COMBINED CHEMO-THERAPY TREATMENT OF ADVANCED CANCER CERVIX

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Summary

One hundred seventy-one patients of advanced carcinoma cervix were treated by combined chemotherapy of intravenous MMC (Mitomycin-C) and Cyclophosphamide. Good response was seen in 67 cases, 53 cases showed moderate response and 51 no response. These studies provide evidence that conbination therapy with MMC and Cyclophosamide increases the survival time of patients with advanced cervical cancer of good haemoglobin contents, and increase vascularity.

In spite of modern surgical and radiotherapy treatment of the primary site, cancer cervix continues to be a major oncologic problem in India, specifically in advanced stage. Majority of advanced cases have metastases at the time of initial presentation beyond curative treatment. Systemic therapy with cytotoxic drugs can reach and destroy the malignant cells anywhere in the body. The present communication of use of combination therapy with MMC (Mito-mycin C) and cyclophosphamide by intravenous infusion, was found effective in the treatment of patients with advanced cervical cancer at J.K. Cancer Institute, Kanpur (India) between January 1970 to December 1974.

Material and Methods

A total No. of 5496 cases of cancer cervix were registered during period of 1970-74. The cases were staged according to international classification and were further subclassified. Four types of patients were selected for this study. One, who had not received any treatment, second those who were operated and got recurrence in follow-up clinic, third those who were irradiated for primary site and got recurrence and fourth those who received surgical and radiation treatment. In each patient a complete blood, urine and histopathological examination of primary site were undertaken. A complete radiographic survey was done in necessary patients.

All patients were given MMC in a dose of 4 mg. in 24 hours on days 1, 3 and 5 of each week; Cyclophosamide was given as protracted infusion for 2 days (day 2 and day 4) of each week in a dose of 500 mg. in 24 hours.

The drugs were dissolved in 500 ml of 5% dextrose solution in water and were given by infusion therapy. Therapy was discontinued at the onset of complications such as leucopenia, anemia and diarrhea.

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Following recovery from complications, drug therapy was again continued as intravenous infusion of the combination of these two drugs on next alternate weeks. The total administered doses of MMC and Cyclophosphamise were 36 mg. and 3 gm. respectively in 3-4 weeks time. Detailed hematological tests were carried out prior to further administration of these drugs for maintenance therapy after 3 months if necessary.

The objective response to combination therapy was assessed on the basis of symptoms and survival time was determined from day 1, when infusion was started.

Response and Survival

After the completion of treatment all the patients were encouraged to attend in follow up clinic regularly, but many of them failed to turn up. They were further communicated by postal reminders. The untraced cases were presumed dead, only when definite reply was not received after 3 self addressed postal reminders.

On follow up, all the cases were thoroughly examined and skiagrams were taken in needed patients to compare with the previous lesion. Any complication or toxicity were recorded.

Complications and Toxicity

Various complications and toxicity which occurred during course of treatment are shown in Table 1, which were noticed on first and second day, and relieved by antiemetic drugs. No major complications were noticed during treatment. Haematological toxicities were also minimal.

TABLE I

Complications and Toxicity in 171 Patients of Cancer Cervix

Complication & toxicity	No. of patients
Nausea	27
Vomiting	13
Pyrexia	12
Malaise	10
Leucopenia	7
Anemia	7
Thromobocytopenia	2

Results

Of the 171 patients treated, 97 patients were of stage III B and 74 cases of stage IV. These patients were further subgrouped according to haemoglobin contents and nature of previous treatment (Table II).

TABLE II

Number of Cases in Different Stages in Connection to Haemoglobin Percentage

Group of patients	Stage III B				Stage IV			
	a 6-10 gms.	b 10-12 gms.	c Above 12 gms.	Total	a 6-10 gms.	b 10-12 gms.	c Above 12 gms.	Total
1. No treatment given	25	22	7	54	29	14	3	46
2. Recurrance after Surgery	3	7	2	12	2	3	2	7
3. Recurrance after Radiotherapy	9	4	4	17	4	4	1	9
4. Recurrance after Surgical + Radiotherapy treatment	7	5	2	14	7	3	2	12
	44	38	15	97	42	24	8	74

TABLE III

Clinical Response of Cases in Different Groups of Different Haemoglobin Percentage

Group of patients	Good							Satisfactory							NO						
	Stage IIIB			Stage IV				Stage IIIB			Stage IV				Stage IIIB			Stage IV			
	a	b	c	a	b	c		a	b	c	a	b	c		a	b	c	a	b	c	
1	7	20	7	4	9	2		15	1	—	7	4	1		3	1	—	18	1	—	
2	1	5	2	—	2	1		1	1	—	1	1	1		1	—	—	1	—	—	
3	—	1	1	—	1	—		3	2	2	1	2	1		6	1	1	3	1	—	
4	1	1	—	—	1	—		3	1	—	3	1	1		3	3	2	4	1	1	
	9	27	10	4	13	3		22	5	2	12	8	4		13	5	3	26	3	1	

Chemotherapy treatment was accepted by all the patients. Subjective response as sense of well being with relief from symptoms and objective response in the form of growth regression and parametrial regression were noticed and on these basis good and satisfactory response were noticed (Table III). The response of treatment was better in high haemoglobin content patients in stage III B and those who were not irradiated before.

Two year survival rates were seen in good response patients while one year survival rate in satisfactory response cases. The patient who does not show any response, died within six months of the treatment.

Discussion

Radiotherapy is considered to be the treatment of choice in carcinoma cervix, but in practice majority of patients failed to show complete regression of tumour, specially in advanced stage which constituted the main bulk of the patients seen in India. Thus cancer cervix has also been the subject of numerous trials of chemotherapeutic agents. (Hall and Good 1961; Mathew 1976). The present communication is the trial of combined chemotherapy treatment with MMC and cyclophosphamide.

The use of chemotherapy in cancer cervix has been minimally tested and the availability of several chemothepeutic drugs having different modes of action and toxicity has made possible the clinical evaluation of combination chemotherapy in ceevical cancer (Wasserman and Carter 1977). Response in all these studies tended to occur in patients with distant metastases which had not been previously irradiated. In these, response of the chemotheiapy agent were evaluated

in all type of the patients of advanced stage.

Toxicity was within acceptable level and no majir complications were noticed during treatment.

The success of treatment depends on various factors such as general condition, clinical stage or volume of disease as well as nature of previous treatment. The results obtained in our series are encouraging. In the published series (Bertaglia *et al* 1978; Byfield *et al* 1976; Goolsey *et al* 1968; Smith *et al* 1972; Taguchi 1979) chemotherapy were tried after radiation, but there are certain definite disadvantages in this schedule, because the radiation reduces the vascularity of the tumour and thus if the chemotherapeutic drugs are given before radiation, the drugs reach the malignant cells as well as to micrometastestic cells. On the contrary, if the vascularity be poor the chemotherapeutic drugs are of no use. Such type of the observation were noticed in our series. The patients who were previously irradiated for primary site, the response were poor.

From this study and the foregoing discussion it has been concluded that combined chemotheracy can control micrometastasis as well as distant metastases. Haemoglobin content in the blood, vaseularity, and volume of disease (clinical stage) is the most prognostic factor in advanced cancer cervix in relation to chemotherapy treatment.

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