Original Article-2

Epithelial Ovarian Cancer– an Audit of Patients Treated Over 15 Years

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ABSTRACT

Background: We report our experience with chemotherapy in advanced epithelial ovarian cancer.

Patients and Methods: One hundred and twenty four patients of epithelial ovarian carcinoma (EOC) were seen between1990-2004. Of these, 87 were considered evaluable for this audit. Patients were referred either pre or post-operatively. In the initial part of our clinical practice, 9 patients received whole abdominal radiotherapy. The following chemotherapy regimens were used: cyclophosphamide, doxorubicin and cisplatin (CAP, n=24); cyclophosphamide and cisplatin (CP, n=37), Paclitaxel and cisplatin (PC, n=17). The median follow up for whole groups is 37months (range 5 to 186 months).

Results: The median age of the patients was 44 years (18-69 years). Compliance to chemotherapy was a function of number of cycles along with the average time between each cycle (planned interval - 21 days). Prescribed 6 cycles could be delivered in 66%, 92%, and 47% cases of CAP, CP and PC schedules, respectively with an average cycle time of 31days, 27 days and 28 days in the 3 arms. Significant overall, GI toxicity (grade 3 & 4) was seen in 35%, 13% and 31%, respectively. Similarly, grade 3 and 4 hematological toxicity was seen in 29%, 10% and 14%, respectively. The early mortality (within 4 weeks of chemotherapy cycle) documented was of 2, 1, 4 cases, respectively in the 3 arms. The estimated 5 year overall survival (OS) was 18% & 36% for patients treated with CAP & CP regimen. It has not reached yet for patients treated with paclitaxel and cisplatin. The median disease free survival (DFS) was 12,15 and 15 months, respectively.

Conclusions: It is a small comparative audit of 3 regimens. Present study confirms the results obtained in earier studies with large no of patients. It is likely that the perceived differences between the various regimens are only the result of retrospective nature of the study and small numbers.

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INTRODUCTION

Primary debulking surgery followed by platinum based chemotherapy is currently standard treatment approach for advanced epithelial ovarian cancer.

The purpose of this audit was to evaluate the toxicity profile and outcomes of the 3 principal chemotherapy regimes practiced in our department . All these patients have undergone surgery in community hospitals, which could be regarded as uncontrolled with respect to the degree of cytoreduction achieved.

PATIENTS AND METHODS

Between January 1990 and December 2004 all the patients of advanced epithelial ovarian cancers registered and treated by adjuvant therapy, are part of this audit. Baseline hematological, biochemical evaluation, radiological assessment of the abdomen and pelvis, either by ultrasound or a contrast enhanced CAT scan, was done in all

cases. The tumour marker serum CA-125 was available after 1994. Majority had a CA-125 level estimation after surgery. Cardiac reserve status for doxorubicin, and renal function for cisplatin were determined prior to administration of the drugs. Pre and post chemotherapy hydration and antiemetic cover for cisplatin and appropriate pre-medication for paclitaxel administration were followed.

Patients were referred either after cytoreductive surgery for adjuvant chemotherapy or with a diagnosis of carcinoma ovary for upfront (neoadjuvant) chemotherapy, which was to be followed by cytoreductive surgery. Those patients who had undergone incomplete initial surgery were referred for further surgery on completion of chemotherapy. Information regarding response, survival data, acute hematological, gastro-intestinal and other toxicities, compliance and crossover to other chemotherapy regimens were retrieved from case notes. Intended chemotherapy doses and cycles are shown in table no. 2. Acute morbidity of treatment was reported using the Radiation Therapy Oncology Group (RTOG) toxicity reporting criteria retrospectively.[6]

The patients were followed up after the completion of treatment at regular 3-6 monthly intervals with clinical and gynaecological examination. CA-125 was usually advised annually during follow up or at the time of suspicion of recurrence. CAT scan of abdonon & pelvis was advised after completion of chemotherapy to assess response and during follow up if a relapse was suspected.

Table 1. Patients Characteristics

	N=87 (%)
Median age in years (range)	44, (18-69)
Nulliparous:multi parous:unknown	13 :70:4
Histopathology*	
Mucinous	16(18)
Serous	22(25)
Adenocarcinoma (not specified)	40(46)
Other epithelial	9(10)
Stage *	
II	14(16)
III	45(52)
IV	24(28)
Unknown	4(5)
CA-125 (n=42)	
Preop – Median (range)	259 (6.18 - 4969)
Postop- Median (range)	78 (2.30 - 4045)
Type of chemotherapy	
CAP	24(29)
CP	37(44)
PC	17(20)
Others/RT	9(10)

*Percentages do not match due to rounding off. CAP: cyclophosphamide, doxorubicin and cisplatin; CP: cyclophosphamide and cisplatin; PC: paclitaxel and Cisplatin; Others- Hydroxyurea, Melphalan; carboplatin alone

Table 2- Compliance, acute toxicity and response

	CAP (n=24)	CP (n=37)	PC (n=17)
CT compliance Number of cycles	16/24 (66%)	34/37 (92%)	8/17 (47%)
Prescribed CT dose schedule	C=500mg/m^2 A=50mg/m^2 P=50mg/m^2	C=750mg/m^2 P=75mg/m^2	P=175mg/m^2 C=75mg/m^2
Average CT cycle time	31	27	28
Upper GI toxicity (Grade 2,3&4)	22%	13%	23%
Lower GI toxicity (Grade2,3&4)	13%	--	8%
Haematological toxicity (Grade 2, 3&4)	29%	10%	14%
Alopecia	50%	15%	33%
Neurological toxicity	17%	29%	33%
No of early death	2	1	4

CAP: cyclophosphamide, doxorubicin and cisplatin; CP: cyclophosphamide and cisplatin; PC: paclitaxel and cisplatin. CT-Chemotherapy

Table 3 : Response to Treatment

	CR	PR	NR	Not mentioned
RT+Other CT agents	5/9(56%)			4/9
NACT	8/18(44%)	1/18(6%)	2/18(11%)	7/11
Post surgical CT	31/44(71%)	6/44(13%)	7/44(16%)	
Salvage	11/21(52%)	1/21(5%)	9/21(43%)	

CR- Complete response, PR-Partial response, NR- no response, CT- chemotherapy, NACT -Neoadyuvant chemotherapy,

The choice of salvage treatment, in case of relapse, depended upon the time to relapse and site of relapse. Usually, for relapses after 1 year of completion of initial chemotherapy, the same regimen was repeated; but in case of earlier relapses, an alternative regimen was considered.

Data has been reported as medians and ranges. Survival expectations have been reported with the Kaplan-Meier method and the log-rank test used to determine statistical significance of differences. P-values <0.05 have been considered significant.

Table 4- Response to salvage chemotherapy

Type of chemotherapy	N (%)	CR %
CAP	3(14)	33%
CP	7(33)	50%
PC	6(29)	40%
Carboplatin + paclitaxel	5(24)	60%
Others	2(3)	31%

CAP: cyclophosphamide, doxorubicin and cisplatin; CP: cyclophosphamide and cisplatin; PC: paclitaxel and cisplatin. CT-Chemotherapy

RESULTS

Between January 1990 and December 2004, 124 patients with advanced epithelial ovarian cancers were registered. 15 patients did not receive treatment as their disease was far too advanced, 16 patients took treatment elsewhere and in 6, reasons were not known. In the initial part of our clinical practice, whole abdomen radiotherapy (RT) with or without pelvic and paraaortic RT was planned in 9 patients. This audit deals with the remaining 78 patients that were treated by surgery and chemotherapy.

The Median follow up of all the patients alive was 37 months (5-186 months). The demographic profile of the patient is shown in Table 1. The compliance rate of 74% (58/78) in this audit was the function of number, dosage and interval between 2 cycles (including minor variations). The average cycle length for the entire cohort and for all cycles was 28 days (4 weeks) i.e. 1 week greater than the planned interval. The reasons for noncompliance were delays in the treatment due to low total leukocyte count, patient default, public holidays and some of the initial patients were given chemotherapy at 4 weekly interval.

Toxicity: The hematological, gastrointestinal, alopecia and neurological toxicities are reported in table-2. Hematological and upper gastrointestinal toxicity was significantly higher in the CAP and PC group as compared to CP group. Alopecia too was seen in CAP and PC arms only. Neurological toxicity was increased in PC and CP groups. Neurological toxicity was seen in the form of paraesthesias. Neurological toxicity is a function of dose of cisplatin and Paclitaxel. Both drugs showed different neurological profile i.e. Paclitaxel group observed generalized parasthesias, tingling, numbness and myalgias. Cisplatin, on the other hand showed distal paresthesias and tinnitus. Significant hearing loss was seen in 2 cases. Long term renal toxicity was not seen in any of these patients. No cardiological toxicity was documented with doxorubicin.

Early Chemotherapy related death mortality (death due to any cause reported within 1 month of chemotherapy administration) was documented in 7 cases. The cause of death could have been chemotherapy related, progressive disease and other causes or unknown causes. There were 4 deaths encountered in the paclitaxel group- one died of neutropenic sepsis on day 20 of 1st cycle; second died on day 6 of 5th cycle for unknown reason at home; third on day 20 of 3rd cycle for reason not known; fourth died on day 15 of 2nd cycle due to intestinal obstruction and progressive disease. 2 patients died in CAP group; both died after 1st cycle - one on day 12 and the other on day-21 due to hematological toxicity. Chemotherapy toxicity as a direct cause of death could be ascribed in 1 patient in the PC arm and 2 in CAP arm.

There were no crossovers to other schedule in between as the response was assessed radiologically or by CA-125 markers only after the stipulated number of cycles were completed.

The choice of salvage treatment (n= 21) depended upon the time to relapse i.e. usually, for relapses after 1 year of completion of initial chemotherapy, the same regimen was repeated; but if earlier, an alternative regimen (between the other 2) was considered. There was no difference in complete response rate with any of the salvage regimes (Table 4). The average CR rate was 43% (range-31-60% with different combinations).

Estimated 10 year and 5 year overall survival was 25% and 29% respectively (median 24months) (Fig 1) The estimated disease free survival at 10 years and 5 years was 25% and 25%, respectively (median 14 months) (Fig 2).

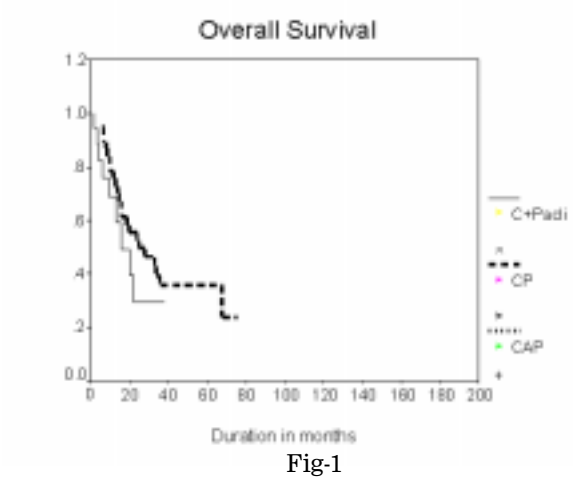

Fig-1

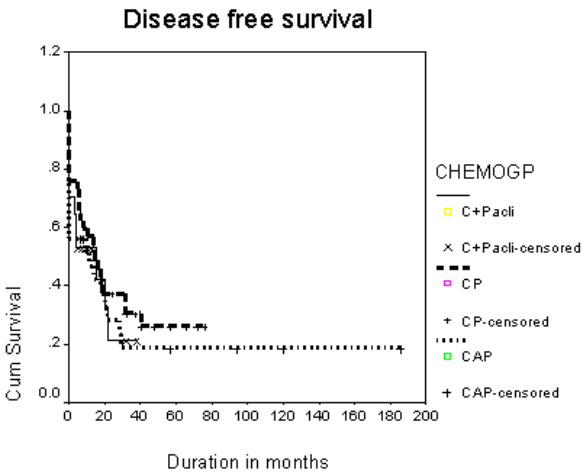

Fig-2

Neoadjuvant Chemotherapy (NACT)

In this audit, 18/87(20%) patients received 2-8 cycles of anterior chemotherapy, which was followed by surgery, and further chemotherapy (only in those who received less than 6 cycles of NACT). The reasons for opting for this therapeutic sequence was presence of pleural effusion (8), tense ascitis with or without peritoneal or omental deposits (7), large liver metastases (2) and patient's refusal to immediate surgery (1). With this sequence, 3 patients had significant hematological toxicity, and 2 GI toxicity (in the form of nausea and vomiting). Two patients died after 1 and 3 cycles of chemotherapy. The overall response rate was 44% (8/18). Six patients were lost to follow up within 1 to 24 months. The rest 4 are alive and free of disease at the time of reporting.

DISCUSSION

Initial debulking surgery followed by platinum based chemotherapy is the mainstay of treatment for advanced ovarian cancer. Earlier trials emphasized on the impact of volume of residual disease and the need for primary maximal surgical effort.[8,9] The present audit reflects the existing gynecological surgical approach over this period in our setup, wherein the primary surgery was less than optimum in all cases. Thus, the residual burden to be taken care by chemotherapy was greater. We evaluated the safety and efficacy of 3 chemotherapy regimes practiced as first line in this analysis. Although cisplatin was a common drug in all the 3 groups, cisplatin related toxicity, such as neurological toxicity, was largely seen in the CP and PC group wherein the cDDP dose was standard (75mg/m^2). CAP regime (cDDP dose @ 50mg/m^2) in the dose range mentioned, showed increased hematological toxicity and alopecia. Similarly Paclitaxel is also known to cause haematological toxicity and alopecia apart from neurological toxicity. The schedules followed in this audit were of lower intensity; hence the toxicity pro-

files were largely acceptable. Colony stimulating factors were not given prophylactically for neutropenia. Routine emetic cover included injectable ondansetron and ranitidine. In those patients where emesis was not controlled by regular measures, granisetron and dexamethsone were administered. The GI toxicity documented in this study is high (especially PC group). Episodes of diarrhoea which followed neutropenia and septicemia were also included in GI toxicity.

The experience with CP has been the largest (n=37) in this audit. This regimen was associated with outcome similar to CAP. Our experience with Paclitaxel has been limited. The 2-year results however have shown a superior freedom from disease as first line therapy (70% at 2 years for PC_versus 35% for CP and 30% for CAP; p=ns). Overall survival however was not different in these 3 sub-groups (At 2 years -47% vs. 50% for CP and 36% for CAP). This may have been due to successful salvage rates with 3 regimes. Moreover, –since the time periods in which the 3 regimes that were used were different and so the comparisons may not reflect the true picture (maturity of PC dataset is much less as compared to the other 2 arms).

The early mortality was high in the present series. The 8% early death rate is the death that has occurred either due to toxicity, or disease progression or other (including unknown) causes. It was difficult to ascribe the cause of death in patients who died at home. Since this was a retrospective audit, it was not possible to mention the exact number of chemotherapy related deaths based on the information from case notes. No attempt was made to interpret the exact cause of death from case records but reported as early mortality (if death occurred within 4 weeks of chemotherapy administration

There are multiple studies addressing the CAP versus CP issue and this has been further reviewed by several randomized trial[2, 10] and Advanced Ovarian Cancer Trialists Group (AOCTG)[11] and Ovarian Cancer Meta-analysis Project (OCMP)[1] overviews. Their results suggested that such an addition of doxorubicin yielded survival benefit.[9] However, they concluded that it was unclear whether this was due to addition of doxorubicin or increase in dose intensity since CAP and CP comparisons were confounded by difference in dose intensity in studies during that period. This implies that CP arm may have been equally effective if cDDP or cyclophosphamide have been administered at higher doses, thus ensuring, less (cardiac and hematological) toxicity and cost.

Paclitaxel was introduced in 1996 as the agent of choice for EOC. Gynecology Oncology Group (GOG) studied Paclitaxel and cisplatin combination concluded that this combination may be the first line treatment of this disease.[3] GOG 111 trial recommendations were not accepted by all for the following reasons: firstly, although treatment crossover was allowed between protocols, but paclitaxel had a limited availability as a 2nd line at that time. Secondly, since the meta- analysis had suggested that CAP is superior to CP, CAP should have been the standard arm instead of CP.[1] Hence, although it is clear from these trials that paclitaxel combination is an effective first line therapy, but there is an equally strong evidence for the use of single agent carboplatin as used by ICON 2 and 3.[4, 5, 10, 12, 13] They have shown equal outcomes when a platinum agent is used in adequate doses albeit singly. In fact, ICON 3 clearly suggests that paclitaxel is effective in these tumours, but may optimally be used as second line therapy following progression after single agent carboplatin therapy (reported in a third of patients in this trial). This strategy definitely needs to be looked into by the Indian researchers, as is it offers similar results without being prohibitively expensive.

However, the adequacy of primary surgery needs to be taken into account prior to administration of a single agent carboplatin, as the experience from ICON 2 and 3 is on patients in whom a TAH+BSO has been done along with

complete staging workup.[4,5]

Buyse et al[14] attempted to explain the differences between the results of various randomized trials available in literature. They compared the results of meta-analysis comparing CAP with CP and those of ICON 2 trial (CAP versus single agent Carboplatin). Superimposition of the survival plots of the standard arm (CAP) in both these comparisons made it possible (at least theoretically speaking) to compare their respective study arms. They inferred that CP (in the doses that were administered) was inferior to single agent carboplatin (AUC 5) which was as efficacious as CAP, as seen in the ICON 2 trial. Consequently, ICON 3 trial, which compared PC with either carboplatin or CAP, did not show benefit probably because the control group in this trial was superior to control group in earlier trials of ICON group. This approach by Buyse et al has provided valuable insight when direct comparisons between randomized trial yield ambiguous results.[14]

The data from Indian subcontinent is scarce. Pubmed search results revealed a study of 40 patients of advanced ovarian cancer treated by CAP observed a 3 year overall survival of 45%.[15] Population based Mumbai cancer registry report 5 year survival of 25% with this malignancy, which is similar to the present audit .[16]

Another unresolved question is whether inversion of the therapeutic sequence may affect the survival rate used in patients with neoadjuvant chemotherapy has primarily been used in patients with a poor performance status and those with massive tumour burden.[7,16] This practice has been studied in an EORTC trial with the aim of downsizing the tumour chemically in order to achieve radical resection subsequently (has been reported to result in over 90% optimal cytoreduction in a phase II trial). The present audit, with its limited experience with NACT cannot suggest the feasibility of such a sequence and needs to be studied further. In India, wherein the patients' often present in advanced and inoperable stages, chemotherapy may provide the desired cytoreduction and make it amenable to surgery. Moreover, the medical referral system is such that the patient when first seen by the local gynecologist, due to paucity of adequate Gynecology Oncology teams and setups, is operated upon by them. The surgery is inevitably sub-optimal and incomplete. These issues make NACT an option which needs to be studied further.

Thus, observations in present-study are of retrospective nature and have its own limitations, and should be interpreted with caution. Role of single agent carboplatin as well as use of neoadjuvant chemotherapy needs to be studied further for its routine use.

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