

Chemotherapy for Advanced Epithelial Ovarian Cancer

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Epithelial Ovarian Cancer

INTRODUCTION

Epithelial ovarian cancer (EOC) is the second common gynecological cancer among women in India. Its incidence varies from 4.5 to 5.5 per 100,000 women in India¹. Compared to west, incidence in India is low. At our institute, between 1991 and 2000, 815 patients were diagnosed to have ovarian tumour; 83% were epithelial, 9.5% germ cell, 3.2% stromal cell, 3.2% metastasis to ovary with primary elsewhere and 1% of cases had other categories of tumour (table-1). Before planning for chemotherapy for a patient with EOC, it is important to know detailed operative findings so as to decide pathological stage, amount of residual disease, post-operative CT scan of abdomen & pelvis and serum CA-125 levels. Proper assessment of any associated co-morbid conditions e.g. diabetes mellitus, ischemic heart disease is very important to reduce chemotherapy induced toxicity.

Table-1 : AIIMS Experience (1991-2000)

Histological subtype	No of Patients	Percentage
Epithelial	677	83.0
Germ Cell	78	9.5
Stromal	26	3.2
Metastatic	26	3.2
Others	08	1.0
Total	815	100

Following is the list of investigations required prior to proper planning of chemotherapy.

Table-2 : Investigations

Hemogram
Urine R/E
Liver and renal function tests
Chest X-ray P/A View
Details of the operative findings + Extent & location of residual disease
Histopathology & Grade of the tumour
CT scan of abdomen & Pelvis
Serum CA-125
Echocardiography or MUGA scan (for women above age of 45 years or earlier if indicated)

Early Stage

Patients with stage I & II are considered as early stage disease, though many investigators consider stage I only as early stage. Even in early stage disease histologic subtype and tumour differentiation (grade) have important bearing on the prognosis. Patients with stage IA & IB disease with grade I-II differentiation are considered to have low risk disease and have low risk of recurrence after surgery. The exceptions are- clear cell histology and high grade tumour (grade III) which have unfavorable prognosis and are considered as high risk disease. There is now consensus that women with low risk disease can be kept on close follow up after surgery without any post-operative chemotherapy. Patients with high risk disease i.e. stage IA, IB with high grade tumour or clear cell histology and those with stage IC (irrespective of grade) should receive adjuvant chemotherapy. It is widely accepted that early stage tumours that breach the capsule, or ruptured at surgery, or those associated with positive washings or ascitis that contain malignant cells have a worse prognosis².

Choice of chemotherapy in early stage disease have been a subject of debate in past, but now most investigators agree that 4 to 6 cycles of paclitaxel and platinum (either cisplatin or carboplatin) should be given. In the past, for

patients with stage I A & B , high grade disease, we have used single agent oral melphalan 0.2 mg/kg/day for 5 days every 4 weeks for 9 months. But after the reports of development of secondary leukemia following melphalan in 5-7% of patients at 5 years, we have abandoned this practice. General guidelines for the management of early stage are given in table-5. For patients with stage II disease, it is our practice to give 6 cycles of adjuvant chemotherapy using paclitaxel plus carboplatin.

Advanced Disease

For patients with advanced EOC , initial cytoreductive surgery is considered the gold standard³. All such patients should receive post operative chemotherapy . In early 1990's, all such patients had received cisplatin, and cyclophosphamide +/- adriamycin. Mc Guire et al (1996) for the Gynecology Oncology Group in a randomized study compared cisplatin and cyclophosphamide vs paclitaxel and cisplatin. Paclitaxel + platinum combination was superior (in terms of clinical response rates, pathological complete response rate , overall and progression free survival) to cisplatin + cyclophosphamide⁴. Subsequently, similar results were reported in the Intergroup trial⁵. These results were true both for patients with optimal (residual disease ≤ 1 cm) and sub-optimal debulked (residual disease > 1 cm) after surgery. Therefore, currently, paclitaxel + platinum (cisplatin or carboplatin) is the preferred chemotherapy combination as a first line. Our practice is to give atleast 6 cycles of chemotherapy and/or 2 cycles after achievement of complete response (CR) to all such patients after initial debulking surgery. We assess patients for response to chemotherapy at the end of 3 to 4 cycles with repeat clinical examination, serum CA-125 and CT scan of abdomen and pelvis. Those who achieve CR receive 2 more cycles of same chemotherapy. For patients with good partial response , we repeat assess-

ment at the end of 6 cycles and give 2 more cycles in complete responders. Response criterias are given in table 3. About 80% of patients respond to chemotherapy with clinical CR in half of them (30-40%). When these patients are subjected to second look laparotomy , about 20-30% are found to be in pathological CR⁷. Patients with evidence of persistent / progressive disease are advised re-exploration. With above approach, 5- year survival is 30 to 55% for patients who have nil or minimal residual disease (≤ 1 cm) after initial surgery. On the contrary, 5- year overall survival is 10-20% for patients with gross residual disease (>1 cm). Thus, amount of residual disease after initial debulking surgery is one of most important prognostic factor³.

Rate of fall of serum CA-125 can be a useful guide to response to chemotherapy. Most responding patients demonstrate 50% or higher decrease in serum CA-125 levels following 2 cycles of chemotherapy compared to pre-chemotherapy levels.

Table- 3 Response Criterias

Complete response : disappearance of all known disease on clinical and radiological examination along with normalization of CA-125 lasting for 4 weeks.

Partial response : ≥ 50 % reduction in the maximum diameter of a single measurable lesion or in case of multiple lesions a ≥ 50 % decrease in sum of the products of the perpendicular diameters of the multiple lesions.

Progressive disease greater than 25% increase in the size of the target lesion or in case of several target lesions, a greater than 25% increase in sum of the products of the perpendicular diameters of these lesions or the appearance of any new lesion. The new appearance of pleural effusion or ascitis is considered as progressive disease.

Chemotherapy Regimen

Commonly used chemotherapy regimens are given below.

Inj Paclitaxel 135 mg/m² IV 24 hours infusion
 day 1
 Inj cisplatin 75 mg/m² IV day 2
 Q 3 weekly x 6 cycles

OR

Inj Paclitaxel 175 mg/m² IV 3hours infusion
 day 1
 Inj Carboplatin (AUC 5-6) IV 2 hour infusion
 day 2
 Q 3 weekly x 6 cycles

Cisplatin can be replaced by carboplatinum. Dose of carboplatinum is to be calculated by Calvert's formula= (GFR +25) AUC 6 .

Cockcroft -Gault
 formula for GFR = $\frac{(140-age) \times \text{body wt in kg}}{72 \times \text{serum creatinine (mg\%)}} \times 0.85$

Both cisplatin and carboplatin have shown equivalent activity in this disease. However, carboplatin causes significantly less nausea / vomiting, and is clearly less nephrotoxic, neurotoxic and ototoxic than cisplatin (table-4) and is thus preferred over cisplatin for treatment of advanced epithelial ovarian cancer ⁸.

Table-4 : Comparison of cisplatin and carboplatin

Toxicity	Cisplatin	Carboplatin
Nausea/vomiting	+++	+
Nephrotoxicity	++	-
Neuropathy	++	-
Thrombocytopenia	-	+ / ++
Ototoxicity	+	-

Thrombocytopenia can be a major toxicity of carboplatin therefore dose of carboplatin must

be calculated carefully as above. For new patients , area under curve is taken as 6 (upper limit) and for patients with recurrent disease and previously treated with platinum compounds, AUC as 4 to 5. 3

Neoadjuvant Chemotherapy

In many patients with advanced EOC , optimum debulking may not be possible. Rather , aggressive surgery (e.g. bowel resection, peritoneal / diaphragmatic stripping or enblock resection of the ovaries, uterus, and sigmoid colon performed for optimal debulking) may be associated with considerable intra and post operative morbidity (e.g. haemorrhage, shock, fistula formation) , prolonged ICU stay and infections with mortality in 2-3% of patients³. Patients with poor performance status , and those with lesions involving diaphragm, base of small bowel mesentery, liver parenchyma, retroperitoneal nodes and upper abdominal structures (e.g. stomach and splenic hilum) are often unresectable. Benefit of initial surgery in such patients with gross residual disease is not obvious. CT scan of abdomen and pelvis could be of help in identifying such patients prior to surgery ⁹⁻¹⁰.

A number of investigators in small retrospective studies have reported use of neoadjuvant chemotherapy (primary) in patients deemed inoperable. This approach of using 3 to 4 cycles of primary chemotherapy followed by surgery results in , reduction in size of tumour with optimal cytoreduction in 60-90% of patients. Operative morbidity is reduced with decreased blood loss, decreased ICU stay and decreased post-operative hospital stay. Overall and progression free survival of such patients is comparable to those treated with conventional approach of debulking surgery (with gross residual disease) followed by chemotherapy¹¹⁻¹³.

Guidelines for Follow up

Our policy is to follow up these patients every 4 to 6 weeks during the first year; every 3 months during the 2nd & 3rd year, every 6 months during 4-5th year then once a year life long. On each visit , a detailed physical examination including pelvic examination is done. Serum CA-125 is repeated every 3 months during first 3 years, then 6 monthly till 5 years then yearly. Chest Xray ,

CT scan or US abdomen & pelvis every 6 months (or earlier if indicated).

Table-5 : Guidelines for treatment of Epithelial Ovarian cancer

Stage	Treatment Approach	5 year OS Literature	5 year OS At AIIMS
Stage I Low Risk Stage IA, IB Well or moderately differentiated	Surgery alone	92%	86%
Stage I High risk A, & B, high grade/ Clear cell histology/ IC	Surgery followed by adjuvant chemotherapy (4 to 6 cycles)	IA-88% IB-82%	77%
Stage III	Surgery followed by adjuvant chemotherapy (6 cycles)	Optimum debulking =30-55% Sub-optimal =10-20%	18%
Stage IV	Surgery followed chemotherapy (6 cycles)	12-17%	15%

OS-Overall Survival

Recurrent Disease

Management of relapse EOC is a challenging task. Most patients relapse with abdomino-pelvic disease . Uncommon sites of relapse include- liver, chest (pleural effusion) , spleen, lymph nodes, CNS or skin. The risk of relapse is proportional to initial stage of disease (table-6). Treatment of relapse depends upon a no factors e.g. treatment-free interval from last chemotherapy, response to prior chemotherapy, no of metastatic sites and performance status . Treatment - free interval is the most important predictor of response to salvage chemotherapy. Patients who relapse after a long period have a high probability of response to second line chemotherapy . On the contrary , patients relapsing within 6 months of last chemotherapy are generally resistant and unlikely to achieve meaningful response to same or similar drugs. Drugs such as topotecan, oral etoposide, gemcitabine, liposomal doxorubicin have been reported to result in response rates of 15-28% in the setting of refractory disease. However, the duration of response is generally short, < 6 months. Patients who relapse with localized disease after a long

treatment-free interval can be benefited with debulking surgery followed by chemotherapy. Patients with visceral relapse should receive systemic chemotherapy.

Table-6 Risk of recurrence

FIGO Stage	Risk of Relapse (%)
I	10-23
II	20-40
III	30-80
IV	>80

Treatment of patients with raised CA-125

Many patients have elevated serum CA-125 without clinical or radiological evidence of relapse. Our policy in all such patients is to repeat serum CA-125 after 2 – 3 weeks to rule out laboratory error. If it is still elevated then carefully observe the patient over next few weeks with repeat serum CA-125 at 2-3 weeks interval. The median time from first increase in CA-125 value to clinical /radiological evidence of relapse may vary from 6 weeks to 6 months. At present there is no data to recommend chemotherapy in patients with isolated CA-125 relapse. Patients with slow increase (<20% increase from base line value) are advised close follow up only. Patients with rapid rise of CA-125 are reviewed carefully for symptoms/ clinical and radiological disease. Patient having any of above are advised salvage chemotherapy. Best therapeutic approach in such a situation is not clear. Options varies from oral hormones (tamoxifen) to single agent oral etoposide (VP-16) or single agent platinum based therapy to combination chemotherapy.

Conclusions

Significant progress has taken place in the management of epithelial ovarian cancer during the past decade. Most patients with low risk EOC can be cured with surgery alone today. Patients with high risk disease or those with advanced disease , should receive adjuvant chemotherapy to reduce the risk of recurrence. Paclitaxel and platinum based chemotherapy is the standard combination for such patients. High relapse rates despite initial high response rates to chemotherapy reflects the development of acquired resistance to chemotherapy. Many new approaches e.g. re-

versal of drug resistance, Intraperitoneal chemotherapy, monoclonal antibody / gene therapy are currently under investigations.

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