Comparative Study

Concurrent Low Dose Carboplatin with Radiotherapy Versus Radiotherapy alone in Management of Locally Advanced Head and Neck Cancer Patients

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Abstract

A prospective study was performed to evaluate the efficacy and safety of concurrent chemotherapy with single agent low dose Carboplatin and radiotherapy on survival, functional and quality of life outcomes in locally advanced head and neck cancer patients. *Material and Methods :* Sixty inoperable, previously untreated locally advanced head and neck cancer patients were planned to be treated with radical radiotherapy 66 Gy with concurrent single agent chemotherapy with low dose Carboplatin 150 mg IV weekly up to 6.3 weeks (Group A) and conventional radical radiotherapy alone (Group B). *Results :* After completion of therapy in Group A complete response was observed in 19/30 (63%) patient and in control group B in 10/30 (33%).Grade II mucosal toxicities were observed in 40% of cases and 33 % of cases in study and control group respectively. *Conclusion :* Concomitant single agent chemo radiotherapy with low dose Carboplatin could be a better choice in advanced stage of Head and Neck carcinoma in terms of survival, acceptable toxicities together with enhanced response and quality of life.

Keywords

head and neck malignancies, concurrent chemotherapy, carboplatin, radio sensitizer

Introduction

Cancer of the head and neck is the frequent malignant tumour in world[1]. Annually, ten million new cancer cases are reported worldwide, out of which half a million are cancers of head and neck[2,3]. In India incidence is more than 25% of all malignancy. Majority of cases 70%- 80% are locally advanced (Stage III- IV) at the time of diagnosis with lymph node involvement in 30 -35 % of patients[4].

Currently management in these cases comprised multimodality approach which aims at improved survival, local control, reduction of distant metastasis and above all preservation of organ function without jeopardizing the overall outcome. In addition to radiotherapy and surgery, concomitant chemo radiotherapy is designed to be third definitive treatment in locally advanced head and neck cancer[6, 7].

Superiority of combined radiotherapy and chemotherapy to RT alone has shown in most of the randomized clinical trials in these tumours. Metaanalysis of chemotherapy on head and neck cancer MACH-NCI demonstrated 12% reduction in the risk of death corresponding to an absolute improvement of 4% in 5-year survival with CT & RT[8]. In most of the trials combination chemotherapy used with

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radiotherapy. These encouraging results and improvement in efficacy is accompanied by a significant increase in mucosal, cutaneous, hematologic toxicities. Worse impacts on nutritional status were also significant. Moreover, compliance, treatment interruption, prolonged treatment time were also major concern with combination chemotherapy.

To overcome these reactions without much impact on efficacy, single agent chemotherapy have been tried.

It is clear, the drug schedules that deliver drug in smaller doses on a more frequent basis are also quite effective in improving outcome. More frequent administration could provide radiosensitizing chemotherapy during a larger proportion of the course of RT.

Smaller individual doses of drug may lead to less chemotherapy induced morbidity without compromise of efficacy[9, 10].

Platin based chemotherapy is known to have dual properties such as direct action on malignant cells and radiosensitization. Carboplatin possesses well defined single agent activity against head and neck cancer, and produced excellent responses in previously untreated patients. As well as its ease of outpatient administration, lesser degree of nausea and vomiting, reduced nephrotoxicity, improved nutritional status during therapy and predictable myelotoxicity has important advantages over Cisplatin. These advantages prompted to use carboplatin in present study.

This study has been undertaken to analyze the efficacy in terms of loco-regional control, treatment related toxicities and quality of life with concurrent low dose carboplatin chemotherapy over radiotherapy alone in locally advanced cases of head and neck malignancy.

Material & Methods

In this study, 60 patients of carcinoma head and neck cases were enrolled and followed up.

Eligibility criteria were

- Previously untreated,
- Histopathologically proved patients of squamous cell carcinoma of head and neck region were randomly selected in the study group and control group.
- Only patients with stage III and IV were included in the study.
- All patients with their biochemical and haematological status within the normal limits were included.
- Patient with Karnofsky Performance status > 70.

A detailed history was taken and a thorough local and systemic examination was conducted. The following investigation were done in all patients: hemogram, renal function test, liver function test, chest x-ray, x-ray soft tissue neck, and CT scan face and neck if necessary. After clinical examination and routine investigations, patients were staged according to American Joint Committee on Cancer staging, 2002 staging system.

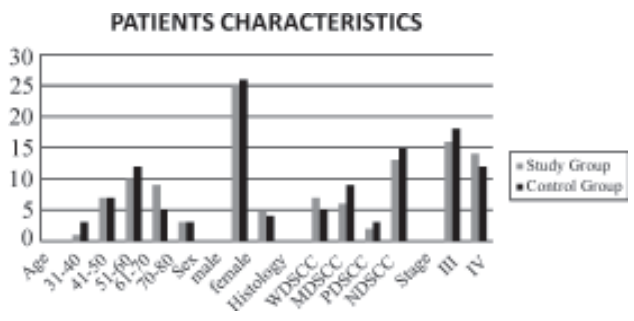
Patients were randomized into two separate groups of 30 patients each. The criteria for putting a patient in a group were random. Group A (the study group) receiving RT and chemotherapy; and group B (the control group) being treated by Radiotherapy alone. All the patients were planned and treated on Theratron 780 E and Equinox 80, cobalt 60 machine to a dose of 66Gy in 33 Fr /5 days/ week using bilateral parallel opposed field to face and neck. Spinal cord was spared after 44 Gy in each case.

In the study group chemotherapy was given concurrently on weekly basis. Chemotherapy consists of carboplatin 150 mg IV with proper hydration. During the whole course of treatment patients were closely observed for radiation reaction and acute toxicities. Patients were managed conservatively. Toxicities were graded as per RTOG toxicity criteria. After completion of treatment patients were kept on monthly follow up. On each follow up patients were assessed for response as well as acute and late toxicities.

Results

The majority of patient in the study were in 5th – 6th decade, mean age was 58 years. Male to female ratio in the study group was 5.0: 1 as compared to 6.6:1 in the control group suggested the incidence of the disease was predominant amongst the males (**Fig. 1**).

Fig. 1
Patients Characteristics



Response

After completion of treatment, patients who had no clinical evidence of disease either at the primary site or in the regional lymphnodes nor had any evidence if distal metastasis, were considered as 'complete remission'. Those who had > 50% decrease of the tumour size and regional lymph nodes were considered 'partial remission' (PR).

All patients were completed six months of follow up. As shown in **Table 1** & **2** 63.33% patients had no evidence of disease in the study group as compared to control group; 33% patients were disease free.

Table 1
Response after completion of treatment

No	Response	Group A		Group B	
		No	%	No	%
1.	CR	18	60	13	43.33
2.	PR	10	33.33	10	33.33
3.	NR	2	7	7	23.33
4.	PD	0	0	0	0

Table 2
Responses at the End of last follow up

No	Response	Group A		Group B	
		No	%	No	%
1.	NED	19	63.33	10	33.3
2.	Residual	8	27	15	50
3.	Recurrence	3	10	5	17

Toxicities

Acute toxicities were acceptable. More toxicity was observed in study group in comparison to control group. Toxicities were acceptable, neither interruption nor treatment prolongation were required in both groups. However, eight patients were required blood transfusion.

Table 3
Haematological toxicities in study group

Grade	Anaemia		Leucopenia		Platelets	
	No	%	No	%	No	%
0	5	17	19	63	21	70
I	13	43	8	27	6	23
II	8	27	2	7	2	7
III	3	10	1	3	1	3
IV	1	3	—	—	—	—

Table 4
Cutaneous toxicities during radiation therapy

Grade	Study Group		Control Group	
	No	%	No	%
I	18	60	22	73
II	10	33	8	27
III	2	7	—	—
IV	—	—	—	—

Table 5
Mucosal toxicities during treatment

Grade	Study group		Control group	
	No	%	No	%
1	8	27	18	60
2	12	40	10	33
3	10	33	2	7
4	—	—	—	—

Discussion

Cancer of the head and neck constitutes one of the commonest malignancies in India. Radiotherapy has been the main mode of treatment for head and neck cancer. But

still the results are not satisfactory as incidence of local recurrence and distant metastasis is high. The major cause of failure of radiation to control large tumours, whether primary or secondary is the presence of hypoxic malignant cells at or near the centre of the tumour and their decreased radiosensitivity[12]. The existence of hypoxia both in head and neck primary tumors and metastatic lymphnodes has adverse impact on the prognosis of patients treated with radiotherapy[13, 14].

The rationale for concurrent chemoradiation is that chemotherapy can sensitize tumours to radiotherapy by inhibiting tumour population, killing hypoxic cells, inhibiting the repair of sublethal radiation damage, sterilizing micrometastatic disease, to increase local control by overcoming radioresistance and to eradicate systemic micrometastasis and decreasing the tumour mass which leads to improved blood supply and reoxygenation[15]. whereas radiotherapy may sensitize tumors to chemotherapy by inhibiting the repair of drug induced damage and by decreasing the size of the tumor mass, repair of drug induced damage and by decreasing the size of the tumor mass, leading to improved blood supply and enhanced drug delivery[15].

In phase II studies clinical CR reported is in the range of 65% and 70%, with weekly concurrent carboplatin with radiation therapy in these tumours[15]. Jeremic B *et al* studied 159 patients of head and neck cancer with stage III and IV and carboplatin infusion 25 mg /m^2 daily used during External radiotherapy and observed a significantly higher overall response rate with a p value of 0.0011 and a significantly longer median survival time[16].

Ausili Cefaro G *et al* studied the use of prolonged continuous infusion of carboplatin and concomitant radiotherapy in advanced head and neck cancer patients. They used carboplatin in a dose of 30 mg/m^2 body surface area for a period of 14 days. Total dose of 420 mg of carboplatin and External radiotherapy 65-70 Gy with standard fractionation was used and they observed complete response in 7 patients out of 17 patients[17].

Marmiroli L *et al* published report of combined radio chemotherapy for organ preservation in head and neck cancer. In 1992 a protocol of concomitant radiochemotherpy with continuous infusion of carboplatin for 14 consecutive days at the daily dose of 30mg/m^2 and concomitant radiotherapy with conventional fractionation (1.8Gy to a total 65-70 Gy) was started. Over a 3- year period, 56 patients with advanced head and neck cancer were treated. Most patients were stage III (7) and IV (17 - 65%); T4 20%, N3 23%, 17/20 patients (70%) showed complete clinical response, 6 partial clinical response with a single non responder (overall response 95%). After a mean follow up from 22 to 60 months, 9 patients were still free of diseases (37.5%) median survival was 26.7 months; 38 months in responders, 2 years survival of patients with complete response was 59%[18].

Glicksman AS *et al* in their study with concurrent Cisplatin and hyper fractionated radiotherapy in advanced head and neck cancer observed complete response in 75% of patients at primary site and 46% of patient's secondary site. They concluded that Cisplatin have a basis of radiobiological and cell kinetic percepts and showed results that compare favourably with other reports of management of patients with advanced head and neck cancer which forms a basis of platinum based concurrent chemotherapy used as radiation sensitizer[19].

Conclusion

This study indicates carboplatin 150 mg weekly showed encouraging response in terms of complete and partial response and found to be well tolerated.

Concomitant low dose carboplatin with radiotherapy could be a better choice in advanced stage of head and neck cancers.

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