

Intra Arterial Infusion of Cyclophosphamide in Oral Carcinoma

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Chemotherapeutic agents have been used for the treatment of malignant lesions for a number of years. Recently these drugs have found a definite place in the armamentarium for the management of malignant lesions. These drugs are being used on their own and also in combination with surgery or radiotherapy to enhance the benefit of latter procedures.

More recently Sullivan (1958) have brought about renewed interest in Kloop's (1950) original intra-arterial infusion with the substitution of continuous rather than intermittent infusion. Another advantage claimed for this type of infusion is that the continuous infusion is more likely to destroy the maximum number of cells. Certain cells which are in the susceptible stage of division may be affected but the others that are in the resting phase, may not be affected at all. Thus by giving continuous infusion the maximum number of cells are destroyed.

Material :

Advanced lesions of oral cavity chiefly carcinoma showing histologically proved local recurrence, after radiotherapy or surgery were selected for infusion. Such patients were unsuitable for the other type of treatment such as surgery or irradiation. Infusions were given in them as a "Salvaging procedure."

These patients were grouped as follows:

1. Carcinoma cheek	14
2. Carcinoma tongue	2
3. Carcinoma lip	2
4. Melanoma	1
	19

Cyclophosphamide (Endoxan) a drug belonging to Alkylating agent group, was employed for infusion. The advantages claimed for using this drug are greater margin of safety, greater affinity to tumour cells, good tolerance, less haematological

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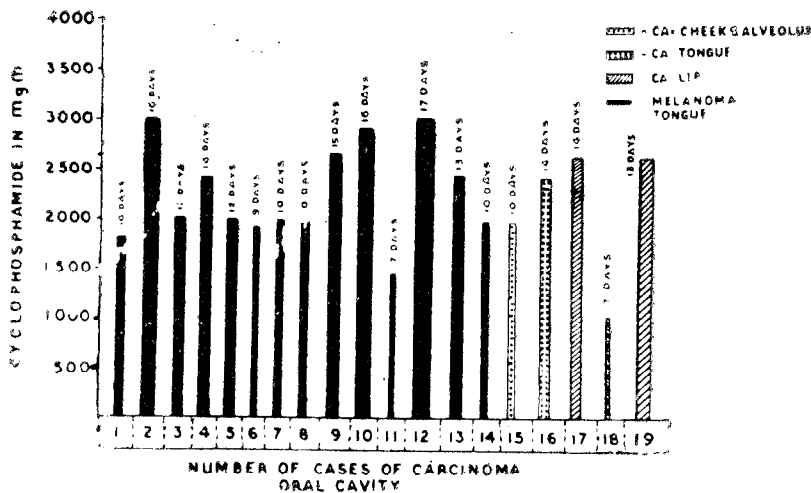
depression and easy availability in the market. Various dosage schedule have been tried out but optimal regimen has not been established as yet. The dose is determined in accordance to the individual need of the patient and taking into account the patient's reaction and blood picture. In most of the cases cyclophosphamide was given in daily dosage of 4 mgm per Kg. body weight intra-arterially. In twenty four hours the total dosage varied from individual to individual depending upon the co-operation of the patient, development of local complication at the infusion site and systemic complications. In our series the total dose of cyclophosphamide varied from 1400 mgm to 3000 mgm (Histogram. 1)

Technique :

The intra-arterial infusion was established by catheterising the external carotid artery either through the superior thyroid or through the superficial temporal artery in a retrograde manner. (Espiner et al, 1962; Ramsden and Duff, 1963) The procedure

was invariably carried out in the operating room under local anaesthesia Polyethylene catheter was introduced into the vessel by direct exposure and arteriotomy. For knowing the distribution of the arterial supply and the correct placement of the catheter in the tumour bed a new technique in the form of injecting Evan's blue dye was used. On injection of this dye the skin, mucous membrane including tumour area became blue in colour which disappeared in a few minutes as opposed to methylene blue (Engest, 1962). Hence, this test can be repeated again if necessary to change the position of the catheter. If desired this dye can be injected during infusion to assess any displacement of the catheter. The catheter was placed close to the tumour bed and was fixed with the artery. It was brought out of the wound and then anchored to the skin by a tape in order to prevent displacement. The catheter was connected to a sterilised infusion set and bottle containing saline solution with the dissolved chemothe-

HISTOGRAM SHOWING DOSAGE IN ORAL CARCINOMA CASES



rapeutic drug. To keep the infusion running the bottle was generally elevated to a



Fig. 1—Case No. 18. Carcinoma lower lip—Preinfusion photograph

height of 10-12 feet above the floor level to overcome the back pressure of the blood (Espiner et al, 1962 and Westbury et al, 1962)

The infusion was given for a period ranging from a few days to few weeks depending upon the clinical response, blood picture (leukopaenia and agranulocytosis) and the appearance of other toxic effects.

Observations and results

During infusion and after discontinuation of the infusion the patient was observed for objective or subjective response. The subjective responses were relief from pain, feeling of well being, disappearance of foul smell, decrease in salivation, improvement in deglutition and opening of the mouth. The objective responses were classified as complete or partial regression, and no response (Burn,

1966). Complete regression is defined as the total disappearance of visible and palpable tumour with no histological evidence of residual cancer after the therapy. Partial regression is defined as any appreciable reduction in the size of the tumour. No response means no objective improvement in terms of tumour size.

All patients except one case of melanoma had previous treatment in the form of radiotherapy, surgery or both. Sixteen cases received radiotherapy alone and two cases had radiotherapy and surgery both. In majority of the patients the radiotherapy was given 2-4 month prior to the Infusion. In four patients the irradiation was administered 7-8 months earlier while two cases had irradiation 2½ years back.

The subjective and objective results are presented in Table I. Three patients died during infusion therapy hence the response could be evaluated in sixteen



Fig. 2—Post Infusion photograph showing complete response. The pointer is showing the melted away tumour

patients only.

Objective responses :

1. *Complete response* was obtained in three patients (Table I, Fig. 1 & 2).

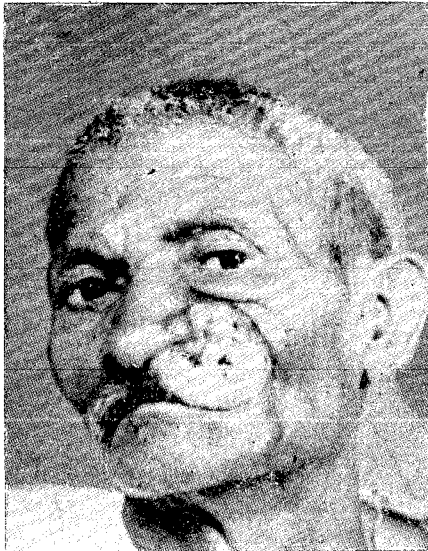


Fig. 3—Case No. 1. Pre-infusion photograph

Two of these were Epidermoid carcinoma of cheek and the lip and the third one was a case Melanoma tongue.

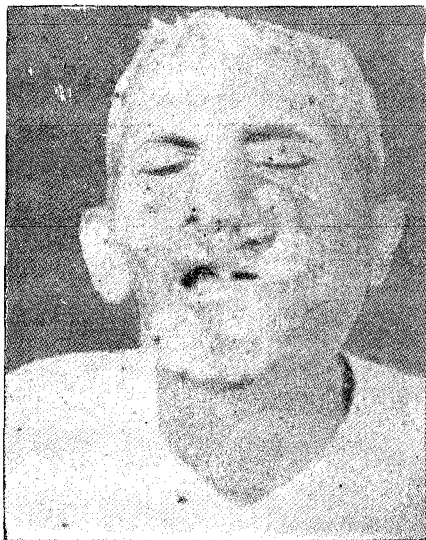


Fig. 4—Post-infusion photograph showing partial response.

2. *Partial response* in the shape of fifty percent regression was obtained in eight cases (Table I, Fig. 3 & 4) and certain changes in histology like cytolysis, reduction in mitosis and decreased tumour cell activity were observed. This group comprised of carcinoma cheek six cases and carcinoma tongue two cases.

3. *No response* was obtained in five (Table I, Fig. 5 & 6) This group comprised of four cases of carcinoma cheek and one of carcinoma lip. Previous radiotherapy to the tumour has been implicated to vitiate the effect of the infusion therapy (Burn et al, 1960; Jussawala, 1964) and our own experience aptly supports this contention (Table I). Klopp et al (1950) had suggested that in order to achieve good response of the drug the blood supply of the tumour area must be good, Espiner et al (1962) have noted that the previous radiotherapy restricts the blood supply to the tumour area by radiation fibrosis. Possibly the post irradiation fibrosis and endarteritis may jeopardise the good tumour response.

The duration of the objective relief from the tumour was variable ranging from one and a half months to seven months. The shortest period of relief for one and half months was seen in one case of carcinoma lip (Case No. 7) while longest in a case of carcinoma cheek (Case No. 9) which lasted for seven months. Majority of the cases were having relief for 3-5 months only. Shanta (1964) has reported convincing local resolution in five cases which made subsequent surgery possible. Two of her cases survived for 3 years.

Table No. I
Showing response in the 19 cases treated by intra-arterial cytotoxic drug infusion

Case No.	Case Diagnosis	Subjective Response										Objective Response				Change in histology	Response	Complications	Duration
		Relief from pain	Disappearance of foul smell	Improvement in swallowing	Decrease in salivation	Improvement in opening of mouth	Tumour regression in size %	Dryness of ulcer	Margins of ulcers	Bleeding on touch	No tumour cells								
1.	Ca. Cheek	+	+	+	+	+	60	+	Flattened	-	-	-	-	P	Severe headache; acute oedema face; anorexia	6 months			
2.	Ca. Cheek	-	+	+	+	+	20	+	Everted	-	-	-	-	N	Hemiplegia; Alopecia	2 months			
4.	Ca. Cheek	+	+	+	+	+	50	+	Flattened	-	-	-	-	P	Catheter leakage	4 months			
5.	Ca. Cheek	+	+	+	+	-	10	+	Everted	-	-	-	-	N	Catheter leakage	2 months			
8.	Ca. Cheek	+	+	+	+	-	0	+	Everted	+	-	-	-	N	Catheter displacement; Dysphagia; Diarrhoea	operated 15 days later			
9.	Ca. Cheek	+	+	+	+	+	100	+	Flattened	-	-	-	-	C	Facial nerve palsy (Temporary)	7 months			
10.	Ca. Cheek	+	+	+	+	+	60	+	Flattened	-	-	-	-	P	Nil	6 months			
11.	Ca. Cheek	+	+	+	+	+	25	+	Everted	-	-	-	-	N	Jaundice	3 months			
12.	Ca. Cheek	+	+	+	+	+	60	+	Flattened	-	-	-	-	P	Nil	4½ months			
13.	Ca. Cheek	+	+	+	+	+	50	+	Flattened	-	-	-	-	P	Facial nerve palsy (permanent)	4½ months			
14.	Ca. Cheek	+	+	+	+	+	60	+	Flattened	-	-	-	-	P	Nil	5 months			
15.	Ca. Tongue	+	+	+	+	+	50	+	Flattened	-	-	-	-	P	Severe Headache; Facial nerve paresis (Temporary)	6 months			
16.	Ca. Tongue	+	+	+	+	+	75	+	Flattened	-	-	-	-	P	Facial nerve palsy (Temporary)	5 months			
17.	Ca. Lower lip	-	-	-	-	-	increased in size	-	Everted	+	-	-	-	N	Catheter plugging	1½ months			
18.	Ca. Lower lip	+	+	+	+	+	100	+	Flattened (dried)	-	-	-	-	C	Catheter leakage; local sepsis	3½ months			
19.	Melanoma tongue	+	+	+	+	+	100	+	Flattened	-	-	-	-	C	Nil	2 months - died due distant metastasis			

Case No.	Diagnosis	Complications
3	Ca. Cheek	Acute Laryngeal oedema
6	Ca. Cheek	Acute Laryngeal Oedema and brain stem injury.
7	Ca. Cheek	Massive haemorrhage from tumour ulcer area.

Mid lesions, which are supplied from both sides, responded better when the drug



Fig. 5—Case No. 5 Carcinoma Cheek
Pre-infusion photograph



Fig. 6—Post Infusion photograph showing no response was infused on both sides. One patient (Case No. 18) of carcinoma lower lip showed complete response after infusion of drug on both the sides while another

similar patient (Case No. 17) did not show any improvement after one side infusion alone.

The higher dose of cytotoxic drug did not alter the response of the tumour. One patient (Case No. 8) received infusion of 2400 mgm of cyclophosphamide but had no response. Therefore, it seems that the regression of the tumour depended directly on the sensitivity of the malignant cells to the drug.

Palliation such as this cannot be achieved without a price and the complication rate of the method is the price paid. The major complications encountered were acute laryngeal oedema in two patients; haemorrhage, hemiplegia, jaundice and acute oedema of face in one case each. The minor complications like wound infections, severe headache and fever in two cases; and reversible alopecia in one case.

The hopeless cases of malignant lesions of oral cavity, that are thought to be unsuitable for other forms of treatment such as surgery or radiotherapy are treated palliatively by continuous intra-arterial infusion of cyclophosphamide and it has a definite place as a salvaging procedure. Bearing in mind that these patients are surgical and radiotherapy rejects the results obtained can be considered well worth the trial.

Summary

Nineteen cases of advanced oral carcinoma were treated by continuous intra-arterial infusion by cyclophosphamide. A newer technique by using Evan's Blue dye for visualizing the arterial supply was used

and was found effective as the colour disappeared after a few minutes.

The response to the therapy has been evaluated and results are presented. In

three patients the disease was brought to the point where surgery could be performed resulting in long term freedom from disease.

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