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Perspectives In Malignant Ovarian Tumours

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INTRODUCTION

Gynaecologic cancers constitute 34.8% of all cancers in women (MMTR). In the Indian registries, it varies from 22.3% in Trivandrum to 34.8% in Chennai. Of all gynaecologic malignancies, ovarian cancers occupy the 2nd rank, way down after cervical cancer. This is similar in all Indian registries and majority of other developing countries. In the affluent countries however, gynaecologic cancers constitute only 8-14% of all cancers in women, the top ranking cancer being endometrium, followed by ovary. Cervical cancer is significantly lower (Table 1 & 2).

Table 1 : Proportion (%) of Gynaecological cancers to all female cancers Worldwide statistics:1993-1997 (Source:C15 Vol.VIII,2002:IARC)

Sites / India	All Gyn.Cancers	Ovary	Endomet.	Cervix	Others	Rank
Chennai	34.8	4.9	2.5	25.9	1.5'	Cervix
Mumbai	25.7	6.9	2.9	14.7	1.2	
Bangalore	30.0	4.8	2.6	21.3	1.3	Ovary
Delhi	29.7	6.6	2.7	19.3	1.1	Endo-
Trivandrum	22.3	5.6	2.9	13.1	0.7	metrium

Table 2 :Proportion (%) of Gynaecological cancers to all female cancers Worldwide statistics:1993-1997 (Source:C15 Vol.VIII,2002:IARC)

Sites / Affluent Countries	All Gyn.Cancers	Ovary	Endomet.	Cervix	Others	Rank
U.S.White	13.5	4.3	6.2	2.0	1.0	Ovary
U.S.Black	12.7	3.2	4.4	3.9	1.0	
U.K.	12.3	5.5	3.9	2.1	0.8	Endo
Finland	14.0	4.7	6.5	1.6	1.2	metrium
Japan	8.9	3.4	2.5	2.7	0.3	
Singapore, Indian	20.9	8.3	5.7	6.5	0.4	Cervix
DEVELOPING COUNTRIES						
Columbia, Cali	25.2	5.1	3.3	15.7	1.1	
Brazil	27.3	2.9	3.1	19.7	1.6	Cervix
Zimbabwe	29.4	3.3	2.3	22.7	1.1	
Thailand	24.9	3.6	2.4	17.9	1.0	Ovary
Philippines	23.9	7.3	4.2	11.6	0.7	
China	8.4	3.6	2.8	1.6	0.4	Endo- metrium

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Ovarian Cancers represent a heterogenous group of diseases. No other organ in the body gives rise to such diverse and interesting varieties of tumours. Over 80% of ovarian cancers develop from the surface epithelium. These constitute the most fatal cancers in women. In contrast, the relatively infrequent germ cell tumours of the ovary are highly curable.

INCIDENCE AND RISK

The CIR & ASR of ovarian cancer is 4.6 & 5.5/ 1,00,000 population (MMTR) which is significantly lower than in the affluent countries. There is considerable geographic and ethnic variation in incidence rates, suggesting the possible role of life style in etiology. The differential world pattern reflects a high incidence of cervical cancer and lower incidence of ovarian and breast cancer in the developing countries than in the affluent countries.

The cumulative risk of ovarian cancer in India ranges from 1 in 106-218 whereas the risk in the affluent countries is between 1 in 58-99. The risk in India is almost 3-4 times lower. The differential risk for endometrium and breast cancer is also similar (Table 3 & 4).

Table : 3 Crude Incidence Rate (CIR), Age standardized rate (ASR) and Cumulative Risk (0-74 years) of Carcinoma Ovary, Endometrium and Breast in India and Affluent countries

Registries	Ovary			Endometrium			Breast		
	CIR	ASR	Risk*	CIR	ASR	Risk*	CIR	ASR	Risk*
Chennai	4.6	5.5	164	2.3	3.2	264	19.5	23.9	38
Mumbai	5.6	8.0	110	2.3	3.9	197	19.7	28.9	31
Bangalore	5.3	5.1	170	1.9	2.9	278	14.4	21.1	42
Delhi	5.7	8.6	106	2.3	4.1	197	18.8	28.7	32
Trivandrum	4.1	4.5	218	2.1	2.4	358	17.8	19.7	48
U.S. White	18.9	13.2	68	27.7	18.7	44	134.1	92.1	10
U.S. Black	9.5	8.8	99	13.0	12.7	63	87.9	83.1	11
U.K.	21.9	15.1	58	15.7	10.3	78	124.6	85.2	11
Finland	17.6	10.8	82	24.6	14.4	55	114.1	72.4	13
Japan	10.5	7.1	141	7.8	4.8	189	48.1	33.1	29
Singapore, Indian	8.7	9.2	89	6.0	6.9	110	32.4	36.7	24
Compared to India	Slightly more			2 times more			Slightly more		

* cumulative Risk

Table : 4 Crude Incidence Rate (CIR), Age standardized rate (ASR) and Cumulative Risk (0-74 years) of Carcinoma Ovary, Endometrium and Breast of Developing countries

Registries	Ovary			Endometrium			Breast		
	CIR	ASR	Risk*	CIR	ASR	Risk*	CIR	ASR	Risk*
Columbia, Cali	8.1	10.1	85	5.1	6.8	114	29.6	37.3	24
Brazil	4.6	5.5	162	4.8	6.9	107	38.1	49.1	18
Zimbabwe	2.7	7.8	95	1.9	7.8	110	7.4	20.3	46
Thailand	5.6	5.2	193	3.6	3.5	251	17.5	16.1	61
Philippines Manila	9.2	13.5	68	5.4	9.0	89	34.2	54.2	17
China	8.7	6.0	152	6.8	4.7	182	41.6	27.2	34
Compared to India	Slightly more			2 times more			Slightly more		

* Cumulative Risk

Table 5 : Trend of Carcinoma Ovary, Endometrium Breast and Cervix:1982-1999

Registries	1982	1983-87	1988-92	1993-97	1998-99	
CARCINOMA OVARY						
Chennai	2.7	4.0	4.2	4.6	5.2	↑
Bangalore	3.0	3.1	3.1	3.5	3.5	
Maumbai	4.1	4.2	4.5	5.6	6.1	
CARCINOMA ENDOMETRIUM						
Chennai	1.5	1.8	1.9	2.3	2.7	↑
Bangalore	1.2	1.3	1.5	1.9	2.1	
Mumbai	2.1	2.0	2.1	2.3	2.8	
CARCINOMA BREAST						
Chennai	14.3	14.3	16.6	19.5	22.1	↑
Bangalore	11.4	15.8	17.7	14.4	16.8	
Mumbai	13.2	11.6	14.6	19.7	20.0	
CARCINOMA CERVIX						
Chennai	32.4	34.2	27.7	24.6	24.6	↓
Bangalore	22.5	19.1	18.3	15.5	13.9	
Mumbai	12.6	12.9	12.9	12.9	12.3	

TREND OF OVARIAN CANCER IN INDIA

Ovarian cancer incidence is slowly but steadily increasing. Between 1982 & 1999, the CIR has increased from 2.7 to 5.2 which is significant (almost double). Similar rising trend in endometrial and breast cancer has also been documented. There is an increasing cancer burden at all sites (Table 5,6).

Table 6 : Estimated Burden of New Cancer Cases Among Women in India

	1985	1992	% Change	2001	% Change
Population (in millions)	356	420	+18.0	503	+41.3
CIR/10^5					
Cervix	23.0	21.2	-7.8	18.9	-17.8
Breast	13.9	14.8	+6.5	18.0	+29.5
Ovary	3.8	4.6	+21.1	5.3	+39.5
Endometrium	1.7	2.1	+23.5	2.6	+52.9
No of Cases					
Cervix	82,000	89,000	+8.5	94,000	+14.6
Breast	49,500	62,000	+25.3	89,000	+79.8
Ovary	13,5000	19,3000	+43.0	26,600	+97.0
Endometrium	6,000	8,800	+46.7	13,000	+117.0

Source : NCRP Consolidated Reports

HEREDITARY OVARIAN CANCER

Molecular genetics

At least 10% of all epithelial ovarian cancers are associated with autosomal genetic predisposition. 90% of these occur in the context of the breast and ovarian cancer syndrome with 60% attributable to BRCAI & 30% to BRCA2. Another 5% are associated with hereditary non polyposis colorectal cancer (HNPCC) caused by mutation of one of several DNA mismatch repair genes.

The life time risk of developing ovarian cancer in association with BRCA mutation is approximately 40%.

HEREDITARY MANIFESTATION OF OVARIAN CANCER

Three different types of manifestations are documented:

1. Breast or ovarian cancer syndrome where both cancers are seen in excess and in some cases with the same incidence (HBOC).
2. Ovarian Cancer associated with excess of colorectal and endometrial cancer (HNPCC).
3. Site specific ovarian cancer - is a variant of the breast ovarian cancer syndrome in which early onset breast cancer is rare.

CLINICAL SIGNIFICANCE OF BRCA MUTATION IN OVARIAN CANCER

It occurs at an earlier age and are biologically high grade tumours.

Recent studies show that patients with BRCA mutations have better survival than those without BRCA mutation and this is related to better chemo responsiveness. This is reported to be due to the role of BRCA protein in repair of DNA damage induced by chemo therapeutic agents.

EPIDEMIOLOGY & ETIOLOGY

There is a distinctly higher incidence of ovarian cancer in the affluent populations. Ovarian cancers run parallel to breast and endometrial cancers (Table 5).

Pregnancy and lactation are protective, the risk of ovarian cancer reducing with more number of children. Late age at first child is an added

risk factor. 10% of ovarian cancers are associated with autosomal genetic predisposition.

EARLY DETECTION

Late diagnosis is the rule in ovarian cancer and accounts for the poor outlook. Of the ovarian cancer that report for treatment 80% belong to state III and IV and only 20% belong to stage I & II. This unfavourable distribution is because ovarian cancers are seldom symptomatic in the early stage.

The reasons for late diagnosis are the lack of characteristic symptoms. A small enlargement of the ovary does not cause any significant symptom till it is large enough to cause pressure effects or produces ascitis. A lucky patient could have either a torsion or haemorrhage which will result in seeking early medical advice. The reasons for delay are both patient and physician related.Most often the patient has vague abdominal discomfort, or weight loss or loss of appetite and lands up with a gastroenterologist.

Early detection of ovarian malignancy requires a high index of suspicion. The importance of careful physical examination in peri & post menopausal women with pelvic or abdominal symptoms cannot be over estimated.

The presence of an adnexal mass mandates further investigations. In the reproductive period, a small unilateral, asymptomatic, cystic mass can be kept under observation for a few weeks. If the mass shows evidence of regression, one can wait but if it increases in size, it will need further investigation.

Any tumour that is bilateral, solid or irregular in consistency, symptomatic or asymptomatic and associated with ascitis, needs exploration.

SCREENING FOR OVARIAN CANCER

There is ongoing effort to design an efficacious, cost effective ovarian cancer screening method. The existing tests, routine pelvic exam, CA-125 and transvaginal ultrasound are being optimized and combined as a multimodal strategy.

New serum markers are under development and evaluation, the promising ones at present are HE4 & mesothelin.

Ovarian cancer screening with peritoneal lavage and pouch of Douglas aspiration cytology had poor acceptance.

Ovarian cancer detection is expected to improve when multiple markers are used. Large well designed randomized trials are under way but will take years for results to be available.

ONGOING TRIALS

1. PLCO Screening Programme

   (Prostate, lung, colorectum and ovary)

   CA-125 and Transvaginal ultrasound are used simultaneously annually as a first line screening.

2. UK Trial: uses CA 125 initially followed by trans vaginal ultra sound based on CA-125 value (> 30 u/ml).

RISK FACTORS

The risk factors identified are age and ovarian cancer family history and/or breast cancer which could be used to identify a sub population of women who can be given the benefit of screening. A patient with a family history of either ovarian, breast or colon cancer needs aggressive surveillance.

RECOMMENDATIONS FOR SCREENING

1. Screening with ultrasound and CA-125 in post menopausal women as part of a clinical check up.
2. Those with hereditary ovarian cancer syndrome need specialized care and surveillance.

Surveillance and Management is difficult since early detection methods are limited.

Although annual CA-125, pelvic exammation and trans vaginal ultra sound are recommended, it cannòt be accepted as proof. Women with family history of ovarian cancer need careful surveillance. They also need breast Screening. Prophylactic oophorectomy reduces risk significantly but does not offer 100% protection.

EVOLVING CONCEPTS IN MANAGEMENT OF OVARIAN CANCERS

Management of ovarian cancer is a major challenge for gynaecologic oncologists. Despite a vast amount of clinical and laboratory research, improved surgical techniques and an everexpanding armamentarium of chemotherapeutic agents, it still continues to be the most lethal of gynaecological malignancies and a cause of considerable morbidity.

Upto 1960s, management of ovarian cancer was essentially surgery (maximum surgery possible.[1-2] The pattern of spread and recurrence in ovarian cancer required radiotherapy to the whole abdomen. Lack of tolerance to RT (over such a large area) limited its value. The advent of chemotherapy by 1970 virtually displaced radiotherapy from ovarian cancer management. Chemotherapy also introduced the concept of multidisciplinary approach in therapeutic oncology.

Surgery however still plays a major role in the comprehensive management of ovarian cancers.

Meta Analysis of primary cytoreductive Surgery by a number of investigators has made important observations.[3]

1. Extent of cytoreductive surgery varied widely based on experience and determination of the surgeon or the skepticism regarding the need for such extensive surgery , based on survival data.
2. Response to chemotherapy and survival was clearly related to volume of residual disease (Griffith & Fuller).[1]
3. The volume of residual disease - is it a biologic difference or surgical skill?

   It could be the result of a less aggressive tumour, which is more amenable for resection than the skill of the surgeon and the residue becomes small/optimal. A more aggressive tumour can end up in a sub optimal residue.
4. For a patient with a mass larger than 10 cms or with clinical ascitis, potential cure by chemotherapy was minimal even if maximum cytoreduction has been achieved prior to chemotherapy (Hacker).[2]
5. Value of primary radical cytoreduction, in improving survival has been questioned by some investigators.
6. Using primary cytoreductive surgery to increase proportion of patients with optimal residue in case of advanced disease confers only a small survival benefit on the group as a whole. Meta analysis by Hunter et al[5] on primary cytoreductive surgery suggests that only a small improvement in median survival is achieved by maximum primary cyto reductive surgery.
7. Potter et al[6] questioned the role of bowel resection when sub optimal residual disease existed at the end of surgery.

The available data thus raises three major issues **and highlights the need for reappraisal in our concepts** of ovarian cancer management.

1. Is primary surgical cytoreduction mandatory?
2. Should primary cyto reduction followed by adjuvant chemotherapy be accepted as standard care in locally advanced disease?
3. What is the role of neoadjuvant chemotherapy/primary chemo debulking followed by interval debulking surgery.

INTERVAL DEBULKING

In the evolution of malignant ovarian cancer management, we need to trace the evolution of the concept of interval debulking and define optimal debulking.

PRIMARY SURGICAL STAGING & DEBULKING

Concept of primary surgical cyto reduction was introduced prior to introduction of imaging technics like ultrasound, CT scan, tumour markers, advent of laparoscope and availability of chemotherapeutic drugs. The data presented above would indicate that any cytoreduction must be as aggressive as possible and should aim at optimal debulking since the outlook would depend on volume of residual disease. The available data also documents that

even after primary aggressive cyto reduction, a sub optimal residue is an unfavorable factor. The reported rates of maximum cyto reduction varies widely based on experience, expertise and determination of the surgeon. The patient's general condition to withstand prolonged surgery is yet another factor.

The concept of primary surgical cyto-reduction has never been questioned or evaluated in a randomized setting.

DEFINITION OF OPTIMAL DEBULKING/ CATEGORIZATION OF RESIDUAL DISEASE

The definition of optimal debulking had been changing over the years from the largest residue of 2 cms to less than 0.5 cm. Today, residual tumour volume has been identified as a prognostic factor. Total tumour volume less than 1 gm i.e 1x1 cm and not the size of the largest residue is considered optimal. Multiple seedling peritoneal metastases carries a poor outlook. Today there are ongoing studies with total surgical peritonectomy in these cases.

At the Cancer Institute(WIA),Chennai, we follow the following guidelines. It is appreciated that smaller the residue, singly or totally, the better the outlook. Any cut off value is empirical.

RESIDUAL DISEASE CAN BE DEFINED AS:

1. No residue (all macroscopic tumour removed, peritoneal cytology negative).
2. Minimal Residue (all gross tumour removed, cytology positive).
3. Optimal Residue (< 2cms where both chemotherapy and radiation are likely to be effective and useful).
4. Gross Residue (residue > 2 cms , multiple residual lesion & Non resected tumours).

CANCER INSTITUTE EXPERIENCE

Our experience in locally advanced breast cancer and oral cancers over many years documented significant enhanced response and survival with combined neoadjuvant chemotherapy plus radiation stressing the importance of a multi modality combined approach to management. We have therefore practiced neoadjuvant chemotherapy followed by surgery in all locally advanced ovarian cancers over many years.

The stage distribution of ovarian cancers at the Institute highlights that locally advanced disease constitutes over 70% of all cases (Table 7).

Table 7 Stage Distribution of Ovarian Cancer (n=886) Cancer Institute, 1984-2001

Stage	%
I	6.7
II	7.3
III	33.1
IV	13.3
SNP	39.6
All stages	100.0

RATIONALE OF NEO-ADJUVANT CHEMO-THERAPY

Neo-adjuvant chemotherapy has a direct cytotoxic effect. It reduces tumour bulk with rapid improvement of quality of life. At surgery, it makes the planes of resection more obvious & therefore far easier surgery. If & when surgery is successful, further chemotherapy can be given when the residual burden is minimal. It provides an opportunity for change of chemotherapy schedule if indicated.

Complications after interval surgery are minimal.

Dose Intensive neo-adjuvant chemo-therapy will increase the number of patients with minimal residual disease.

Chemotherapeutic response is usually seen within 3 cycles. Patients resistant to platinum based regimens are unlikely to gain any long term remission from any other regimen or by secondary cytoreduction.

CANCER INSTITUTE PROTOCOL OF MANAGEMENT FOR LOCALLY ADVANCED OVARIAN CANCER

In all locally advanced ovarian cancer with or without ascitis, we practice aggressive neo-adjuvant chemotherapy. No staging laparo-tomy is done or primary surgical cytoreduction is done. Staging is done as per clinical and imaging evaluation. Diagnostic laparoscopy

is accepted if necessary. The object is chemo cytoreduction in an effort to avoid/reduce sub optimal cytoreduction and increase the number of patients with optimal/no residue. At the end of 3-4 cycles, patients are subjected to interval surgery.

Any progression during chemotherapy will contraindicate surgery. Tumours that are non responsive to Taxol-Platinum based regimen are unlikely to benefit by surgery.

At the Cancer Institute, 83 patients were subjected to interval debulking between 1997-2000). All of them have a minimum of 3 year follow up. Of 83 patients, 56 had optimal surgery (67.5%) with a disease - free survival of 41.2% and overall survival of 52.6% (Table 8). The world data on primary optimal surgery is 33% with a DFS of 18.20%.

Table 8:3 & 5 Year Survival (%) Stage IIIC Epithelial Ovarian Cancer Institute Cancer Institute (WIA), Chennai:1990-98

Modality of Treatment	Suitable for Int. Surgery	Debulking Achieved	Survival%		
	No (%)	No (%)	OS 3 yrs.	OS 5 yrs.	DFS 3 yrs.
Primary surgery & Adj. CT (n=74)	17 (20.0)	9 (53.0)	44.4	40.0	44.4
Neo -Adjuvant CT (n=71)	33 (46.0)	21 (65.5)	66.7	59.0	47.6

OS-Overall Survival, DFS-disease free survival

Available data justifies reappraisal of the present concept of maximum cyto-reduction followed by chemotherapy.

STATUS OF NEO-ADJUVANT THERAPY

Neo-adjuvant chemotherapy in locally advanced ovarian cancers continues to have limited acceptance. Available data on benefits of cytoreduction and survival data justifies the need for a carefully planned clinical trial. No doubt, there will be difficulties in defining criteria of eligibility but it can be resolved. There should be no speciality bias.

WORLD TRIALS

The poor survival in locally advanced cancers naturally led to a number of newer approaches. One of the important concepts has been introduced is neoadjuvant chemotherapy and interval debulking.

Some of the studies are:

1. A sub group of patients, who had primary sub optimal cytoreduction were subjected to 3 cycles of chemotherapy followed by interval debulking. Yet another group continued with 6 cycles of chemotherapy.

   The former group who had interval debulking did better than those who did not have the surgery.[4,5]

2. EORTC (1996)[6] also documented that overall survival was significantly better in women who had interval debulking.

3. Other studies reported better quality of life in the latter group.[7,8]

PROPOSED INDICATIONS FOR PRIMARY CHEMOTHERAPY AND INTERVAL DEBULKING

I. Absolute Indications

1. Stage IV disease (except pleural effusion).
2. Metastases more than 1 gm at sites where surgery to "no residual disease" is impossible (porta hepatis, sup. mesenteric artery).

II. Relative Indications for patients with estimated metastatic load of > 100 gm

1. Uncountable peritoneal metastases.
2. Large metastatic plaque in the diaphragm.
3. Large volume ascitis.
4. PS 2-3 (WHO).

SURGERY FOR TERMINAL OVARIAN CANCER

A large percentage of ovarian cancer patients will develop bowel obstruction. The factors in bowel obstruction in an advanced ovarian cancer are multifactorial. It can range from electrolyte imbalance following chemotherapy to compression by tumour masses.

Surgical intervention should be planned after very careful consideration of the possible etiologic factors, correction of medical factors and an overall assessment of the immediate condition of the patient in relation to the future prognosis for the patient. This is an area where the skill of the surgeon is not just the surgical skill but the assessment of the overall situation of the patient. It will be difficult to say as to who will benefit/not benefit/become worse, for how long and at what morbidity? Multiple levels of small bowel obstruction with or without large bowel obstruction is possible.

A short trial with steroids along with small glycerine enema can be very useful in some patients.

MANAGEMENT OF RECURRENT DISEASE

Options are few and management controversial. Good supportive care would be the best.

ROLE OF RADIOTHERAPY IS LIMITED

Can be useful in vaginal recurrence, or small pouch of Douglas recurrence.

OPTIMISING CHEMOTHERAPY IN OVARIAN CANCER

Chemotherapy has been responsible for significant improvement in survival in ovarian cancers.

Chemotherapy in ovarian cancer can be primary chemotherapy (neo adjuvant/chemo cyto reduction), adjuvant chemotherapy (post surgery whatever the size of the residue), salvage chemotherapy - when first line treatment fails or at time of recurrence/relapse.

THE ISSUES FOR DISCUSSION ARE:

1. Is combination therapy superior to single agent therapy?
2. If combination therapy is superior, how many drugs?
3. Are Platinum and Taxol mandatory components of ovarian cancer regimen? If platinum or Taxol is essential, Revise platinum or Taxane?
4. What is the optimal schedule, dose intensity and length of chemotherapy?

EVOLUTION OF CHEMOTHERAPY IN OVARIAN CANCERS

Ovarian cancers are highly chemosensitive tumours. Upto 1970s, the drugs used were essentially alkylating agents. They were used either as single agents or in combination. The regimen used were cyclophosphamide (CTX) , methotrexate and 5-FU or CTX with adriamycin. The results were far from satisfactory.

INTRODUCTION OF PLATINUM

Cisplatin was introduced in 1970 and little later Carboplatin. Both were found to be highly active in advanced ovarian cancers.

A series of randomized trials were undertaken.

1. Cisplatin singly was compared with non platinum containing regimen.
2. Cisplatin containing regimen, 2 drug combination. Cisplatin+CTX was compared with 3 drug regimen - Cisplatin+CTX+ADR

The results clearly documented a superior survival in platinum containing regimen. Also 2 drug combination was as good as 3 drug regimen. No definite advantage was seen with addition of anthracyclines.

CARBOPLATIN

With the introduction of Carboplatin further randomized trials compared single agent cisplatin Vs carboplatin. There was no significant difference in efficacy between cisplatin and carboplatin.

Platinum based regimen, either cDDP or carboplatin came to be accepted as standard care protocol. Carboplatin was preferred due to its better toxicity profile and ease of administration.

TAXANES

One of the major handicaps faced in the chemotherapy of ovarian cancers is the cross-resistance. In late 80's, taxanes were found to be useful in platinum resistant ovarian cancers. Randomised trials by GOG and other groups in Europe and Canada evaluated.[9,10]

1. Combination of Taxane + cDDP Vs Taxane+Carboplatin.

2. Platinum+ Taxane Vs Platinum+CTX.

Taxane containing regimen was distinctly superior. Carboplatin was preferred due to better toxicity profile.

The conclusion of the above trials were:

1. Single agent cDDP & Carboplatin showed equal efficacy but carboplatin is preferred in view of lower toxicity & ease of administration.

2. In Taxol combination, carboplatin is preferred.

3. Of Taxanes, docetaxel is preferred.

(Thus, paclitaxel+platinum derivative have become the standard combination).

Enhancing therapeutic effects of Platinum Increase in no of cycles from 5-6 to 8-12 did not yield any advantage. Increase in dose intensity using standard dose vs 50% increase also did not document any definite advantage.

ISSUES UNDER INVESTIGATION

The role of maintenance therapy/consolidation chemotherapy is under investigation.

Since Taxanes are cycle specific, additional cell kill can be expected even after 5-6 cycles. An ongoing GOG trial compares 3 cycles vs 12 cycles.

Newer Drugs under evaluation are liposomal anthracycline (Caelyx), Topotecan and Gemcitabine.

NEWER APPROACHES IN OVARIAN CANCERS

Gene Therapy

Investigation and development of gene therapy as an anti cancer strategy in human ovarian cancers are ongoing. Preclinical and clinical trials so far have not documented anti tumour activity.

IMMUNOLOGIC APPROACHES

Ovarian tumours are immunogenic. Many ovarian cancer related antigens have been identified. For minimal disease state, vaccination and for advanced disease, adoptive T cell therapy, cytokine infusion, antibody therapy are all under investigation.

High Dose Chemotherapy with stem cell transplant has not yielded worthwhile improvement in survival and is investigational.

INTRAPERITONEAL (IP) CHEMOTHERAPY

Intraperitoneal chemotherapy for ovarian cancer has number of theoretical advantages.

In our experience IP chemotherapy can be useful in microscopic and minute residues following debulking surgery or systemic chemotherapy. It's greatest potential therefore will be in the multimodality approach in early ovarian cancer.

The author has used it routinely as a consolidation therapy following surgery in I B, C, II B & C and in those stage III cases where we have achieved a pathologic remission.

ONGOING TRIALS

In small volume disease, I.V cDDP Vs Intraperitoneal cDDP is being evaluated.

PROGNOSTIC FACTORS

The major factors that determines survival, overall and disease free are stage of tumour, residue after surgery, histology and grade of tumour, age of patient. Other factors like performance status, co-morbid conditions and prior treatment also play a role. Of all these, residue after surgery is the most important.

BIOLOGICAL VARIABLES UNDER STUDY

Many biological variables that predict response to chemotherapy and survival are being evaluated extensively. Some of them are tumour ploidy, proliferative fraction, receptor and oncogene expression, tumour suppressor genes etc. However, with the available data none of them can be considered as independent factors in treatment planning.

LAPAROSCOPY

The introduction of laparoscopy has added a new dimension to diagnostic capability in intra abdominal lesions. In gynae-oncology, it has helped in pre treatment evaluation in cancer of the cervix, endometrium and ovary. It can be of significant value in evaluating chemo-therapeutic response and useful prior to interval debulking.

The role of laparoscopy in therapeutic gynaecologic oncologic surgery is yet to be documented. Data on survival and complications are not yet available. No randomized trials have been done to document its value. A randomized trial in early cervical cancer is planned at the Cancer Institute. In ovarian cancers, the role of laparoscopy will be doubtful.

GYNAECOLOGIC ONCOLOGY

In conclusion, I would like to reiterate that gynaecologic oncology is a speciality by itself. It is not just mastering ultra radical surgery or administering chemotherapy or application of radiation therapy but one with knowledge and skill to utilize all effective forms of therapy.

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Abbreviations : CIR - Cancer Incidence Rate, ASR - Age standardized Rate, MMTR - Madras Metropolitan Tumour registry, DFS - Disease-free survival, OS - Overall Survival, CTX - Cyclophosphamide