

CHEMOTHERAPY IN MANAGEMENT OF ADVANCED OVARIAN CANCER*

by

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Ovarian carcinoma is one of the most malignant tumours in females. Fortunately, its incidence in Chittaranjan Cancer Hospital is not very high, only 281 cases were seen out of 7639 cases of carcinoma of female genital tract during the period of 1950 to 1965 (4 per cent).

The place of surgery and/or radiotherapy in the management of this disease is very limited. Occasions will not be rare when, after doing laparotomies, it will be found that the disease has spread widely and beyond the scope of any treatment. Chemotherapy is now being tried in such circumstances in an attempt to arrest the progress of disease and to minimise the sufferings of the patient.

A number of interesting results have been reported by various authors by the use of alkylating agents in the management of these cases (Aboul Nasr, Frick *et al*, Masterson & Nelson, Rutledge & Burns). As many varieties of cytotoxic drugs are not available in India, treatment in the present study had to

be restricted to the drugs available in the market.

Material and methods

During the period of July '63 to December '66 (3½ years), 17 patients of carcinoma of the ovary were treated by available chemotherapeutic agents. The average age in this series was 45.6 years, with an age range of 22 to 65.

Prior to chemotherapy, 15 patients were operated on, 10 in our institution and 5 in other hospitals. In Table 1, the details of operations are given.

TABLE I
Treatment done prior to administration of Chemotherapy

A. Surgery	No. of cases
(1) Total hysterectomy with bilateral salpingo-oophorectomy	5
(2) Sub-total hysterectomy with removal of both tubes & ovaries (cervix could not be removed due to extensive adhesions)	1
(3) Removal of ovarian tumour on one side	3
(4) Removal of ovarian tumour on both sides	1
(5) Only biopsies taken from ovarian tumour and omentum	4
(6) No details about operation available	1
B. Post-operative external radiation given	8

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The rest were not operated, one of them was in such an advanced stage of disease that it was thought useless to do the surgery and the other died before laparotomy. Eight of these patients were later on treated with a course of external radiation.

According to laparotomy findings, the staging was done as per international classification:—

Stage I b — 1 case
 Stage II — 3 cases
 Stage III — 10 "

No report available in 1 case.

The histo-pathology of these cases was as follows:—

Types	No. of cases
Papillary cyst-adenocarcinoma	7
Pseudomucinous cyst-adenocarcinoma	5
Granulosa cell carcinoma	1
Metastatic epidermoid carcinoma	1
No report available	1

Cytotoxic drugs

The cytotoxic drugs used in this study are given in Table 2.

After giving each course of drugs, haemological investigations were done for Hb%, total R.B.C. and W.B.C. and platelet count. If there was any fall in blood count, the next course was withheld until the blood condition had improved.

In 7 patients, only one kind of drug was used and the other 10 patients were treated by a combination of drugs. In the single variety, methotrexate was given in 2 cases, thio-tepa in 2 cases, chlorambucil in 2 cases and endoxan in 1 case. In the combination group, double combination of drugs was given in 7 cases and triple combination in 3 cases.

The drugs were continued until some subjective improvement was achieved without causing much physical inconvenience. In none of the cases was a sensitivity test of the tumour to the drugs done, as facilities were not available.

Complications of therapy

The toxic reactions produced by the drugs are given in Table 3.

TABLE II

Cytotoxic drugs—dosage and method of administration

Drugs	No. of cases	Dosage & administration
A. Alkylating Agents		
(1) Cyclophosphamide (Endoxan)	8	200mg daily I.V. upto 2gm, followed by 200mg orally daily.
(2) Triethylene Thio Phosphoramide (Thio-Tepa)	9	15mg I.M. daily for 4 days followed by 15mg weekly. Also given intra-peritoneally.
(3) Chlorambucil (Lukeran)	8	0.2mg per kg of body weight orally in divided dosage for 1 week, repeated every 5/6 days.
B. Anti-metabolites—Methotrexate		
	8	10 to 15mg orally for 5 days repeated after 7 to 10 days.

TABLE III
Complications of therapy

Anor- exia	Vomit- ing	Stoma- titis	Derma- titis	Alope- cia	Bleed- ing	Blood—Fall of		
						Hb%	W.B.C.	platelet
3	4	3	3	3	2	4	1	2

The toxic reactions were noted in 12 patients and were more with methotrexate than with the other drugs. In one case, Hb%, W.B.C., and platelet count fell to an alarmingly low level and the condition was improved by blood transfusion. There were no reactions in 3 cases.

Methods of Evaluation

As five-year salvage rates of these patients treated by chemotherapy are very few, most of the results reported by various authors have been evaluated by subjective and objective responses. The present writer agrees with Masterson and Nelson (1965) that though objective response is our primary object, subjective response is equally important so far as palliation of these patients is concerned.

The subjective symptoms of the patients and their response to treatment by cytotoxic drugs have been shown in Table 4. One of them was asymptomatic and many had more than one presenting symptom.

Relief pain was noted in 11 patients. There was no relief in 2 patients.

Objective response

The objective response is difficult to assess as it is not always possible to make a precise measurement of any pelvic or abdominal mass in these cases. However, the response has been noted according to 3 terminologies given by Masterson and Nelson (1965).

1. Regression — reduction in the size of tumour and the response is maintained at least for 6 months.

2. Arrest — no measurable reduction in the size of previously expanding lesion, but at the same time, there is no further expansion for a minimum period of 6 months.

3. Progression — where there is obvious expansion of the lesion during the therapy.

The objective response in this series has been shown in Table 5.

TABLE IV
Subjective Symptoms and their response to treatment

Symptoms	No. of patients	Relief of symptoms	No relief of symptoms	Not assessed
Pain	14	11	2	1
Bleeding	3	3	—	—
Ascites	10	5	3	2
Oedema of legs	3	2	1	—
Miscellaneous	2	1	1	—

TABLE V
Objective response of tumour to treatment

No. of patients	Regression	Arrest	Progression	Not assessed
17	3	6	5	3

Out of 3 patients who could not be assessed, as they did not have sufficient amount of trial with the drugs, 1 of them died before laparotomy and the second one within 3 weeks of laparotomy. In the third case, the drugs were not continued further as the patient developed an intestinal fistula on 20th post-operative day and she was lost sight of.

From the above table it could be seen that the regression of tumour was noted in 17.6 per cent of cases, which is more or less the same as that reported by Frick *et al* (1965). Arrest of tumour was noted in 35 per cent of cases.

Salvage rate

About 50 per cent of patients in this series died within the first year and about 75 per cent within first year and a half. About 17 per cent survived more than 2 years from starting of the drug therapy. This observation is more or less the same as that of Rutledge and Burns (1966).

In figure 1, the salvage rate of patients treated by single variety of cytotoxic drugs has been compared with those treated by combination of drugs. It could be seen from the above graph, that the salvage rate of patients treated by the combination of drugs is better than the single ones. None of the patients treated by the single variety survived more than 18 months whereas in the combination

COMPARISON OF SALVAGE RATE OF PATIENTS TREATED BY A SINGLE VARIETY OF CYTOTOXIC DRUGS WITH THAT BY A COMBINATION GROUP OF DRUGS

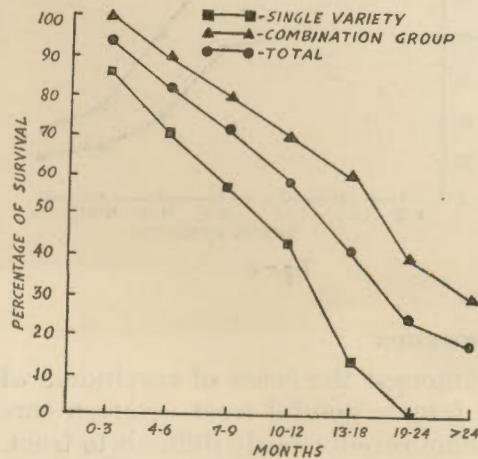


Fig. 1

group, 4 patients survived more than 18 months and 3 of them more than 2 years. Unless a large series of patients are being treated, it is difficult to come to any conclusion that treatment of this type of cancer by a combined group of cytotoxic drugs gives better results than when treated by one kind.

In figure 2, the salvage rate of patients in this series has been compared with the group of patients with carcinoma of ovary not treated by any cytotoxic drugs. It can be seen that there is actually no difference in the long term salvage rate of the two series. This observation agrees with that of Frick *et al* (1965).

COMPARISON OF SALVAGE RATE OF PATIENTS TREATED BY CHEMOTHERAPY WITH THOSE NOT TREATED BY CHEMOTHERAPY

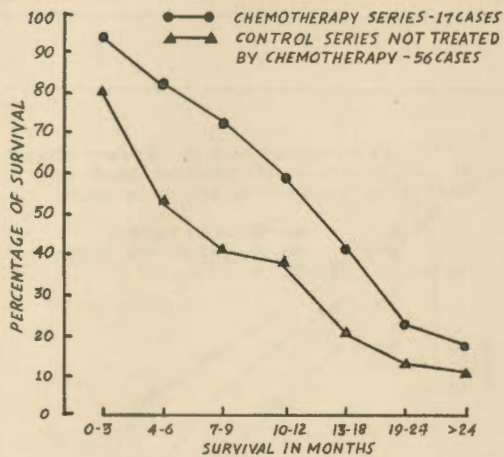


Fig.-2

Discussion

Amongst the cases of carcinoma of the female genital tract, ovarian carcinoma is notoriously difficult to treat. The limitations of surgery and radiation in the treatment of these cases are well known. Cytotoxic drugs are being tried nowadays in such cases with the object of interfering with the metabolism of the tumour. But none of the drugs so far available have been found to be curative, although some good results have been reported recently.

From this small series it could be seen that there are some subjective and objective responses in a group of patients treated by these drugs. The subjective response was noted in 65 per cent of cases and objective response in the form of arrest or regression of tumour in about 53 per cent of cases. But, the ultimate survival rate has not been improved in any way. The long term salvage

rate of patients treated by cytotoxic drugs remains almost the same with those not treated by them. Nevertheless, it is found that the sufferings of these patients have been minimised to a great extent by the use of these drugs, even though for a short period of time, and this seems to be of definite benefit. It is also observed in this small series that treatment by a combination of cytotoxic drugs gives better results than treatment by a single variety.

But there are many problems which are yet to be solved. A few of them which are worrying the present writer, may be cited below:

1. How long the treatment should be continued?

2. Should the drug therapy be stopped when a good response is obtained?

3. Whether treatment should be given even in an asymptomatic stage?

In one case of this series who was asymptomatic, a course of cytotoxic drugs was given and the patient was alright. After one year when intraperitoneal metastases occurred, cytotoxic drugs were again started but were not able to control the progress of the disease. From this experience, a maintenance regime of treatment was given to all patients who were treated afterwards. Still, a lot of work is required to solve these intricate problems.

Summary

1. Seventeen cases of ovarian carcinoma treated by chemotherapy have been presented.

2. Subjective response was noted in 11 out of 17 cases (65 per cent). Regression of tumour was noted in 3

cases (17.6 per cent). Arrest of tumour was noted in 6 cases (35 per cent).

3. The salvage rate by the use of combined group of cytotoxic drugs was better than with single ones, but the ultimate salvage rate has not been improved at all.

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