A RANDOMISED TRIAL COMPARING CISPLATIN + ADREAMYCIN VERSUS CISPLATIN PLUS CYCLOPHOSPHMIDE VERSUS CISPLATIN PLUS ADREAMYCIN PLUS CYCLOPHOSPHAMIDE IN ADVANCED OVARIAN CARCINOMA.

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SUMMARY

22 Patients with Ovarian cancer, FIGO stage 1 = 2 patients, state III = 16 patients, stage IV = 1 patient & unknown stage = 3 patients were randomly allocated to receive PA (Cisplatin in 50 mg + Adreamycin 50 mg IV every month) or PC (Cisplatin 50 mg + Cyclophosphamide 500 mg I.V. every month). 7 patients were subjected to PA regime, 8 patients were give PC regime & 7 patients were treated with PAC regime.

The following clinical response rates were observed PA regime 57.1% C.R. 28.6% PR; PC regime 25% CR 62.5% PR; PAC regime 57.1% cR 28.6% PR. The clinical response rates in all the three regimes appear similar showing about 85% total response in all three rregimes; but when comparison is done in response rates in patients who have under gone complete surgery with less than 2 am residual disease and treated with three different regimes then the PAC regime is definitely superior showing 1000% CR. PC regime shows only 33.3% CR while PA regime shows 50% CR. The usefulness of adreamycin containing regimes had been outlined. The cost of PAC regime is the limiting factor.

INTRODUCTION

Improving the duration of the survival of the patients having stage III or stage IV ovarian cancer remains a major challenge. In the history of cancer chemotherapy, the first step towards this challenge was the use of alkylatig agents, mainly Malphalan postoperatively. The median survival increased from 6 months without chemotherapy to about 12

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months with chemotherapy. The second step was the introduction of polychemotherapy regimens, the most successful of which was Hexa CAF. Median survival was further increased to between 10 and 29 months. The third step was the use of Cis-platin alone or in combination. This appeared to be more effective than the alkylating agents. Median survival observed was between 15 and 30 months. Incorporation of Cis- platin i.e. Cis diamine dichloro platinum in the first line regimes had produced response rates of upto 80% to 90%.

Unfortunately, Cisplatin related peripheral neuropathy, cumulative nephrotoxicity and nausea-vomiting have substantially increased the overall toxicity of these multimodal treatments.

It is now mandatory to verify whether the addition of other cytotoxic drugs to Cisplatin could further improve the results with acceptable toxicity. In order to answer this question, a randomised study was started at the Gujarat Cancer & Research Institute, Ahmedabad in June, 1983.

Most of our patients come from the lower socio-economic class. The cost of Cisplatin is Rs.300 per 50 mg injection and that of Adreamycin is Rs 700 per 50 mg injection. The full course would consist of 6 to 8 such doses. One of the aims of the present study was to find out whether the addition of a costly drug like Adreamycin would improve the efficacy of Cisplatin in terms of the response rate.

MATERIAL AND METHODS

22 patients admitted in the last five years were included in the evaluation of the three combinations of chemotherapy in a randomised fashion.

All the patients except one were subjected to initial surgery with the intention of maximum tumour volume reductio which included total abdominal hysterectomy with bilateral salpingo ooophorectomy, infracolic omentectomy and removal of other tumour masses. One patient was considered unfit for surgery on medical grounds and was put straight away on chemotherapy.

The patients were graded as per the FIGO classification for the various stages of malignancy. The amount and localisation of the residual disease were carefully recorded.

After surgery, the patients were subjected to three types of chemotherapy in a randomised fashion as per the details given in Table 1. The 22 patients were almost equally distributed in the 3 groups. Regime A consisted of cisplatin + adreamycin. Regime B consisted of Cisplatin + Cyclophosphamide. Regime C consisted of Cisplatin + adreamycin + Cyclophosphamide.

Prior to the administration of intravenous chemotherapy, the patients were rapidly hydrate and after the drip, mannitol was given for diuresis. The patients were clinically evaluated for response prior to each treatment from the second cycle onwards. Complete response was defined as disappearance of all measurable tumour for two months or more. Partial response was defined as reduction i the product of two measurable tumour diameters by more than 50%. No response was considered when the patients with measurable tumour did not fulfil the criteria of complete or partial response. Apart from the routine hematological investigations

TABLE 1

THE SCHEDULE OF CHEMOTHERAPY IN ALL THREE REGIMES

	THERAPEUTIC PROTOCOL					
Regime	Drug Name	Daily dose	Route	Day	Frequency	No. of patient
A	CISPLATIN	50mg	I.V.	1	Recycle every	7
	ADREAMYCIN	50mg	I.V.	1	3-4 weeks	
B	CISPLATIN	50mg	I.V.	1	Recycle every	8
	CYCLOPHOSPHAMIDE	500mg	I.V.	1	3-4 weeks	
C	CISPLATIN	50mg	I.V.	1	Recycle every	7
	ADREAMYCIN	50mg	I.V.	1	3-4 weeks	
	CYCLOPHOSPHAMIDE	500mg	I.V.	1		

and renal function tests ECG was recorded in patients receiving Adreamycin. The side effects were carefully recorded.

Of the 22 patients, 15 are still coming for follow-up. 5 patients have died. Even with the best efforts, 2 patients were lost to follow-up and were considered dead.

RESULTS

It is seen from Table II that most of the tumours in all the 3 groups were of the epithelial histology. Tumour arising from the stroma or from the germ cells were cound to be the rare varities.

It is seen from table III that Stage III was the most commonly encountered stage in the present study.

Table IV shows the type of surgery carried out in the 3 groups. amongst the 3 groups, the percentage of complete surgery is maximum in the group which received the regime B whereas in the other two groups,

TABLE II
DISTRIBUTION OF PATIENTS AS PER HISTOLOGY

HISTOLOGY	No. of patient in R.A. PA(%)	No. of patient in R.B. PC(%)	No. of patient in R.C. PAC(%)
EPITHELIAL	6(85.7)	8 (100)	4(57.1)
GERM CELL	1(14.3)	-	-
STROMAL	-	-	3(42.9)
TOTAL	7	8	7

R.A. = Regime A R.B. = Regime B R.C. = Regime C.

TABLE III
DISTRIBUTION OF PATIENTS AS PER FIGO STAGE

FIGO Stage	No. of patient in R.A. PA(%)	No. of patient in R.B. PC(%)	No. of patient in R.C. PAC(%)
I	-	-	2(28.6)
II	-	-	-
III	6(85.7)	5(62.5)	5(71.4)
IV	-	1(12.5)	-
Unknown	1(14.3)	2(25.0)	-
TOTAL:	7	8	7

FIGO = International Federation of Gynaecologists & Obstetricians (1976)

TABLE IV
DISTRIBUTION OF PATIENTS AS PER INITIAL SURGERY

INITIAL SURGERY	No. of patient in R.A. PA(%)	No. of patient in R.B. PC(%)	No. of patient in R.C. PAC(%)
COMPLETE	2(28.6)	3(37.5)	2(28.6)
DEBULKING	3(42.9)	5(62.5)	5(71.4)
INOPERABLE	1(14.3)	-	-
SURGERY	1(14.3)	-	-
TOTAL:	7	8	7

the percentage of complete surgery is marginally less. It is evident that there is an imbalance in the amount of residual disease present in the 3 groups, after surgery. On an average, the patients who received the regimes A and C had a more bulky disease than the patients who received the regime B. This slight imbalance in the amount of residual disease affects the clinical response rates as is seen in the next table.

Apparently, Table V shows that the clinical response rates in all the three regimes are similar in terms of total response which is the sum of complete response and partial response. When we consider the rates of complete response, it is found that the addition of Adreamycin to Cisplatin increases the percentage of clinical complete response rate in advanced ovarian carcinoma. Complete response was achieved in 57.1% of patients treated with regimes A or C, both of which contain

TABLE V
DISTRIBUTION OF PATIENTS IN ALL THREE REGIMES AS PER THE RESPONSE

RESPONSE	No. of patient in R.A. PA(%)	No. of patient in R.B. PC(%)	No. of patient in R.C. PAC(%)
COMPLETE	4(57.1)	2(25.0)	4(57.1)
	+(85.7)	+(87.5)	+(85.7)
PARTIAL	2(28.6)	5(62.5)	2(28.6)
NO RESPONSE	1(14.3)	1(12.5)	1(14.3)
TOTAL:	7	8	7

TABLE VI
RESPONSE RATES ACCORDING TO TREATMENT IN PATIENT WITH COMPLETE SURGERY

RESPONSE	COMPLETE SURGERY R.A.	R.B.	R.D. 2cm R.C.
COMPLETE RESPONSE	1(50.0)	1(33.3)	2(100)
PARTIAL RESPONSE	-	2(66.6)	-
NO RESPONSE	1(50.0)	-	-

R.D. RESIDUAL DISEASE

Adreamycin. Only 25% of patients achieved complete response with regime B which does not contain adrreamycin. Our results thus demonstrate the usefulness of Adreamycin.

The response rates in the debulking group can not be compared with accuracy because in some patients, the residual tumour was a few cm in size while in the others, it was very bulky.

Although in Table V, the total response rates appeared similar in all the 3 regimes about 85% total response it is seen from Table VI that significant differences are found when the debulking group is excluded from

TABLE VII
TOXICITY OBSERVED IN ALL REGIMES

	R.A. PA(%)	R.B. PC(%)	R.C. PAC(%)
NO OF PATIENTS	7	8	7
ANAEMIA	4(57.1)	4(50.0)	1(14.3)
LENKOPENIA	3(42.9)	-	-
THROMBOYTOPENIA	1(14.3)	-	-
RENAL	-	1(12.5)	-
NEUROLOGIC	-	(1(12.5)	-
ALOPECIA	7(100)	8(100)	7(100)
NAUSEA & VOMITTING	7(100)	8(100)	7(100)

TABLE VIII
COMPARISON OF CLINICAL RESPONSE IN DIFFERENT SERIES

Author	R.A. PA(%)	R.B. PC(%)	R.C. PAC(%)
1. Bruckner 1978	-	-	T.R.90%
2. Ozols Robert 1985	-	-	T.R.68%
3. Steiner Marina 1985	T.R. 73.4%	-	-
4. Tate Thigpen 1985	T.R. 48%	-	T.R.76%
5. C. Sessa 1985	-	T.R. 60%	T.R.64%
6. Conte P.F. 1986	-	T.R. 54.3%	T.R. 56.2%
7. Lokich Jacob 1986	-	T.R. 74%	-

T.R. = Total response.

consideration for the reason mentioned above. In the patients having undergone complete surgery with less than 2 cm residual disease, the PAC regime i.e. the regime C stands out as the most effective one, shwing 100% complete response.

It is seen from Table VII that toxicity of all the 3 treatments were acceptable. Apartfrom nausea, vomiting and hair loss which were universal, only a minority of patients experienced severe toxicity. One patient had to discontinue Adreamycin because of neuro-toxicity and hence had to cross-over from regime C to regime B. In another patients, the treatment cycle had to be delayed because of the renal toxicity of Cisplatin.

Table VIII compares the clinical response rate achieved in different series. The response rates achieved in the present series compare well with the other series withhigh response rates. Until more effective cytotoxic

drugs are found, the PAC regime appears to be the one with reasonably high efficacy.

In the present series, the survival data of the 3 regimes is difficult to compare because of the small number of the patients treated.

DISCUSSION

In 1950 and 1960 attempts were made to treat advanced Ovarian Carcinoma (stage III & IV, inoperable cases) withsingle 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.

In 1974, cisplatin was reported to produce tumour regression in patients resistant to alkylating agents. These promising results were widely confirmed in subsequent studies, and today cisplatin is the drug of choice in advanced ovarian cancer.

In the last years treatment of advanced ovarian cancer has been characterized by an ever increasing aggressiveness; alkylating agents have been substituted by more effective combination chemotherapy, aggressive debulking surgery has proven its efficacy to stage the patients properly and increase response to subsequent chemotherapy and finally, second and third look laparotomies have become popular for a better definition of response.

This study demonstrates that the addition of adreamycin to cisplatin and cyclophophamide increases the percentage of clinical complete response in ovarian cancer. These results are in line with those reported in several pilot studies (Table VIII) that demonstrate that PAC is a highly effective induction regimen. This study further demonstrates that PAC regimen ws significantly superior to PC&PA mainly in the sub set of patients with less than 2 cm residual disease.

CONCLUSION

This study reports several findings that are relevant for the treatment of advanced ovarian cancer.

No. 1 Adreamycin is an effective drug that can significantly increase the clinical response rate achievable with Cisplatin and Cyclophosphamide.

No. 2 The PAC regime is superior to the other 2 regimes and is recommended, however, the cost can be limiting factor.

No. 3 The PAC regime is equatoxic with the other 2 regimes and is suitable for administration on OPD basis.

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