USE OF CHEMOTHERAPEUTIC AGENTS IN THE TREATMENT OF OVARIAN MALIGNONCY (A CLINICAL SUTUDY)

by

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Introduction

Treatment of ovarian cancer is disappointing and frustrating because of late diagnosis in the majority of cases. In most patients at exploratory laparotomy the disease has advanced to stage III or IV and has often exceeded the limits of surgery. Thus chemotherapy may be used as the only modality of therapy following incomplete surgery, or in combination with operation as primary therapy.

In this study, our experience of treating ovarian cancers with chemotherapeutic agents are discussed.

Material and Methods

Records of 66 patients of ovarian cancers who had been treated at N.R.S. Medical College Hospital, Calcutta were reviewed. Forty-eight of these were epithelial cancers and 18 were of other types. Out of these 48 epithelial cancers, chemotherapy was not used in 12 cases and in 36 cases chemotherapy was used either as primary therapy because of inoperability or as adjuvant therapy in the primary treatment of ovarian cancer along with operation.

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Cyclophosphamide was used as the first chemotherapeutic drug in 29 cases. These 29 cases comprise the study group in this series (Table I).

Patients' response to chemotherapy was evaluated arbitrarily as follows:

A. *Response*

Where there was measurable reduction in the size of the lesion or control of serous effusion for at least 2 months.

B. *No Response*

(a) Arrest

There was no measurable reduction in the size of the tumour, but at the same time there was no further expansion.

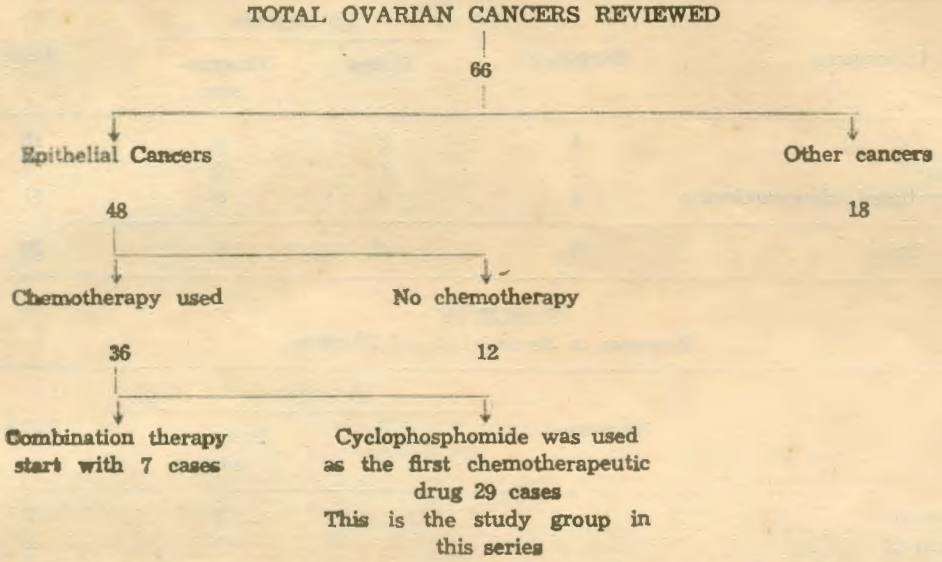
(b) Progression

Even during therapy there was obvious expansion of the lesion or appearance of serious effusion.

All these 29 cases had laparotomy prior to chemotherapy. Fifteen cases were inoperable and only biopsy was taken, 6 cases had incomplete removal of mass and in 8 cases panhysterectomy was done.

In 19 cases, only cyclophosphamide was used. In 7 cases cyclophosphamide was followed by chlorambucil, in 1 case cyclophosphamide was followed by Mitomycin C and in 2 cases cyclophosphamide was followed by combination therapy—thiotepa and 5 FU.

TABLE I
Study Group



Result

Response was positive in 15 cases (51.7%) and negative in 14 (48.3%). Out of the 14 cases, 7 showed progression during chemotherapy.

Table II shows the correlation between operability and response to cyclophosphamide. Six out of 15 inoperable cases showed response.

Table III shows the correlation between response and histology of tumour.

Response persisted only for 2 to 5 months in 3 cases, 6 to 12 months in 8 cases and 4 cases are still living for 2 to 4 years. One patient of short response died at 4th month and 2 cases were tried with other chemotherapeutic agents. One out of 8 cases whose response persisted for 6 to 12 months died at 8th month and other 7 cases failed to turn up for follow-up.

Out of the 14 non-responders, 6 patients who showed progression, died within 3 months and the remaining 8 cases (including 1 case of progression) were treated with other chemotherapeutic agents. Thus 10 cases were treated with second line chemotherapy.

Table IV shows the second line chemotherapy and their response. Three patients responded in this group.

TABLE II
Co-Relation Between Operability and Response to Cyclophosphamide

Operability	Response	No response		Total
		Arrest	Progression	
Inoperable	6	6	3	15
Incomplete surgery	3	1	2	6
Panhysterectomy	6	0	2	8

TABLE III
Co-Relation Between Histology of Neoplasm and Response to Cyclophosphamide

Type of Carcinoma	Response	No response		Total
		Arrest	Progression	
Serous	9	2	4	15
Mucinous	2	1	0	3
Undifferentiated adenocarcinoma	4	4	3	11
Total	15	7	7	29

TABLE IV
Response to Second Line of Therapy

Drugs	Response	No response		Total
		Arrest	Progression	
Chlorambucil	2	2	3	7
Mitomycin C			1	1
Theo-TEPA & 5 FU	1		1	2
Total	3	7		10

Table V shows mortality in this series. In the whole series there were 18 deaths, 7 cases failed to turn up for follow up and 4 cases are living more than 2 years. All these 4 cases who are still living had panhysterectomy followed by cyclophosphamide therapy.

TABLE V
Time of Death

Time of death	No. of cases
Within 3 months	6
3 to 6 months	3
7 to 9 months	8
10 to 12 months	-
Total	18

Out of 18 deaths, 6 died within 3 months. These cases were inoperable and all the 6 cases had progression of disease during cyclophosphamide therapy. Three patients died between 3 to 6 months. Of the 8 cases who died between 7-9 months, one had panhysterectomy followed by cyclophosphamide therapy. Ascites developed within 4 weeks and so chlorambucil started. The patients responded but died at 7th month. One patient died after 11 month of treatment. This patient had partial removal of mass followed by cyclophosphamide therapy. The response persisted only for 3 months and so this case was later treated with thiotepa and 5 F.U.

Table VI shows the survivability of responders and non-responders to cyclophosphamide. Average survivability of responders was 13.6 months and of non-responders was 4.8 months.

Discussion

Clinical research is exceedingly difficult to achieve with cancer chemotherapy.

TABLE VI

Survivability of Responders and Non-Responders to Cyclophosphamide

Responders		Non-responders	
No. of cases	survivability in months	No. of cases	Survivability in months
1	4	1	2
2	6 did not turn up	2	2
3	6 ,,	3	2.5
4	6 ,,	4	2.5
5	6 ,,	5	3
6	7 ,,	6	3
7	7 ,,	7	5
8	7 ,,	8	5
9	7	9	6
10	8	10	6
11	11	11	7
12	24 Still living	12	7
13	26 ,,	13	8
14	30 ,,	14	9
15	47 ,,		
Average survivability 13.6 months		Average survivability 4.8 months	

It is very unusual for the clinician to attain the clarity of result which is achieved in the laboratory. Moreover, there is no discriminating objective test which might indicate tumour response to chemotherapy in a few days. Interpretation of results is more difficult in cases where the drug is given as adjuvant therapy in the primary treatment of ovarian malignancy with operation because lesion remaining after operation are often difficult to measure accurately.

However, in the present study 51.7 per cent cases showed objective response to initial chmotherapy with cyclophosphamide. This tallies with Decker *et al* (1968) who found 48 per cent response with cyclophosphamide. Alkylating agents are the most useful and frequently employed chemotherapeutic drugs used in the treatment of ovarian cancers. Despite difference in molecular structure among alkylating agents, the therapeutic response remains remarkably similar at equivalent dosages as proved by the studies of different authors. Materson and Nelson (1965) got 50% tumour response with chlorambucil and Rutlege (1968) 49% with phenylalanine mustard. Cyclophosphamide was used in the present series. It produced minimal side effects other than hair loss in about 60% cases and bone marrow depression, which was avoided by periodic WBC count and dosage adjustment.

The average survival time among patients who responded to initial chemotherapy was 13.8 months in contrast to an average survival time in non-responders of 4.8 months. Friedman (1965) alsc got similar results.

Treatment of non-responders to the first trial of chemotherapy is a problematic one. Eight cases of non-responders who survived more than two months and 2 cases of responders who showed short

response were treated with second line-chemotherapeutic agents. Seven out of these 10 cases were treated with chlorambucil, another alkylating agent and 2 cases in this group responded.

Many investigators also found that switching from one alkylating agent to another is useful in prolonging the response in some cases. Two cases received combination therapy with 5 FU and thiotepa, of which 1 responded and lived for 11 months. Toxicity was more than single drug therapy. This patient needed several blood transfusions. In the series of Smith and Rutledge (1970) 50% cases showed tumour response with combination therapy comprising actinomycin D, 5 FU and cyclophosphamide. The combination of chemotherapeutic agents reflects the inadequacy of a single drug and represents an attempt to better use of available drugs in the hope of achieving at least a degree of control in the hopeless cases. Every one is now looking for more specific chemotherapeutic agents in order to improve the result.

From our small experience it is evident that chemotherapy can be carried out without major complication and in a significant number of cases substantial improvement for a period of time can be achieved. We agree with Lewis (1976) when he says "without reservation it may be concluded that chemotherapy can be credited for playing a significant role in this turn for the better".

Acknowledgement

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