

EVALUATION OF TWO COMBINATION CHEMOTHERAPY IN ADVANCED OVARIAN CARCINOMA

By

KALPANA DAVE AND ANILA KAPADIA

SUMMARY

Two combination chemotherapy i.e. Regime—A consisting of CYT + ACT + 5-FU and Regime—B of CYT + ADM + DDP were evaluated in 12 and 10 patients of advanced ovarian carcinoma respectively. The overall mean and median survival rate was 9.09 and 9.00 months for R-A and 17.3 and 18 months for R-B. Complete and partial response rates were 16.6% and 58.3% for R-A and 40% and 50% for R-B. The drug toxicity level was much lower for R-B. Disease free survival is more with R-B. (40%) as compared to R-A. (8.3%). Thus, R-B. is recommended but the cost of the drug especially of cisplatin is the limiting factor.

Introduction

In advanced ovarian carcinoma single alkylating agent or combination chemotherapy is usually the treatment of choice. Initial attempts to treat the stage III and IV of advanced ovarian carcinoma, mostly inoperable, with the use of single alkylating agents were criticised because of less than optimum doses given to the patients. However, alkylating agents are the cornerstone in the therapy of advanced ovarian carcinoma since 1952, but the use of cisplatin against ovarian cancer by Wiltshaw and Krona in 1976 has made a radical change in the prognosis of ovarian carcinoma. In this particular study an attempt has been made to study two combination chemotherapy, one with cisplatin and another without cisplatin.

From: Department of Gynaecology, Gujarat Cancer and Research Institute, Asarwa, Ahmedabad-380 016, India.

Accepted for publication on 21-1-88.

Materials and Methods

In the present study, 22 patients admitted during the last five years in our Institute were included for the evaluation of two combination chemotherapy in a randomised fashion. After admitting them detailed history taking and clinical examination were carried out along with various investigations such as blood counts, blood chemistry, liver function tests, chest X-rays etc. Whenever ascites and pleural effusion were present, these were aspirated for cytological evaluation. As and when required, excretion urography, barium enema, ultrasonography were also done to detect any bowel pathology.

Whenever possible and required, patients were subjected to initial surgery with intention of maximum volume reduction which included abdominal hysterectomy, bilateral salpingo-oophorectomy, infra-

colic omentectomy and removal of other tumor masses.

With the help of the above mentioned procedures, patients were graded as per International Federation of Gynaecology and Obstetrics, FIGO (1976) Classification for the various stages of malignancy. Patients were also diagnosed histopathologically.

After the completion of these procedures the patients were subjected to two types of combination chemotherapy in a randomised fashion as per the details given in Table I. Out of 22 patients, 12 were subjected to Regime-A and 10 to Regime-B.

Regime—A—Cyclophosphamide (CYT) + Actinomycin (ACT) + 5-Fluorouracil (5-FU).

Regime—B—Cyclophosphamide (CYT) + Adriamycin (ADM) + Cisplatin (DDP).

In both the groups, chemotherapy was administered intravenously. Prior to administration of cisplatin, patients were rapidly hydrated with the help of 5% dextrose in water and after the drip mannitol was administered for diuresis.

Patients were clinically evaluated for response prior to each treatment from the second cycle onwards. During the follow-up complete response was defined as disappearance of all measurable tumour for two months or more and partial response was defined as reduction in product of two measurable tumour diameters by more than 50 per cent lasting for two months or more. No response was considered when patients with measurable tumour did not fulfil the criteria of complete or partial response.

Serial complete blood count, haemoglobin estimation, platelet counts were obtained prior to each course. Blood urea

TABLE I
The Schedule of Chemotherapy in Both the Regimes

Regime	Drugs		Therapeutic Protocol		
	Name	Daily dose mg.	Route	Day	Frequency
A	Cyclophosphamide (CYT)	500	i.v.	1 to 5	Recycle
	Actinomycin (ACT)	0.5	i.v.	1 to 5	every 3 to 4 weeks
	5-Fluorouracil (5-FU)	250	i.v.	1 to 5	
B	Cyclophosphamide (CYT)	500	i.v.	1	Recycle
	Adriamycin (ADM)	50	i.v.	1	every 3 to 4 weeks
	Cisplatin (DDP)	50	i.v.	1	

i.v. = Intravenous

and serum creatinine were measured in patients who received cisplatin. ECG was done in patients receiving adriamycin. Other side effects like nausea, vomiting, stomatitis, fever, alopecia etc. were noted.

The patients were called every month for chemotherapy and were evaluated and followed. Seven patients are still coming for follow-up. The patients lost to follow-up were considered dead.

The mean and median duration of follow-up were calculated by simple statistical methods.

Results

It is seen from the Table II that in both the regimes, patients with epithelial type of ovarian carcinoma were more and evenly distributed i.e. in R.A. 90% and R.B. 70%.

TABLE II
Distribution of Patients in Both the Regime as per Histo-pathological Diagnosis

Histopathological diagnosis	No. of patients in R.A.	No. of patients in R.B.
Epithelial	11	8
Germ cell	—	1
Stromal	—	1
Secondary ovarian	1	—
Total	12	10

R.A. = Regime A, R.B. = Regime B.

It is seen from Table III that 80% patients in both the Regimes were in advanced stage i.e. stages III and IV.

It is evident from Table IV that neither chemotherapy nor radiation were given to 60% patients of R.A. and 30% patients of R.B.

TABLE III
Distribution of Patients in Both the Regimes as per FIGO Stage System

FIGO stage	No. of patient in R.A.	No. of patient in R.B.
I	—	—
II	1	—
III	8	6
IV	2	2
Unclassified	1	2
Total	12	10

FIGO = International Federation of Gynaecologists and Obstetricians (1976).

TABLE IV
Distribution of Patients in Both the Regimes as per previous treatment given to the Patients

Previous treatment	No. of patients in Regime A	No. of patients in Regime B
Previous radiation	5	4
Previous chemotherapy	—	3
No treatment	7	3
Total	12	10

It is seen from Table V that in nearly 30% patients of both the regimes the surgical line of treatment was not possible and debulking was done in 50% of the patients of both the groups. Complete surgery was considered only when residual tumour is < 2 cms.

TABLE V
Distribution of Patients in Both the Regimes as Initial Surgery

Initial surgery	No. of patients in Regime A	No. of patients in Regime B
Complete	1	1
Debulking	6	5
Inoperable	4	1
Surgery not done	1	3
Total	12	10

It is seen from Table VI that the complete response was achieved in 40% of R-B as compared to 17% in R-A. Partial response was almost equal in both the regimes. Thus, 90% of R-B patient have shown partial or complete response against 75% in R-A.

TABLE VI
Distribution of Patients in Both the Regimes as per the Response

Response	No. of patients in Regime A	No. of patients in Regime B
Complete	2 (16.6)	4 (40)
Partial	7 (58.3)	5 (50)
No response	3 (25)	1 (10)
Total	12	10

Figures in parenthesis indicate Percentages.

It is seen from Table VII that the maximum toxicity was observed in patients with A regime as compared to B. This was in the form of reduction of haemoglobin, white blood cells and platelet count.

As it is seen in Graph I, which represents regime-A and B, mean survival was 9.00 and 17.3 months and median survival

TABLE VII
Toxicity observed in Both the Regimes

Haematological		Regime A	Regime B
		57	68
Hgb	Gr. I	5	1
	Gr. II	2	—
	Gr. III	3	—
WBC	Gr. I	1	—
	Gr. II	3	—
	Gr. III	1	—
Platlet	Gr. I	2	—
	Gr. II	5	—
	Gr. III	—	—
Stomatitis	Gr. I	—	—
	Gr. II	2	—
	Gr. III	—	—
Fever	Gr. I	1	—
	Gr. II	—	—
	Gr. III	—	—

Hgb = Haemoglobin Gr. = Grade.
WBC = White Blood Cell

was 9 and 19 months 'respectively in both groups.

It is seen from Table VIII that 9 patients in regime A and 7 patients in regime B survived while 3 patients in both regime died. In regime A all patients died

TABLE VIII
Response Rate in Both the Regimes by Various Investigators

Investigator	Regime A		Regime B	
	Evalu-able patients	Response rate	Evalu-able patients	Response rate
Stanhope (1977)	145	6%	—	—
Bruckner (1978)	—	—	24	50%
Ozols Robert (1985)	—	—	—	68%
C. Sessa (1985)	—	—	—	C.R. 22%
				P.R. 42%
Thigpen Tate (1985)	—	—	—	76%
Conte P. F. (1986)	—	—	—	C.R. 40.6%
				P.R. 15.6%
Present study	12	C.R. 16.6%	10	C.R. 40%
		P.R. 58.3%		P.R. 50%

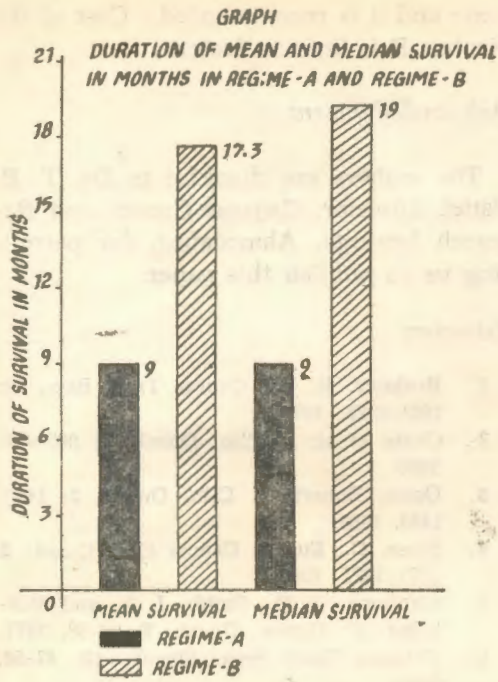


Fig. 1
Duration of mean and medium survival in months in regime—A and regime—B4
Regime—A
Regime—B

TABLE IX
Current Status of Patients in Regime A and Regime B

	Regime A	Regime B
Total No. of patients	12	10
Survival Total	9 (75)	7 (70)
N.E.D.	1 (83)	4 (40)
A.W.D.	8	3 (30)
Death Total	3 (25)	3 (30)
D.O.D.	3 (25)	1 (10)
D.O.C.	0 (0)	*2 (20)

* Serum haepatitis
N.E.D. = No evidence of disease clinically
A.W.D. = Alive with disease
D.O.D. = Died of disease
D.O.C. = Died due to other cause
Figures in parenthesis indicate percentages.

due to disease, while in regime B, one patient died due to disease while 2 patients died due to serum hepatitis, in which there was no clinical evidence of disease.

In regime A, only one patient had no evidence of disease, while in regime B, 3 patients out of 7 had clinical evidence of disease, and 4 patients are free of disease. These 4 patients who are free from disease, are candidates for second look laparotomy, but 1 patient is not ready for it, and 3 patients will be operated within short time.

Discussion

In 1950 and 1960 attempts were made to treat advanced Ovarian Carcinoma (stage III and IV, inoperable cases) with single alkylating agents and many investigators have tried in this direction with not much encouraging results. These trials have been criticised for their use of agents in what is now considered to be less than optimum doses.

As shown in Table VIII, when CYT + ACT + 5 Fu Regime A was used by Stanhope *et al* (1977) the response rate was 6% but when Bruckner (1978) tried DDP + ADM + CYT, the response rate was 50%. This itself shows the superiority of Regime B type of treatment. Over the years, the same Regime B showed improvement in response rate. Ozols Robert (1985) found it to be 68% while Thigpen Tate (1985) found it to be 76%. During the same year, on the contrary, Sessa (1985) got lower results in the form of 22% C.R. and 42% P.R. When compared to the results of Conte (1986) with that of present series (1986), the C.R. is 40.6% and 40.0% respectively, while the P.R. is 15.6% and 50% respectively. Thus it is evident that a cisplatin based combination

chemotherapy regimen offers a patient with advanced ovarian carcinoma the greatest likelihood of achieving a C.R. and prolongation of survival.

It is also worth noting that Regime A combination was more toxic than Regime B combination.

Finally looking at the overall response, survival rate as well as toxicity of drug, Regime B combination seems to be better than Regime A combination.

Summary and Conclusion

Two different combination chemotherapy i.e. Regime A CYT + ACT + 5 Fu and Regime B DDP + ADM + CYT were tried in 12 and 10 patients with advanced ovarian carcinoma at our Institute. Over all results showed that latter combination was more effective and less

toxic and it is recommended. Cost of the Regime B is limiting factor.

Acknowledgement

The authors are thankful to Dr. T. B. Patel, Director, Gujarat Cancer and Research Institute, Ahmedabad, for permitting us to publish this paper.

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As shown in Table VIII when CYT + ACT + 5 Fu Regime A was used by Stanhope et al (1977) the response rate was 50% but when Brukner (1978) used DDP + ADM + CYT the response rate was 50%. The table also shows the toxicity of Regime B. Over the year the response rate showed improvement in Regime B showed improvement in response rate. Over the year the response rate was 50% while Stanhope (1977) found it to be 50%. During the year 1985 found it to be 50%. The results of the study show that the response rate in the form of C.R. and survival rate was 50%. When compared to the results of Stanhope (1977) and Brukner (1978) the response rate was 50% and 50% respectively. The results of the study show that the response rate was 50% and 50% respectively. The results of the study show that the response rate was 50% and 50% respectively.

TABLE IX
Comparison of response rate in Regime A and Regime B

Regime	No. of patients	Response rate (%)	Toxicity (%)
Regime A	12	50	50
Regime B	10	50	50

The results of the study show that the response rate was 50% and 50% respectively. The results of the study show that the response rate was 50% and 50% respectively. The results of the study show that the response rate was 50% and 50% respectively.