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UNRESECTABLE HEAD AND NECK CARCINOMAS;
CONCOMITANT CHEMO-RADIOTHERAPY WITH CISPLATIN AND 5-FLOUROURACIL

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BSTRACT... anaim64@yahoo.com Introduction: Cancers of the head and neck are estimated to be the most prevalent cancers in the world. Data from various cancer centers of Pakistan reveal that epithelial head and neck cancer is one of the most frequent cancers varying from 12 to 25% of the total new patients seen annually. Objectives: To see the effect of concomitant chemo-radiotherapy on the survival of patient, to assess the toxicity of different treatment arms and the effect of age, sex and bulk or tumour on survival and compare the literature. Setting: Radiotherapy Department, Nishtar Hospital, Multan. Duration: 2 years. Material and Methods: Sample Size: 200 patients. Results: Out of 130 patients, 83 were males and the remaining 47 were females. The male to female ratio being 1.8:1. The mean age of the patients included in the study was 52 years, range being 22-80 years. The patients of head and neck cancer in the trial had different sites of involvement. In the trial the patients presented with various symptoms such as pain, swelling, ulcer, bleeding, dysphagia, dyspnea, hoarseness of voice and nasal obstruction etc. No patient had early stage disease. All the patients in the trial had the experience of nausea and vomiting, it was more marked in patients having radiotherapy; either alone or in concomitant with chemotherapy. The patients having concomitant chemo-radiotherapy i.e. group-C also had diarrhoea as a side effect. The effect on the liver function test was more pronounced in patients of group-A. The renal function was seen to alter more in patients receiving chemotherapy with cisplatin, whether as induction or as a concomitant to radiotherapy. Conclusion: Concomitant chemo-radiotherapy in locally advanced, unresectable head and neck carcinoma is statistically superior to induction chemotherapy followed by radiotherapy and the standard radiotherapy alone.

Key words: Concomitant Chemo-Radiotherapy, Cisplatin, Unresectable.

INTRODUCTION

Cancers of the head and neck are estimated to be the most prevalent cancers in the world1. Data from various cancer centers of Pakistan reveal that epithelial head and neck cancer is one of the most frequent cancers varying from 12 to 25% of the total new patients seen annually2'3'4'5'617. It is most prevalent cancer in Karachi7, and is less common in Northern Areas of Pakistan8. These figures are derived from departmental (Radiotherapy Institute and Pathology Departments) based data[23'4'5'6'7'8].

The relative frequency of head and neck cancers in Nishtar Hospital, Multan is 22%9. The majority (70-80%) of patients with head and neck cancer present in the advanced stages i.e. Ill & IV, this is different from the western world literature where most of the patients present at an earlier stage. In Pakistan the late presentation is possibly due to poverty, lack of medical attention, socio-economic conditions and ignorance.

The most effective treatment of advanced inoperable head and neck cancer has not been defined yet10. However, the standard treatment has been radiotherapy and surgery in the early stage (II or II). Radiotherapy and surgery alone have response rates of upto 90% in early stages7, while in advanced stages; it is up to 29%[10].

With higher TNM stages at diagnosis of head and neck cancer, there is a lower proportion of patients who achieve complete response, durable local control and have lower survival[11'12]. These cancers and their treatment often produce considerable morbidity and toxicity, affecting function, nutritional status and appearance. Hence new combined treatment modalities for locally and regionally advanced head and neck cancers are needed to improve survival, quality of life or both[1'11]. There have been significant advances in head and neck oncology in combined modality approaches, using chemotherapy and radiotherapy, which show promise.

Advanced head and neck cancers have poor survival because 50% of these cases have local recurrences and 10-30% have distant metastatic spread[12'13]. Chemotherapy is called induction of neo-adjuvant chemotherapy; when it is used before the standard therapy (i.e. radiotherapy or surgery), it is called sequential of adjuvant chemotherapy; when it is used after the standard therapy and it is called simultaneous or concomitant chemotherapy; when it is used at the same time as the standard therapy. The role of chemotherapy is palliative in recurrent or metastatic disease[12'14]. It also has a place in organ strategies e.g. cancer of larynx[13].

The aim of both the pilot and randomized trials incorporating chemotherapy with radiotherapy and surgery in advanced head and neck cancer is improved survival. The results have shown that induction chemotherapy followed by radiotherapy or surgery does not have much effect on survival but leads to organ preservation[13'14'15'1617]. But a few trials say that induction chemotherapy also improves survival,

Use of chemotherapy simultaneously (concomitantly) with radiotherapy has shown to improve survival in many pilot studies and is considered to be the most promising approach to improve survival in advanced head and neck cancer.

Advances in surgery, radiotherapy and chemotherapy have been slow to be implemented in our country. With the development of expertise in cancer treatment and the availability of facilities in the country there is now a trend to embark upon the use of newer treatment modalities like

chemotherapy.

The present study reflects this new attitude of trying aggressive and innovative methods of treatment; such as chemotherapy used in combination with radiotherapy either before radiotherapy (induction)18 or simultaneously with radiotherapy (concomitant)19 or radiotherapy alone; in a disease which carries great morbidity and mortality.

The main focus of this study is squamous cell carcinomas of the lining of upper aero-digestive tract; which extends from lip to the esophagus. Excluded from this discussion are the melanomas, lymphomas and sarcomas as well as carcinomas of the thyroid, esophagus and salivary glands.

PURPOSE OF STUDY

1. To see the role of chemotherapy used in combination with radiotherapy either before radiotherapy (induction) or simultaneously with radiotherapy (concomitant) and compare this with radiotherapy alone, in locally advanced head and neck carcinomas.
2. To compare the literature.
3. To see the effect of concomitant chemo-radiotherapy on the survival of patient, to assess the toxicity of different treatment arms and the effect of age, sex and bulk or tumour on survival.

MATERIAL AND METHODS

Sample Size

200 patients. Duration

2 years.

Inclusion Criteria

1. Ambulatory patients.
2. Well oriented in time and space.
3. Patients having performance status according to Karnofsky classification of 60 and above.

Exclusion Criteria

1. Patients having melanoma, lymphoma and sarcoma.
2. Patients having stage-l & II tumours of head & neck.
3. Patients having performance status according to Karnofsky classification of less than 60.

Two hundred consecutive patients with biopsy proven diagnosis of squamous cell carcinoma, muco-epidermoid carcinoma and lymphoepithelioma of head and neck

were entered. All these patients were in locally advanced stage and were unresectable. All patients underwent complete clinical examination; which included physical examination, indirect laryngoscopy, direct laryngoscopy, rhinoscopy and nasopharyngoscopy. Work up to exclude distant metastasis included; complete blood picture, x-ray chest, and liver function test, and abdominal ultrasonography, x-ray of head and neck region including CT scan. Staging of disease was done according to the TNM classification. Patients were randomized into three following groups.

Group A:lnduction chemotherapy with cisplastin (100 mg/m^2) and 5-FU (500 mg/m^2) infusion for 3 days followed by radiotherapy. 70 patients were included in this group. Group B:Radiotherapy alone with cobalt 60 (Co^{60}) - 6600 cGy in 6-7 weeks. 66 patients were included this group. Group C:Concomitant chemo-radiotherapy. 64 patients were included this group.

RESULTS

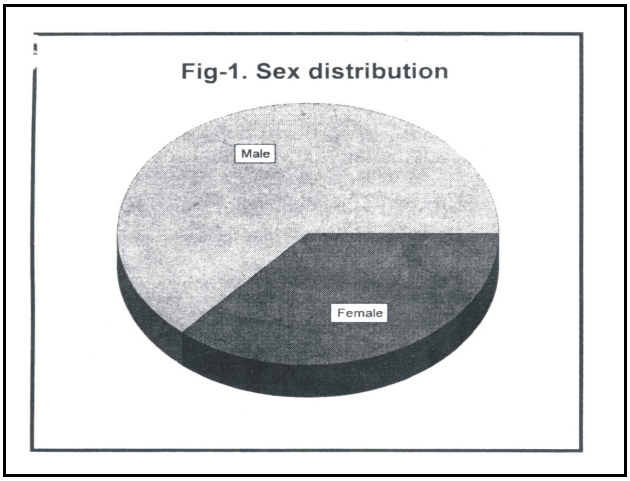
Out of 200 patients 130 patients were evaluateable for response, toxicity and survival. Remaining 70 were lost after having one course of chemotherapy or radiotherapy one session. They were excluded from the study for the purpose of response, toxicity and survival. The randomization of 130 patients into different groups is shown in (Table I). Out of

130 patients, 83 were males and the remaining 47 were females. The male to female ratio being 1.8:1 shows in Fig-l.

The mean age of the patients included in the study was 52 years, range being 22-80 years (Table II).

Table-1. Total number and evaluated patients (Total Number = 200, Evaluated = 130)

A - Induction chemotherapy (3 cycles) + radiotherapy	70 (35%)	44 (33.85%)
B - Radiotherapy alone (control)	66 (33%)	50 (38.46%)
C - Concomitant chemo-radiotherapy	64 (32%)	36 (27.69%)



The patients of head and neck cancer in the trial had different sites of involvement, such as oral cavity, salivary glands, nasoethmoidal sinus complex, lip, nasopharynx, hypopharynx, ear, orbit and metastatic disease of unknown primary as shown in (Table III).

Table-ll. Distribution of patients according to age

Age	Evaluated patients	%age
0-10 years	-	-
11 -20 years	-	
21 -30 years	13	10.0
31 -40 years	13	10.0
41 -50 years	39	30.0
51 -60 years	37	29.0
61 -70 years	20	15.0
71 -80 years	08	06.0

In the trial the patients presented with various symptoms such as pain, swelling, ulcer, bleeding, dysphagia, dyspnea, hoarseness of voice and nasal obstruction etc. (Table IV).

Table-Ill. Site of involvement

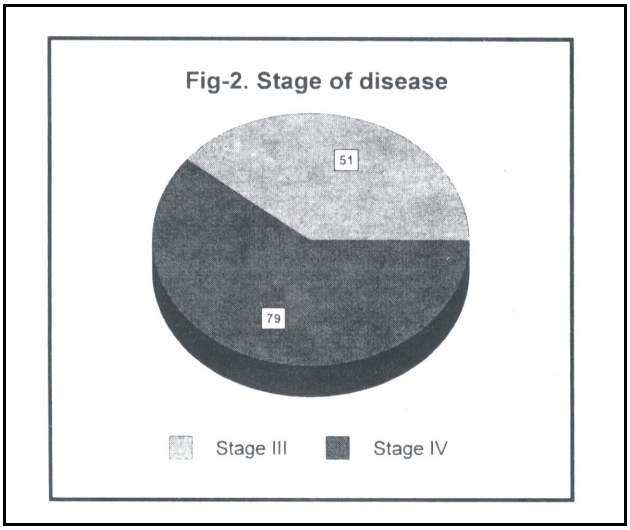
Site involved	Cases %age	Group A	Group B	Group C
Oral cavity	67 (52.0)	20	26	21
Larynx	25(19.0)	10	09	06
Metastatic disease	09 (07.0)	06	01	02
Salivary glands	07 (05.0)	02	03	02
Naso-ethmoidal sinus complex	07 (05.0)	03	03	01
Lip	05 (04.0)	-	02	03

Nasopharynx	04 (03.0)	01	02	01
Ear	02 (02.0)	02	-	-
Oropharynx	02 (02.0)	02	-	-
Orbit	01(01.0)	-	01	-
Hypo-pharynx	01 (01.0)	-	01	-

Table-IV. Incidence of symptoms in patients

Symptoms	No. Of patients	%age
Pain	75	68..0
Swelling	65	50.0
Ulcer	60	46.0
Bleeding	24	18.0
Dysphagia	19	15.0
Dyspnea	10	08.0
Hoarseness of voice	07	05.0
Nasal obstruction	03	02.0

No patient had early stage disease. All had stage-Ill (41%) or stage-IV (59%) disease i.e. locally advanced and unresectable. None of the patients had distant metastasis (Fig-ll).



The toxic effects on the white cell count were of low grade but were seen more in group-A than in the other two groups (P=0.01). The platelet count was seen to decrease in all the groups but it was again seen more in I. group-A (P=0.001). Although mucositis was seen in all groups, yet the highest number of patients having was seen in group-C (P=0.001). All the patients in the trial had the experience of nausea and vomiting, it was more marked in patients having radiotherapy; either alone or in concomitant with chemotherapy (P=0.01) (Table V).

Table-V. Distribution of patients according to white blood cells, platelets, mucosites, nausea and vomiting etc.

Grade	Group-A	Group-B	Group-C
White blood cells			
0	08	14	09
1	21	30	14
2	15	06	09
3	-	-	03
4	-	-	01
Platelets			
0	14	11	10
1	16	31	12
2	14	08	08
3	-	-	05
4	-	-	01
Mucositis			
0	05	02	-
1	18	18	05

2	21	17	12
3	-	10	08
4	-	03	11
Nausea and vomiting			
0	02	07	-
1	18	15	13
2	20	18	16
3	04	07	05
4	-	03	04

The patients having concomitant chemoradiotherapy i.e. group-C also had diarrhoea as a side effect (P+0.001). The effect on the liver function test was more pronounced in patients of group-A (P=0.01).

The renal function was seen to alter more in patients receiving chemotherapy with cisplatin, whether as induction or as a concomitant to radiotherapy (P=0,00001) as shown in (Table VI).

Table-VI. Distribution of patients according to white blood cells, platelets, mucosites, nausea and vomiting etc.

Diarrhoea			
Grade	Group-A	Group-B	Group-C
0	39	43	22
1	05	07	08
2	-	-	06
3	-	-	-
4	-	-	-
Liver function tests			
0	34	43	29
1	07	07	09
2	02	-	-
3	01	-	-
4	-	-	-
Renal functions (creatinine)			
0	25	48	08
1	16	02	18
2	01	-	09
3	-	-	01
4	-	-	-

In the end, the patients in group-A showed a response rate of 39% i.e. complete response of 05% and partial response of 34%; in group-B was 64% with complete response of 10% and partial response of 54% while in group-C the response rate was 100%, having complete response of 33% and partial response of 67% as shown in (Table VII)

DISCUSSION

In this trial we have combined chemotherapy with radiotherapy in induction or neo-adjuvant (group-A and concomitant (Group-C) setting and compared with standard fractionated radiotherapy (control - group-B) in the curative intent therapy or advanced head and neck cancer. Our goals were to increase local control and survival and to assess the toxicities in the three treatment groups. The number of patients entered in each group matched fairly as grades the number, age and the site of involvement. There was significant male preponderance in the concomitant chemo-radiotherapy group. The response rate of 30%, 64% and 100% in group-A, group-B and group-C respectively are significantly different from each other and eh value of calculated chi-square is 51.50 and the data indicates that this rate is very high in group-C, followed by group-B and then group-A (P=0.01). But as compared with the Western literature, the complete response rates and the partial response rates in the three groups are

significantly low[16,17].

It has been reported that the response rate of 60-90% with complete response of 20-50% can be achieved with induction cisplatin and infusional 5 FU regimens[20,21]. In this study the same induction regimen was used but the results showed very low response rate i.e. 39%. This is probably due to the fact that majority of the patients were having performance status of 2 & 3 and were having poor orodental hygiene with problems of oral intake. This factor may have been compounded as the majority of patients in the study had diseases in the oral cavity. It is reported that the oral cavity lesions respond better to combined modality treatment. But in this study, the low response rates, once again may be due to other factors, which could be increased toxicity due to compromised orodental hygiene. All these factors lead to delay in cycles of chemotherapy due to increased mucosal toxicity of chemotherapy, especially 5-FU.

Table-VII. Response of patients 1 the trial

Group	Patients %age	CR %age	PR %age	HR+CR+PR	SD %age	PD %age	Death %age	Lost to follow up
A	44 (63.0)	02 (05.0)	15(34.0)	39.0	20 (45.0)	07(16.0)	03 (4.0)	26 (37.0)
B	50 (76.0)	05(10.0)	27 (54.0)	64.0	17(34.0)	01 (02.0)	-	16(24.0)
C	36 (56.0)	12(33.0)	24 (67.0)	100.0	-	-	02 (6.0)	26 (37.0)

Another possible reason for low response rate with induction chemotherapy could be due to the fact that the patients in this group were given chemotherapy as outpatients and majority of them were from far off places. There was a delay (5-15 days; average 9 days) in their expected time of chemotherapy, in about 80% of the cases. This lack of adherence to treatment schedule could be a factor responsible for poor response rate in these patients.

The response rate in the standard radiotherapy alone group (group-B) is also very low as compared to the literature[22,23]. The reported complete response with radiotherapy alone are in the range of 15-20%. Our data shows a complete response of 10% which is also significantly lower, it may be due to the performance status. Although these patients received treatment regularly as they were treated as in-patients.

The highly significant improved outcome in the concomitant chemo-radiotherapy group (group-C) i.e. respiratory rate and complete response 33% may be due to the fact that all these patients received their chemotherapy and radiotherapy, while having been admitted in the hospital and their mucosal toxicities were fairly well managed.

CONCLUSION

1. Concomitant chemo-radiotherapy in locally advanced, unresectable head and neck carcinoma is statistically superior to induction chemotherapy followed by radiotherapy and the standard radiotherapy alone.

2. The toxicity is significantly more in all the groups but statistically high in the concomitant chemo-radiotherapy group-C.

3. The poor nutritional status and poor orodental hygiene may be factors

responsible for decreased response in the chemotherapy group.

4. The locally advanced unresectable head and neck carcinomas have male preopodrance.

5. Oral cavity is the commonest site of involvement in the head and neck carcinoma.

6. Most of the patients belong to middle or old age group.

7. The older patients get more toxic effects than the younger age group patients.

8. These patients are usually beera chewers, pan chewers and smokers.

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