

Treatment Outcome with Weekly Cisplatin Concurrent with Radiation Therapy in Locally Advanced Head and Neck Squamous Cell Carcinoma.

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Abstract: This study was undertaken to investigate the feasibility of concurrent monochemotherapy with conventionally fractionated external beam radiotherapy and to assess its local response and acute toxicity patterns in patients with advanced locoregional head and neck squamous cell carcinoma (HNSCC). Between September 2005 and September 2007, a study involving 45 patients with stage III and IVA (AJCC-6th) HNSCC who met the eligibility criteria was undertaken. All 45 patients (median age 45 years) were given Cisplatin 40 mg/m² weekly before radiotherapy on every Monday. Patients received radiotherapy (66-70 Grays) to the locoregional sites on Cobalt-60 unit. **Results:** All the 45 patients who received concurrent chemoradiation were available for analysis. The locoregional response rates were as follows: an overall response rate of 88.8% (40 patients), complete response rate of 57.7% (26 patients), partial response rate of 31.1% (14 patients) and stable disease in 11% (5 patients). Only 2 (4.4%) patients were reported dead at the time of evaluation. The survived patients enjoyed good quality of life. **Conclusion:** Patients responded better with concurrent chemoradiotherapy with benefit in terms of survival and good organ preservation along with acceptable and manageable occurrence of schedule and dose related adverse effects.

Keywords: concurrent chemoradiotherapy; inoperable head and neck cancer

INTRODUCTION

Head and neck cancer comprises a huge burden of disease worldwide. It is the fifth most common malignancy globally among adults¹. It comprises 5% of all malignancies worldwide². More than 500,000 new cases are projected annually, globally³.

Loco regionally advanced stage III or IV cancers comprise $\geq 60\%$ of these tumors for which cure rates have been $< 30\%$, with notably high morbidity for surgical as well non-surgical treatment and therefore prognosis has remained poor in this group of patients and this has remained unchanged over the past 30 years.

The treatment of patients with locally advanced unresectable head and neck cancer remains a challenge with poor locoregional tumor control and limited survival when surgery, radiotherapy or both are used. Although radiation and surgery have been the standard of care, the addition of chemotherapy has demonstrated superior locoregional tumor control while showing promise to improve patient survival. In patients with advanced inoperable or unresectable disease, Paccagnella et al demonstrated improved survival after treatment with induction chemotherapy and definitive radiotherapy compared with controls treated with radiation alone. Concurrent chemoradiation has been investigated to take advantage of the radiosensitive capability of many drugs for patients with head and neck cancers to attain an increase in the locoregional control, which would translate into increased survival. The mechanism for enhanced cell kill with concurrent chemoradiation is due to interference with repair process after sub lethal and potentially lethal damage caused by drugs and tumor cell synchronization may also prevent or decrease the emergence of resistant clonogenes⁴.

There are many drugs, which have been investigated as radiosensitising agents such as bleomycin, methotrexate, mitomycin, 5-fluorouracil, cisplatin and paclitaxel. Cisplatin is one of the favored drugs because of its proved radiosensitising effect and its different toxicity profile. This drug has been most extensively studied in the management of HNSCC which can be used alone or in combined with variety of other drugs and has shown improved overall response rate ranging from 23% to 71% with a cumulative rate of 28%. This study was conducted to assess the role of concurrent cisplatin with conventional external beam radiotherapy in patients with locally advanced inoperable head and neck cancers. The objective of this study was to evaluate the response rate, locoregional control, disease free survival and

overall survival in previously untreated, inoperable head and neck cancer patients. The Institute ethical committee reviewed the study design and allowed to carry out the study.

METHODS

From September 2005 to September 2007, 45 patients of locally advanced head and neck cancer attending the department of Radiotherapy, Sher-i-Kashmir Institute of Medical Sciences, Srinagar were included in a prospective non-randomized trial of concurrent chemoradiotherapy. The inclusion criteria were as follows:

- Histopathologically confirmed squamous cell carcinoma of head and neck.
- Only locally advanced tumors (stage III and stage IV-A : Staging by AJCC) only.
- Patients not exposed to surgery, chemotherapy and radiotherapy for current disease.
- Performance status < 2 (ECOG) with any age group.
- No associated co-morbidity with contraindication to chemotherapy.
- Normal renal and liver function.
- Normal Hemogram.
- Written informed consent.

Patient characteristics are shown in table 1. Site and size of primary disease was assessed by inspection, direct and indirect laryngoscopy, and by other appropriate studies if required e.g. CAT scan. Clinically lymph node status was assessed and TNM staging was done as per UICC criteria. Complete blood profile, blood urea, serum creatinine was done before each course of chemotherapy.

Table 1: Epidemiological characteristics of all patients

Characteristic	No. of patients	Percentage
	Age	
10-20	1	2.2%
21-30	5	11.1%
31-40	5	11.1%
41-50	8	17.7%
51-60	12	26.6%
61-70	11	24.4%
71-80	2	4.4%
81-90	1	2.2%

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	Sex	
Male	35	77.7%
Female	10	22.2%
	Addiction	
Smoke	31	68.8%
Smoke + Other (Alcohol+Snuff+Ganja+Tobacco)	7	15.5%
No Addiction	7	15.5%
	Primary Site	
Larynx	19	42.2%
Hypopharynx	7	15.5%
Nasopharynx	4	8.8%
Oropharynx	7	15.5%
Oral Cavity	8	17.7%
	Stage	
III	20	44.4%
IV-A	25	55.5%

TREATMENT DESIGN

Treatment schedule was designed to optimize clinical efficacy and minimize the occurrence of schedule and dose related adverse events in patients. After proper evaluation, all patients received concurrent Cisplatin 40 mg/m² on the first day of every week before radiotherapy, which extended for four weeks in the initial treatment followed by two more weeks of treatment with supplementary radiation. Cisplatin was given by intravenous infusion in normal saline after proper hydration. Patients received potassium chloride, magnesium sulfate and mannitol infusion.

All patients received external beam radiation therapy on a telecobalt60 unit (Theratron 780E), five fractions a week for four weeks to the local site including neck nodes to a total dose of 45 Grays in the initial treatment. This was followed by supplementary radiation therapy of 25 Grays in ten fractions with reduced portals taking the total dose of radiation to 70 Grays excluding spinal cord and other structures wherever necessary.

EVALUATION AND FOLLOW UP

Before each course of concurrent chemotherapy, patients were evaluated and during treatment they were seen weekly by radiation oncologist for normal tissue reaction and tumor response. Routine investigations were performed and if required supportive treatment was given. As per RTOG toxicity criteria, adverse reactions were documented.

Patients were examined at the time of completion of radiotherapy, 6 weeks after completion of treatment and 3 monthly thereafter by radiation oncologist and by otorhinolaryngologist.

RESPONSE

If there was complete disappearance of all viable and palpable tumor without evidence of distant metastasis after completion of concurrent chemoradiotherapy these were considered as having complete response (CR) and where there was >50% regression of the longest perpendicular dimensions of the lesion or nodes, they were grouped under partial response (PR). Rest were considered as having stable disease (SD) or progression of disease (PD).

RESULTS

Tumor response to treatment was recorded in all 45 patients. This included a complete response in 26 patients (57.7%) and partial response in 14 (31.1%) and in 5 (11.1%) the disease remained stable. Among the 26

patients in whom complete response was achieved, recurrence was observed in 4 (15.3%). In two patients failure occurred at the locoregional area and in the other two distant metastasis was observed. These recurrences were observed within a mean follow up of 8 months from the time of local control. With respect to the site, the best response rate was achieved in hypopharyngeal tumors with a complete response rate of 71.4% followed by larynx (63.1%). Table 2 shows the response distribution in each subgroup of patients.

Table 2: Response rates in each subgroup of patients

Site	Patient No.	PR	CR	SD	OR
Larynx	19	6 (31.5%)	12 (63.1%)	1 (5.2%)	18 (94.7%)
Hypopharynx	7	1 (14.2%)	5 (71.4%)	1 (14.2%)	16 (85.7%)
Nasopharynx	4	2 (50%)	2 (50%)	0 (0%)	4 (100%)
Oropharynx	7	1 (14.2%)	4 (57.1%)	2 (28.5%)	5 (71.4%)
Oral Cavity	8	4 (50%)	3 (37.5%)	1 (12%)	7 (87.5%)
Total	45	14 (31.1%)	26 (57.7%)	5 (11.1%)	40 (88.8%)

At one year follow up, only 2 (4.4%) patients were reported dead. Survival was assessed (Table 3) with respect to the gender, age, site of primary tumor, stage, performance score of the patient, T, N and overall stage of the tumor and histopathological differentiation. No significant impact of T, N stage was observed as far as survival of the patients is concerned.

Table 3: Survival relative to patient characteristics

Patient Characteristic	Median survival in months (Kaplan Meier)	Result
Gender	Male	13
	Female	14
Performance Score	0	17
	1	14
	2	11
Age	≤45	15
	>45	12
Site	Larynx	13
	Hypopharynx	11
	Nasopharynx	14
	Oropharynx	14
T Stage	Oral Cavity	8
	1	17
	2	11
N Stage	3	15
	4	12
	0	14
	1	10
Overall Stage	2	14
	3	14
	III	13
HPE Differentiation	IV	14
	WD	11
	MD	15
	PD	14
	UD	17

ACUTE TOXICITY

Patients were assessed as per the Radiation Therapy Oncology Group (RTOG) toxicity criteria. Overall, the treatment was well tolerated by majority of patients. Vomiting occurred in 30% of patients, 14 (31%) patients were reported to have some degree of hematological toxicity and out of these 13 (93%) patients developed mild grade 1 or 2 leucopenia; out of all 45 patients only 1 (2.2%) developed severe toxicity, in the form of grade 3 thrombocytopenia. With a dose of 40 mg/m², no significant renal toxicity was observed in our study. Mucositis was observed in 42 (93%) patients in total. Chronic grade 1 and 2 xerostomia was observed in 28 (62%) of patients. Only 2 (4.4%) patients were reported dead in our study.

DISCUSSION

In developing countries like India, more than 60% of head and neck squamous cell cancers present with advanced disease and carry a poor prognosis which has remained unchanged over the past 30 years. When presenting disease is either inoperable or patients refuse surgical management, role of radiotherapy is limited and remain a challenging problem for the radiation oncologist. With primary radiotherapy given in maximum tolerable doses, locoregional recurrence remains the major pattern of treatment failure. Whether improvement in locoregional control will ultimately be translated to increase survival or not, is a matter of considerable debate⁵.

In patients who have locally advanced and inoperable cancer of the head and neck, the achievement of initial local control (complete response) of the disease with initial definitive treatment with radiotherapy with or without chemotherapy, is an important prognostic factor for overall survival. Complete response was found to be 69% in patients who had received cisplatin 100 mg/m² three weekly concurrently with definitive radiotherapy and the authors of the study concluded that the combination of cisplatin and radiotherapy is an effective and safe treatment in patients with advanced head and neck cancer⁶.

Laboratory data points towards increased radiation sensitivity, particularly under hypoxic conditions when cisplatin is used⁷. Cisplatin has been found to be inhibitive to the repair of sublethal damage.

In our study, where 44.4% of the patients had stage III and 55.5% had stage IV locally advanced cancer, the clinical response was very encouraging. Complete response was achieved in 57.7% of patients with an overall response rate of 88.8% when all the subsites of the head and neck cancer patients were combined. Highest combined response rate was seen in hypopharyngeal cancers where 71.4% achieved such response, lowest response rate was seen in oral cavity group where only 37.5% achieved complete response but overall response rate was 87.5%. Of the 4 patients of nasopharyngeal cancer 2 had complete response and the remaining 2 had partial response (overall response 100%). These two patients were treated with 6 cycles of combination chemotherapy of cisplatin plus 5-fluorouracil to take the complete response to 75%. Among the patients with laryngeal carcinoma, overall response rate was high (94.7%), whereas 63.1% achieved complete response. The patients with partial response were offered surgery but only one patient could be salvaged with such treatment.

Though the use of concurrent chemoradiation in head and neck cancer improves the local control of the tumor but at the cost of markedly increased toxicity due to combined radiotherapy and chemotherapy. Taylor et al⁸ used cisplatin 60 mg/m² and 5-fluorouracil 800 mg/m² in 14-day cycles with conventional radiotherapy. They demonstrated an improved freedom from recurrence in patients treated with chemoradiotherapy compared to induction

chemotherapy. There was, however, an increase in mucositis requiring supportive care in the concurrent group.

A recently completed intergroup study randomized patients with unresectable squamous cell cancers of the head and neck to radiotherapy alone, radiotherapy plus bolus cisplatin, or split course radiotherapy with first and third cycles of cisplatin and 5-fluorouracil. The 2 and 3 year actuarial survival rates were 23% for radiotherapy alone, 35% for radiotherapy plus cisplatin (P=0.016), and 27% for split course radiation plus cisplatin and 5-fluorouracil (P=0.13)⁹. At the time of evaluation of our study, 43 out of 45 (95%) patients were alive with a median survival of 14 months. T and N stage did not significantly affect the survival but it is presumed that appropriate survival analysis is undeserved owing to the early evaluation of results. However, the two patients who died had higher T and N stage.

The use of cisplatin weekly as an outpatient treatment is an extremely attractive schedule from the standpoint of delivery, tolerance, compliance and cost-effectiveness. The radiosensitive effects of cisplatin are evident from both the increase in toxicity as well as complete responses. Mucositis was the predominant toxicity occurring in majority of patients and requiring interruptions in radiotherapy and chemotherapy dose modifications. Concurrent chemoradiotherapy has been proved effective in the management of HNSCC because survived patients offered a good quality of life without any significant financial or cosmetic deficit.

CONCLUSION

Treatment of patients with advanced inoperable head and neck cancers with concurrent weekly cisplatin and conventional external beam radiotherapy is feasible. Mucositis was the most predominant and commonly seen toxicity. While survival data are too early to evaluate, the overall response rate and the high frequency of complete response rates are encouraging.

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I wish to express my gratitude for the help and guidance received from the Members of Board of Trustees and the Central Executive Committee members, of International Medical Sciences Academy, World Headquarters, New Delhi. I am also grateful for the valuable cooperation extended by the members of JIMSA Editorial and Advisory Boards; and also the peer reviewers, for their consistent and continuous effort and support to maintain a high standard of quality of the articles published in the journal.

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