oral candidiasis	11(52%)
4. Febrile neutropenia	0%

[Table/Fig-3]: Systemic infection

DISCUSSION

Benefits of concurrent chemoirradiation in locally advanced head and neck mailgnancy have been widely discussed in many clinical trials and review of the literature showed a 11% overall reduction in mortality [12]. The optimum chemotherapy regimen is not yet known. Platinum combinations, in particular Cisplatin and 5-Fluorouracil, are generally regarded as the "gold standard," but low dose daily single agent chemotherapy may be equally effective as the 4 weekly combination schedules with Cisplatin and 5-Fluorouracil [13].

Newer chemotherapeutic agents have been tried in head and neck cancer, as single agent or in combination with Cisplatin and 5-Fluorouracil. Docetaxel is one of the newer agents which showed an overall response rate between 21% and 42% in patients with recurrent and metastatic squamous cell carcinoma of the head and neck [11] and initial studies with weekly Docetaxel and concomitant radiotherapy showed promising results [14-16]. This particular study attempted to evaluate the feasibility, tolerance and outcome of concurrent Docetaxel with radiotherapy in treating locoregionally advanced inoperable head and neck cancer.

In GORTEC [17] phase II trial (98-02) with concomitant weekly Docetaxel 20mg/sqm and radiotherapy, in carcinoma oropharynx stage III and IV the 3 year overall survival was 47% with locoregional control of 64%. Eventhough these results were comparable with concomitant chemoirradaition studies with Cisplatin or 5–Fluorouracil, the grade III and IV mucositis (84%) and skin toxicities (53%) were high and grade 3 or 4 neutropenia was seen in 5% of the patients. Few phase I studies of weekly Docetaxel with lower doses (10mg/sqm escalating to 20mg/sqm) along with radiotherapy in locally advanced head and neck carcinoma have been reported. They recommended a phase II dose of 12 to 15 mg/sqm for concurrent chemoirradaiton [14-16].

In view of this we administered Docetaxel at 15mg/sqm weekly along with radiotherapy. We included patients with oral cavity, oropharynx, larynx and hypopharynx malignancy with stage III and stage IV disease. Among them 81% (17) received the total dose of 70Gy and 90% (19) received 4 or more cycles of chemotherapy.

Duration of treatment ranged from 50 to 79 d (7.1to 11.2 wk) which is similar to that observed in the GORTEC trial with Docetaxel [17], where the duration of treatment ranged from 49.8 to 77 d while in the Inter group trial [18] with Cisplatin and 5-Fluorouracil arm, it was 46 to 91 d. The major toxicity that occurred in our study was mucosal reaction (grade III-57%), and this was higher than that observed in the RTOG trial [19] with single agent Cisplatin where Grade III mucositis was 28% In the GORTEC trial [17] with 20mg/sqm Docetaxel, it was 84% which is more than that observed in our study. Study by Fujii et al., [16] using a lower dose of Docetaxel (10mg/sqm) showed 41% grade III mucositis and in the Inter Group trial [18] with Cisplatin and 5-Fluorouracil it was 44% which is nearly similar to that observed in our study [16].

Grade III skin reaction noticed in our study was 23%, which was more than that reported in the Intergroup trial [18] where it was 7% and in a study with lower dose of Docetaxel (10mg/sqm) [16] where it was only 2.9%, while it was much higher (53%) in a study using higher dose of Docetaxel (20mg/sqm) [17].

The percentage of patients who experienced grade III dysphagia requiring nasogastric tube during treatment was 38% and grade II weight loss (>10% of the initial weight) was 23%. In the GORTEC trial [17] where higher doses of concurrent Docetaxel (20mg/sqm) was used, 41% required temporary nasogastric or gastrostomy feeding tubes and 20% of patients lost more than 10% of body mass, which is similar to that seen in our study. But in Intergroup trial [18] with Cisplatin and 5-Fluorouracil,Grade III dysphagia was observed in 49%, which was higher than that of our study.

The systemic toxicities experienced in this study with concurrent Docetaxel and radiotherapy were mild and manageable. These toxicities never interfered treatment process. One patient lost life during the treatment period and exact cause of death was unrelated to therapy and primary disease condition.

The locoregional response during first follow up at 6 wk after completion of treatment was complete response in 70% and partial response in 15% patients. The initial complete response seen in our study is superior to that seen in the Intergroup trial [18] with Cisplatin and 5-Fluorouracil where it was 49% and RTOG trial [19] using single agent Cisplatin where it was 71%. In general as this regimen has comparable loco-regional response and complications, with lower risk of systemic toxicities like febrile neutropenia, neurological and cardiological complications, no renal damage and no dose limiting toxicities makes it a very feasible and an attractive option. Unlike Cisplatin containing regimens it is not contraindicated in patients with low creatinine clearance and moreover, this regimen does not need ambulatory pumps, central venous access, or prolonged hospitalization as for infusional 5-Fluorouracil.

Therefore this schedule along with the convenience of once weekly infusion as outpatient makes this regimen a good, suitable and feasible alternative to platinum and infusional 5-Fluorouracil which is presently the standard regimen for chemoirradiation in head and neck malignancy. However the late toxicities, long term response and survival need to be followed up.

CONCLUSION

In this study, chemoirradiation using weekly Docetaxel for locally advanced inoperable head and neck cancer, major toxicities like mucositis and dermatitis were comparable to other studies with no dose limiting or unacceptable complications. Initial overall response seen was good. Weekly Docetaxel of 15mg/sqm concurrent with radiotherapy was well tolerated by majority of our patients with a favorable toxicity profile and good efficacy. Concurrent Docetaxel is a feasible option in head and neck malignancy. The late toxicities, long term benefits and survival need to be evaluated.

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