

## CHEMOTHERAPY FOR ADVANCED ORAL CANCER

\*N. N. Khanna, M.S., M.A.M.S., \*\*A. Khanna, M.S., \*\*\*G. C. Pant, M.S.,  
\*\*\*\*B. Sanyal, M.D. and \*\*\*\*\*S. Khanna, M.D.

Cancer of the oral cavity is extremely common in India and is the most common cancer affecting the Indian male. In spite of its superficial location and easy accessibility, patients continue to come late to the surgeon when the disease is far advanced and beyond the reach of curative surgery or radiotherapy. Many of these patients at the time of first presentation have deep infiltrating tumours involving the bones the skin and other local tissues with multiple nodal involvement which may be unilateral or bilateral. Besides this every surgeon dealing with cancer of the oral cavity is confronted with patients who, after optimal treatment by surgery, irradiation or combination of both experiences recurrence not amenable to treatment by either modality. Such patients pose a challenge to the surgeon for whom at present he has no satisfactory answer.

In the recent past several drugs have been discovered which are effective against oral cancer when used singly and response rates ranging between 15 and 40 percent have been reported. Efforts are being made by different study groups in prospective trials to find out the most effective drug, the best method of administration and the most suitable and yet least toxic dosage schedule, Encouraged by the results of combination chemotherapy used for other cancers, combinations of various drugs have been used for the treat-

ment of oral cancer also. However till date there is no unanimity of opinion as to which is the best combination, the best dosage schedule and the best mode of administration. It is with this background in mind that this study was initiated to try to evaluate the results with one particular schedule tried in 50 patients.

### Methods and Materials

This prospective clinical trial was conducted on 50 patients of advanced oral cancer who fulfilled the following criteria, and were grouped accordingly.

- Group 1 : Patient with advanced oral cancer in clinical stage III or IV.
- Group 2 : Patients who had recurred after previous surgery and no further excision was possible.
- Group 3 : Patients who had recurred or had failed to be controlled by adequate radiotherapy.
- Group 4 : Patients who had recurred after surgery and radiotherapy.

None of these patients had received any prior chemotherapy. All the case had a routine haematological examinations, absolute lymphocyte count, routine laboratory investigation, a skiagram of the jaw bones and a biopsy. Pre and Post chemotherapy photographs were taken for record. All

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\*Professor, Department of Surgery

\*\*Lecturer, Department of Surgery

\*\*\*Professor, Department of Radiotherapy

Institute of Medical Sciences, Banaras Hindu University Varanasi-221005, India.

\*\*\*\*Reader, Department of Radiotherapy

\*\*\*\*\*Reader, Department of Pathology

the patients were put on the following courses of chemotherapy.

1. 5-Fluorouracil 500 mgm/IV on days 1-5.
2. Cyclophosphamide 150 mgm/day orally on day 1-8.
3. Methotrexate 5 mgm/day orally on day 1-5.

The courses of treatment were repeated every six weeks.

During the treatment leucocyte and platelet counts were performed repeatedly and the treatment was adjusted accordingly. The response was recorded according to the criteria laid down by Carter (1972) as follows:

- A. Complete response
  - (I) Lesion was completely healed.
  - (II) No new lesions developed during the period.
- B. Partial response
  - (I) There was more than 50 percent regression in the greatest diameter.
  - (II) No new lesions developed during the period.
- C. No response (Status Quo)
  - (I) The disease existed but did not progress during the course of therapy.
  - (II) The decrease in tumour size was less than 50%.
- D. Progressive disease
  - (I) The patient did not respond and the disease progressed.
  - (II) Fresh lesions appeared.

#### *Subjective Response :*

This included the following :

- (i) Sense of well being
- (ii) Relief of pain
- (iii) Relief of trismus

- (iv) Relief from ankyloglossia
- (v) Reduction in offensive discharge
- (vi) Stoppage of bleeding

#### **Observations**

This study is based on our observations in 50 patients of advanced oral cancer, 46 being males and 4 females. The average age of the patients was 51 years, 11 patients were below 40 years, 20 between 41 to 50 years and 19 above 51 years.

According to the previous treatment received they were classified as shown in Table I. There were 34 primary cases, 6 post surgery cases, 7 post radiotherapy cases and 3 had received both surgery and radiotherapy in the past.

**Table 1.**

Distribution of Cases According to Past Therapy Received.

S. No.	Mode of Therapy	No. of cases	Percentage
1.	Primary	34	68.00
2.	Post Surgery	6	12.00
3.	Post Radiotherapy	7	14.00
4.	Post combined modality	3	6.00
Total		50	100.00

According to the U.I.C.C. system of staging there were 21 cases in stage III and 20 in stage IV.

On histological examination all the cases were squamous cell carcinomas.

#### **Results**

Among the 34 primary cases, 2 had complete response, 24 had partial response, 7 had subjective response only and one case did not

show any response. Among the six post surgical cases, 3 had partial response, 2 had subjective response only and 1 had no response. In the post radiotherapy cases, 2 had partial response, 4 had subjective response, and 1 had a progressive disease. In the 3 cases who had received both surgery and radiotherapy in the past showed complete response in 1 case, partial response in 1 case and no response in one case (Table II).

Some degree of toxicity was observed in 18% of cases. Except in one case where the dose had to be reduced, the toxicity in all the other cases was mild and disappeared spontaneously (Table III).

Table IV shows the relationship of the response to the lymphocyte counts. It was

observed that the patients with higher pre-therapy absolute counts showed a better response as compared to those with lower counts.

**Table III.**

Showing incidence of toxicity.

Toxicity	Number	Percent
Bone Marrow depression	7	14
Nausea and Vomitting	4	8
Diarrhoea	2	4
Matena	2	4
Cystitis	1	2
Alopecia	3	6
No toxicity	41	82

**Table II.**

Results According to Past Therapy Received.

Response	Primary (34 cases)		Post-therapy (6 cases)		Post- radiotherapy (7 cases)		Post-combined modality (3 cases)	
	No.	%	No.	%	No.	%	No.	%
Complete response	2	5.9	—	—	—	—	1	33.3
Partial response	24	70.6	3	50.0	2	28.5	1	33.3
Subjective response	7	20.6	2	33.3	4	57.1	1	33.3
Progressive disease	—	—	—	—	1	14.3	—	—
No response	1	2.9	1	16.6	—	—	—	—

**Table IV.**

Response Versus Absolute Lymphocyte Count.

Response	Less than 2000 (12 Cases)		2001—3000 (23 Cases)		More than 3001 (15 Cases)	
	No.	%	No.	%	No.	%
Complete	—	—	1	4.34	2	13.33
Partial	7	58.33	13	56.52	10	66.66
Subjective	3	25.00	8	34.78	3	20.00
Progressive	1	8.33	—	—	—	—
No response	1	8.33	1	4.34	—	—

The overall results are showed in (Table V.) There were 3 complete responders and 30 partial responders, giving an objective response of 66%. Even those who did not show any objective response showed some degree of symptomatic relief.

**Table V.**  
Over-all Results

Response	No. of cases	Percentage
Complete response	3	6.00
Partial response	30	60.00
Subjective response	14	28.00
No response	2	4.00
Progressive disease	1	2.00
Major toxicities	9	18.00

The duration of response was however short. On an average the response lasted from 2 to 6 weeks. The quality of response lasted from 2 to 6 weeks. The quality of response deteriorated after every successive course of chemotherapy.

### Discussion

Epidermoid carcinoma of the oral cavity continues to be a therapeutic challenge to the surgeon, the radiotherapist and the medical oncologist. Although majority of these tumours remain localised, and distant spread below the clavicles is uncommon, they may infiltrate deeply and spread to the regional lymph nodes either unilaterally or to both sides. Besides this every surgeon dealing with oral cavity cancer is confronted with patients who after optimal treatment by surgery, irradiation or combination of both experiences recurrences not amenable to treatment by either modality. For such patients till recently the surgeon had no satisfactory answer.

In recent years a number of drugs have been discovered which are effective against oral cancer. One of the most effective among them is methotrexate (Bertino 75, Mills 72). On a conservative estimate at least a third of patients with advanced oral cancer will benefit by greater than 50 percent regression of their tumour. Most responding patients will experience an exacerbation within 3½ to 4 months (Bertino 1975). By increasing the dose, the patient may experience serious toxicity.

In order to improve the cure rates, the duration of response and lower toxicity a few reports have appeared in the literature using a combination of drugs. In the present series as well as in those reported by others, an objective response could be gained in about 66 percent of cases. However the number of complete responders is rather low and less than ten percent. Of the responders although greater than 50 percent regression was achieved, the duration of response was short lived, lasting 4 to 6 weeks only.

Best response was obtained in the primary cases, the cases who had not received any prior treatment and the objective response was 76 percent. In the post surgical cases the response rate was 50 percent and those who had received radiotherapy in the past the response come down to 28 percent. This has been reported by other authors as well (Holoye 1978). The poor response to chemotherapy in irradiated cases is explained by a reduced blood supply to the tumour and a suppressed immunological response. Besides this an irradiated tumour is likely to be in a plateau phase rather than in the logarithmic growth phase and is less likely to be maximally affected by the 5-phase active

drugs. Chemotherapy shows the best results in head and neck cancer, if the patient has not taken any previous therapy (Holoye et al 1978).

A fall in the total lymphocyte counts and the absolute lymphocyte counts was observed. The response to chemotherapy was found to be better in cases with an absolute lymphocyte count higher than 3000 per cub mm as compared to those with lower counts.

Some form of toxicity in the form of nausea, vomiting, alopecia, mucositis was observed in a number of cases, but regressed spontaneously serious life threatening toxicity was not observed in this series.

To sum up, the combination of three drugs used in this series gave results superior than those reported with the use of single drugs, the incidence of toxicity was low but the response was short lived.

#### Summary

A combination of three drugs, cyclophosphamide, methotrexate and 5-Fluorouracil was tried in 50 consecutive cases of advanced oral cancer. The overall response rate was 66% and the incidence of toxicity 18%. The response was better in primary cases as compared to those who had received prior radiotherapy. However the response was shortlived.

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