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From the Desk of Director Research

Ovarian cancer, especially epithelial ovarian cancer, is a prevalent gynecologic malignancy whose prognosis in most cases remains poor despite advances in therapy. No effective screening methods for ovarian cancer that have been adequately validated are available. The management of ovarian cancer encompasses a combination of surgical resection and chemotherapy. Despite the benefits of surgical intervention, the specific biology of a patient's disease is central to her response to chemotherapy, duration of remission and ultimate survival. There remains a significant risk for recurrence and resistance to therapy, and hence there is a need to improve upon the current treatment options. New targeted biologic agents hold great promise for improving the outcome of ovarian cancer. Finding the optimum treatment paradigm for ovarian cancer patients would remain the goal of improving outcomes.

The present issue highlights molecular genetics of ovarian epithelial carcinomas, screening, role of surgery, chemotherapy and targeted therapy. We are grateful to Dr Lalit Kumar, Professor Dept of Medical Oncology, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, for providing the 'Guest Article' on "Targeted Therapy in Ovarian Cancer".

Other regular features covered in this issue are "Globe Scan", "Research & Development", "New Technologies" and "Watch-Out". "Workshop on Meditation" organized by the Institute with the Art of Living Foundation has also been described in this issue.

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Views and suggestion from the readers are welcome.

Dr D C Doval

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SPECIAL FEATURE

ROLE OF SURGERY IN OVARIAN CANCER

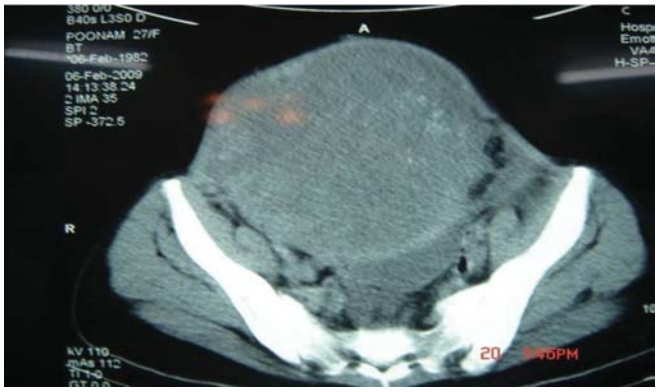
Introduction

As per Delhi Cancer Registry 2006-07, ovarian cancer is the third most common diagnosed cancer and second leading cause of death among women. Since there is as yet no proven screening test for this disease, most women present with advanced disease at diagnosis. A majority of these women have vague, non-specific pelvic, abdominal and menstrual symptoms.

Initial evaluation includes a thorough history and physical examination, imaging studies, assessment of tumour markers (CA-125), possible biopsies and endoscopies. Chemotherapy has an important role in the treatment of this disease in the neoadjuvant, adjuvant and recurrent setting. However, for the medically fit patient, surgery has an extremely important role in the management of ovarian cancer for the diagnosis, primary therapy and treatment of recurrent disease. This is especially true for epithelial ovarian cancer(EOC), which may also include fallopian tube cancer and primary peritoneal cancer which have the same behavioral pattern.

Surgical management of patients with ovarian cancer includes primary cytoreduction, interval cytoreduction and secondary cytoreduction. Primary cytoreduction refers to the initial surgical excision of the tumour and tumour involved organs prior to chemotherapy. According to the Gynaecologic Oncology Group (GOG), optimal surgical cytoreduction is defined as residual tumour less than 1 cm. The National Cancer Institute, as well as all tertiary cancer centres have an important role in providing this quality of surgery, especially in advanced cases. Optimal debulking and removing all gross disease has also been shown to increase survival. Each 10% increase in cytoreduction correlates with a 5.5% increase in median survival.

Interval cytoreduction is performed on patients who have previously received neoadjuvant chemotherapy. Secondary cytoreduction refers to the surgical management of recurrent ovarian cancer, especially for patients with long disease-free interval. Cytoreduction and debulking are interchangeable terms and the previously performed second look operation after completion of primary therapy is no longer considered



Adnexal mass on imaging

relevant. All these procedures should be performed by a specialist trained in ovarian cancer surgery.

Staging Procedure

Accurate surgical staging is particularly important for apparently early stage disease, i.e, woman with an ovarian cancer that appears grossly confined to the ovary. Approximately 25% to 30% of women with apparent early stage disease will be upstaged upon thorough surgical staging.

The staging procedure is normally performed via a vertical incision extending above the umbilicus and a thorough exploration is performed to assess the extent of the disease. Peritoneal washings are obtained or ascitic fluid is removed if present. All peritoneal surfaces and organs are palpated, including the diaphragm, liver, spleen, gall bladder, small and large intestine and mesentery. The retroperitoneum is carefully evaluated for enlarged and bulky nodes. The omentum and adnexa are carefully inspected for any involvement, potential sites of bowel obstruction are evaluated, and addressed. Masses apparently confined to the ovaries are removed intact.

Once the amount and distribution of the disease is delineated, a decision is made regarding the feasibility of optimal tumour debulking. In the absence of gross extra ovarian disease, multiple peritoneal biopsies are obtained along with a pelvic and para-aortic lymphadenectomy. In a trial, 427 women with stage III/ IV ovarian cancer were randomised for either systemic lymphadenectomy or resection of bulky nodes. No statistical difference in the 5-year overall survival rate (48.5% vs 47% respectively) was noted. Systemic lymphadenectomy, however, was associated with increased progression-free survival compared to the no lymphadenectomy arm; 31.2% vs 21.6%. Therefore, the recommendation is to resect bulky tumor-involved nodes in advanced stage ovarian cancer.

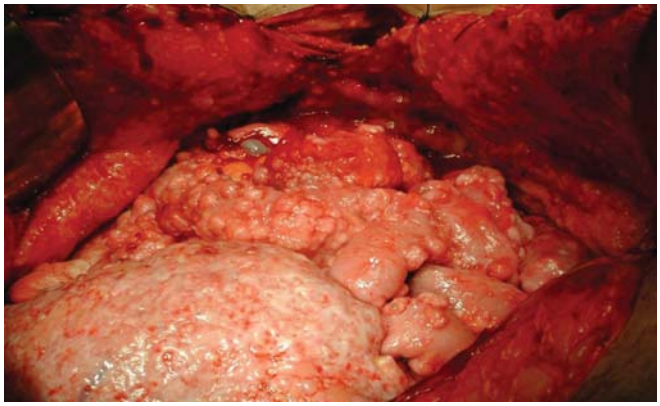
If there is significant disease in an area that cannot be resected, such as small bowel mesentery and large volume disease at the diaphragm or in the rare case that most of the disease involves the bowel or the other vital organs, the surgeon must remember the Hippocratic oaths and "first do no harm", and it might be more prudent to obtain a tumor biopsy specimen and close the abdomen.

Primary Cytoreduction

The cornerstone of a successful ovarian laparotomy is optimal debulking where we leave behind < 1 cm of gross disease. For advanced-stage ovarian cancer, the optimal cytoreduction rate has been shown to vary from 17% to 87%. In a study of 102 patients with stage II and III EOC, residual disease >1.5 cm was identified as a poor prognostic indicator. Hoskins et al also reported on the size of residual disease and overall survival in patients with stage III ovarian cancer. Patients with suboptimal cytoreduction (>1 cm) but with smaller diameter residual disease (<2 cm) still had an increased overall survival compared with those who had larger volume residual disease (>2 cm). For optimal cytoreduction, one may have to perform a variety of procedures, such as splenectomy, diaphragm stripping, partial hepatic or bladder or bowel resection other than performing total abdominal hysterectomy, bilateral salpingo oophrectomy, pelvic and paraaortic lymphadenectomy and omentectomy.

Although the GOG defines optimal cytoreduction as residual disease of < 1 cm, data from more recent studies suggest that overall and progression-free survival are improved to a great extent when maximal cytoreduction is achieved and this has led many to advocate for complete resection with the end goal of no residual disease. However, maximal cytoreduction requires expert surgical techniques usually available at a tertiary care centre as it is often associated with significant preoperative morbidity. Along with improved survival in patients with advanced disease, surgery also improves the associated symptoms, such as bloating, abdominal distension or abdominal pain. Primary cytoreduction is to be followed by chemotherapy, the effect of which is enhanced by optimal debulking.

Computed Tomography (CT) scans have been evaluated to determine their predictive value in identifying unresectable disease. The CT findings which may predict unresectability include presence of an omental cake extending to the spleen, a diaphragm coated by tumour extending to liver serosa, lesions > 2 cm in the suprarenal para-aortic lymph nodes and porta hepatis, parenchymal



Omental cake; Optimal cytoreduction not possible

liver disease, pulmonary metastases and enlarged pericardial lymph nodes. In short, extensive upper abdominal disease makes optimal cytoreduction surgery difficult as analyzed in a study by Brinton et al. Other clinical models prove the same but none of them took into account the surgeon as an independent predictive factor of surgical outcome.

Interval Debulking Surgery

Also known as interval cytoreduction surgery, interval debulking surgery is performed after a few courses of neoadjuvant chemotherapy or in the middle of adjuvant chemotherapy administered after less than optimal primary tumor debulking. Patient age, poor performance status, stage of disease, volume of ascites and serum albumin levels are important determinants in choosing whether patients should be treated with neoadjuvant chemotherapy. Patients with massive ascites, large bilateral pleural effusions, extensive retroperitoneal lymphadenopathy, disease involving the porta hepatis or bulky intraparenchymal liver disease may benefit from neoadjuvant chemotherapy. If these patients have a favourable response to chemotherapy and their performance and nutritional status improves, they should be considered for interval debulking.

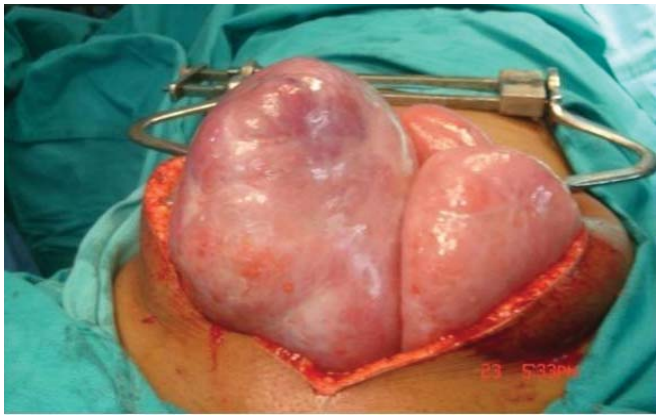
Preliminary data from an EORTC trial (protocol 55971), a randomised study of neoadjuvant chemotherapy followed by interval cytoreduction vs primary cytoreduction in stage III/ IV EOC patients suggested that both are comparable as the overall survival rates were similar, 30 and 29 months respectively. In addition, the patients assigned to the neoadjuvant arm had decreased mortality and morbidity. One disadvantage with neoadjuvant chemotherapy is the potential for developing chemoresistance, which in turn makes tumor cells less responsive to chemotherapy following interval debulking surgery.

Secondary Cytoreductive Surgery

Some patients with recurrent ovarian cancer are good candidates for secondary cytoreduction surgery. Due to lack of large randomised trials, conclusive data are limited regarding the benefits of secondary cytoreduction surgery. Patients with a long disease-free interval, usually at least 12 months after completion of chemotherapy, presenting with localised resectable disease recurrence on imaging, are good candidates for secondary cytoreduction surgery. Such patients are presumed to have chemotherapy-responsive cancer and it is theorized that a second "optimal" debulking may have the same advantage as the primary surgery. Surgical principles for secondary debulking are the same as for primary cytoreduction surgery. A subgroup of patients may be candidates for tertiary debulking based on same criteria.

Surgery for Palliation

In some patients with recurrent ovarian cancer, palliative surgery can be considered for relief of small and/or large bowel obstruction and pain. Such patients are usually malnourished, debilitated and carry quite a burden of chemo-refractory disease. The causes of obstruction are often multifactorial and include mechanical blockage, dense mesenteric infiltration and adhesions. Possible palliative procedures include bowel resection, colostomy or intestinal bypass. Even with palliative methods to remove obstruction, the re-obstruction rate is 10% to 50%. Despite this data, a certain subset of patients will benefit from palliative surgery. Jong et al specified the factors associated with successful palliation as the absence of the following: >3 liters of ascites, multifocal obstruction, palpable bulky tumors, and preoperative weight loss >9 kg. In patients who are not surgical candidates, percutaneous gastrostomy, hydration and hospice should be considered. Also in patients with large krukenburg tumors palliative surgery is indicated.



Krukenburg tumor

Minimally Invasive Surgery

Laparoscopy may be used in the diagnosis and staging of very early disease in young patients or to have a histopathological diagnosis in advanced stage disease. Role of minimally invasive surgery is particularly important in case of incidental finding of ovarian cancer during prophylactic oophrectomy. For patients with apparent early stage disease and/ or good-risk tumors, such as malignant germ cell tumors, low malignant potential lesion, early stage invasive epithelial tumors or sex cord stromal tumors, a fertility sparing surgery can be done. Unilateral salpingo oophrectomy, preserving the uterus and contralateral ovary can be considered. However, a comprehensive surgical staging should still be performed to rule out occult higher stage disease.

Primary invasive mucinous tumors of the ovary are uncommon, so the upper and lower gastrointestinal tract should be carefully evaluated to rule out an occult gastrointestinal primary with ovarian metastases. Appendectomy should be performed in all mucinous tumors and considered in all patients with epithelial malignancies suspicious for involvement of the appendix by metastases. In a retrospective series of 339 patients who underwent fertility sparing surgery by Lactta et al, only 2% progressed to invasive carcinoma. Although the recurrence rate after fertility sparing surgery was 18.5% vs 4.6% after non-fertility sparing surgery, all but one woman with recurrence of borderline tumor or progression to carcinoma was cured. In a study by Park et al, 59 women with stages IA-IC underwent fertility sparing surgery and there were no recurrences in women whose disease was grade 1 or 2. Women with grade 3 or higher stage disease had a significantly higher recurrence rate and lower survival.

Conclusion

Despite the significant advances in chemotherapy and biologic therapy, surgery is a very important modality for diagnosis, staging, and primary tumor debulking in ovarian cancer. However, despite the benefits of surgery, the specific biology of a patient's disease is central to her response to chemotherapy, duration of remission and ultimate survival.

(Dr Rupinder Sekhon, Sr Consultant; Dr Amita Mishra, Sr Resident; Dr Sudhir Rawal, Director Surgical Oncology & Chief Dept of Genito-Uro Oncology)

GUEST ARTICLE

TARGETED THERAPY IN OVARIAN CANCER

Abstract

Management of advanced ovarian cancer continues to remain a therapeutic challenge. Despite aggressive surgical debulking and platinum-based chemotherapy, many patients ultimately relapse and die of their disease. The last decade has seen the emergence of a number of targeted therapies and trials have been conducted to look for new ways to improve outcomes in ovarian cancer. The most promising of these therapies at present is Bevacizumab which have shown improvement in progression-free survival in recently conducted Phase III trials. Maintenance therapy with Bevacizumab is likely to be the new trend in the management of ovarian cancer. The coming years will reveal the potential role of many other targeted therapies.

Introduction

Ovarian cancer is second common gynecologic malignancy in India. Approximately three-fourths of patients have advanced disease (FIGO stage III-IV) at presentation. Five-year survival rates vary from 90% for stage I to 20-30% for women with advanced disease. Primary debulking surgery (with aim of optimum debulking) followed by six cycles of paclitaxel and carboplatin based chemotherapy has been the standard of care for the past 15 years[1]. Despite initial good response in most patients, relapse after treatment free interval of 12-18 months is common. Treatment of patients who relapse is categorized based on their platinum free interval; patients who recur >6 months after last treatment are categorized as platinum-sensitive compared to those whose disease relapses within 6 months of last treatment and are termed as platinum-resistant. Few patients who never achieve disease-free status are termed as having platinum refractory disease. Patients with platinum sensitive relapse are traditionally treated with paclitaxel plus platinum based therapy. Platinum resistant cases, on the other hand, are treated with non platinum based regimens, including oral etoposide (VP-16), gemcitabine, weekly paclitaxel, topotecan, and pegylated liposomal doxorubicin. However, clinical response to second-line therapy continues to be short lived and results in only marginal improvements in progression free and overall survival[2]. In response to this challenge, the idea of overcoming resistant disease with targeted therapy has come to the forefront of investigation in ovarian cancer therapy since the last decade. A number of potential pathways and targets have been identified (Table1). Some of these approaches are currently being tested in clinic in Phase I/ II/ III trials. These are briefly discussed below.

Epidermal Growth Factor Receptors

Epidermal growth factor receptor (EGFR) is a tyrosine kinase (TK) receptor of the ErbB family (ErbB 1-4). The activation of EGFR pathway is known to increase proliferation, angiogenesis, and decrease apoptosis. Several stretegies that target the EGFR include monoclonal antibodies and tyrosine kinase (TK) inhibitors. EGFR is overexpressed in 70% of ovarian cancers and is associated with advanced disease at presentation,

Table 1: Potential Pathways/ Targets in Ovarian Cancer

Pathways/Mechanism	Class	Molecule
Angiogenesis	Monoclonal antibodies VEGF receptor inhibit or	**Bevacizumab:** Humanized recombinant monoclonal antibody to the VEGF ligand **Cediranib (AZD 21 71):** Inhibitor of VEGFR2, 1 & c-kit **Pazopanib:** Inhibitor of VEGFR1, 2, 3 & PDGFR **Sunitinib:** Inhibitor of VEGFR1, 2, 3 & PDGFR **Sunitinib:** Inhibitor of VEGFR1, 2, 3 & PDGFR **AMG 706:** Inhibitor of VEGFR 1, 2, 3, PDGFR **Sorafenib:** Inhibitor of VEGFR, PDGFR, Flt3, C-kit
	VEGF Trap	**Afibercept:** Fusion protein
Epidermal Growth Factor Receptor Inhibitors	Monocional antibodies	Trastuzumab, Pertuzumab, EMF 7200
	TK inhibitors	Gefitinib, Erlotinib, Lapatinib, CI-1033
PDFG Inhibitors	PDGF receptor	Imatinib mesylate, Sorafenib, Sunitinib, Dasatinib, 3G3, CDP860, BIBF1120
Folate Receptor Inhibitors	Monoclonal antibody to folate receptor-α	Farletuzumab (MORab-003), EC 145
Poly -ADP-Ribose Polymerase (PARP) Inhibitors	small molecule in BRCA mutation carriers	Olaparib (AZD 2281, KU-0059436), AGO 146999, ABT 888, BS1-201, INO-1001, MK-4827
Aurora Kinase Inhibitors		MK-0457
Hedgehog Pathway Inhibitors		GDC-0449
m-TOR Inhibitors	P13K/AKT/mTOR	Temsirolimus
VEGF-vascular endothelial growth factor, TK-tyrosine kinase, PDGF-platelet derived growth factor		

poor prognosis and chemoresistance[3]. TK inhibitors-Gefitinib and Erlotinib have shown response rates of 3% and 6% respectively in recurrent or refractory EOC[4-5]. In the same setting, monoclonal Antibodies (Pertuzumab and Trastuzumab) also had response rate of 4% and 7%, respectively[6-7]. In a GOG 160/170 series comparing various novel molecules, e g, Gefitinib, Imatinib, Lapatinib, Sorafenib, Trastuzumab and Vorinostat did not meet the desired response rate of minimum 10% along with a progression-free-survival (PFS) ≥ 6 months of minimum 15%. Only Bevacizumab stood out with a response rate of 22% along with a PFS ≥ 6 months of 40% [6-10].

Angiogenesis Targeted Therapy

Angiogenesis involves sprouting of new blood vessels, changes in permeability and vasodilation, loss of pericyte or endothelial cell adhesion and the incorporation of progenitor cells derived from the bone marrow. Antiangiogenic therapies inhibit new blood vessel growth, induce endothelial cell apoptosis, block the incorporation of haematopoietic and endothelial progenitor cells into new blood vessels, and normalize the vasculature[3]. These effects are mediated by the binding of vascular endothelial growth factor (VEGF) to the VEGF receptors (VEGFR), inhibiting TK receptor activation and downstream molecules, or occluding fragile tumour vasculature by vascular disrupting agents[3]. Due to its central role in tumour angiogenesis, the VEGF/VEGFR axis has been identified as a prime target in novel anticancer drug development. The importance of the VEGF pathway in ascites formation has been shown in preclinical models[11].

Bevacizumab is a monoclonal antibody directed against VEGF-A. Improved survival with this agent has been shown in colorectal[12], breast[13], and non small cell lung cancer[14]. Initial trials in recurrent ovarian cancer or primary peritoneal carcinoma revealed a 21% clinical response rate with 40% experiencing at least 6 months PFS. The median PFS was 4.7 months and the median overall survival was 17 months[8]. In platinum-resistant setting, Cannistra et al performed a Phase II trial of single agent Bevacizumab[15]. As opposed to the GOG trial, this study was closed early due to serious adverse events (41%) with gastrointestinal (GI) perforations in 11% (5/44). The study did show a 16% response rate and a median durable response of 12 weeks[15]. Toxic events that were similar between these two trials included hypertension and vascular thrombosis[8,15]. Garcia et al, in a Phase II study, used Bevacizumab and low-dose metronomic oral cyclophosphamide for recurrent EOC and showed a response rate of 28% with a 6-month PFS of 28%[16].

Recently, three Phase III trials have been completed; these are summarized in Table 2. Bevacizumab in combination with standard chemotherapy followed by Bevacizumab maintenence has shown survival advantage. Initial results of the GOG 218 trial showed that frontline treatment with chemotherapy (Paclitaxel + Carboplatin) plus concurrent and maintenance Bevacizumab prolongs PFS. Grade ≥ 3 GI perforation, hemorrhage or fistula was seen in up to 2.6% patients[17]. In ICON 7 trial-

Table 2: Phase III Trials of Bevacizumab in Epithelial Ovarian Cancer

Trial (Ref.)	Arm	Regimen	Maintenance	Platinum Sensitivity	Results
GOG 218 N = 1873	R1	Pacli-Carbo (AUC 6) x cycles Placebo, Cycle 2-6, q3wk	Placebo q3wk Cycle 7-22	First line	Relative to R1, hazard of first progression or death for R2 was 0.908 (95%) C1: 9.795-1.04, p = 0.16) and for R3 was 0.717 (95% CI: 0.625-0.824, p<0.0001)
	R2	Pacli-Carbo (AUC 6) x 6 cycles Bevacizumab 15 mg/kg, Cycle 2-6, q3wk	Placebo q3wk Cycle 7-22		
	R3	C Pacli-Carbo (AUC 6) x 6 cycles Bevacizumab 15 mg/kg, Cycle 2-6, q3wk	Bevacizumab 15 mg/kg q3wk Cycle 7-22		
ICON 7 N=1528	A	Carboplatin AUC 6 Paclitaxel 175 mg/m2	Observation	First line	Subgroup analysis of poor prognosis patients: 79 Arm B), HR=0.64, 95% CI=0.48 to 0.85, p=0.0022
	B	Carboplatin AUC 6 Paclitaxel 175mg/m2 Bevacizumab 7.5 mg/kg q3wk x 6 cycles	Bevacizumab 7.5 mg/kg q3wk 12 cycles		
OCEANS N=484	A	Gemcitabine 1 gm/m2 day 1 & 8, Carboplatin (AUC 4) day 1 Bevacizumab 15 mg/kg, day 1 q3wk x 6 cycles	Placebo q3wk till progressive dis. or toxicity	Platinum sensitive recurrence	Median PFS (Arm A vs B): 8.4 vs 12.4 months HR=0.484 P<0.0001
	B	Gemcitabine 1 gm/m2 day 1 & 8, Carboplatin (AUC 4) d 1 Bevacizumab 15 mg/kg day 1 q3wk x 6 cycles	Bevacizumab 15 mg/kg q3wk till PD or toxicity		

chemotherapy (Paclitaxel + Carboplatin) plus concurrent and maintenance Bevacizumab showed an overall trend for improvement in overall survival (OS) from Bevacizumab with a larger benefit in poor prognosis patients[18]. In platinum sensitive relapse setting, initial results of the OCEANS trial have shown benefit of Bevacizumab maintenance after a combination of Gemcitabine, Carboplatin and Bevacizumab; PFS was 12.4 months compared to 8.4 months in placebo maintenance arm[19].

VEGF Trap is a fusion protein consisting of the extracellular domains of human VEGF-1 and -2. This protein binds to VEGF-A and placental growth factor. Tew and colleagues reported on a Phase II study evaluating patients with recurrent, platinum-resistant ovarian cancer. This study yielded an 11% partial response, with grade 3/4 toxicities including hypertension, proteinuria, encephalopathy, and renal failure[20].

PARP Inhibition

Poly (ADP-ribose) polymerase (PARP) is a key enzyme involved in the surveillance and maintenance of genomic integrity[3]. It functions both as a molecular sensor of DNA damage (resulting from interruption of the sugar-phosphate backbone or from base injury) and following its detection, efficiently recruits partner proteins to repair damage by the single-strand break repair (SSBR) and base excision repair (BER) pathways. PARP inhibition results in the accumulation of DNA single-strand breaks which convert into DNA double-strand breaks (DSBs). In normal cells, DSBs are effectively repaired. However, tumor cells that are deficient in the tumor suppressor BRCA1 and BRCA2 proteins, (important for efficient repair of DSBs by homologous recombination repair) use alternative DNA repair pathways, such as base excision repair to compensate for nonfunctional homologous recombination. PARP inhibitors may selectively kill tumor cells, exploiting the concept of synthetic lethality by combining base excision repair inhibition with defective homologous recombination DNA repair pathway[21].

Olaparib is an oral small-molecular PARP inhibitor. Preclinical studies confirmed that BRCA-deficient cells were up to 1000-fold more sensitive than wild-type cells to PARP inhibition[21]. In phase I trials, olaparib was well tolerated, and there were no obvious differences in the pattern of toxicities between BRCA and non-BRCA patients. Most recently, Jonathan et al presented data of a randomized, double blind, placebo controlled study during the American Society of Clinical Oncology meeting 2011. Two hundred sixty five patients had received at least two previous platinum based chemotherapy regimens. Patients who had achieved complete or partial response to last platinum based therapy were assigned to receive 400 mg of olaparib twice daily or placebo until evidence of disease progression. PFS was improved by 3.6 months in the olaparib group compared to placebo (HR 0.35, $p<0.00001$). Patients, both BRCA mutated and those with sporadic ovarian cancer, benefited. Overall survival data is not yet mature. The most common adverse events associated with olaparib compared to placebo included nausea (68% vs 35%), fatigue (40% vs 37%), and vomiting (31% vs 14%); most of these were mild to moderate. Grade 3-4 toxicities were – fatigue (7%), and anemia (5%), and 2% of patients discontinued olaparib therapy due to adverse events[22].

Folate Receptor Alpha Inhibitor

Folate receptor alpha (FRA) is over-expressed in the majority of EOC but is largely absent from normal tissue. Farletuzumab (MORAb-003) is a humanized monoclonal antibody (MAb) to FRA and has been shown to suppress tumor growth in vivo of FRA-expressing tumors in rodent xenograft models. A Phase I trial of Farletuzumab in platinum resistant relapse showed no dose limiting toxicity or significant related adverse events[23]. A Phase II trial in platinum sensitive relapse ovarian cancer compared outcome of patients without symptoms (± measurable disease) but with only CA-125 elevation and who received single agent Farletuzumab until progression to those with symptomatic relapse or progression receiving Paclitaxel/Carboplatin and Farletuzumab. Subjects with complete or partial response received single agent Farletuzumab maintenance therapy. In subjects receiving Farletuzumab with Paclitaxel/Carboplatin, CA-125 was normalized in 100% of subjects completing 6 cycles. RECIST scores improved in parallel. 3/8 evaluable subjects have achieved a second remission longer than the first[24]. Currently, a multicentric Phase III trial is under going in relapse setting in which post-chemotherapy maintenance with Farletuzumab in two different doses is being compared to placebo maintenance.

Conclusion

Recent understanding of the molecular biology of epithelial ovarian cancer has led to identification of potential molecular targets. Many novel agents have been developed which are currently being tested in the clinic. Bevacizumab-angiogenesis inhibitor has shown

promise as maintenance therapy, both in upfront treatment as well as in the setting of recurrent disease. The activity of PARP inhibitors in BRCA associated ovarian cancer further supports the importance of screening patients for potential BRCA associated disease and offering mutational testing when appropriate. Treatment targeted to specific subgroups of patients based on robust predictive biomarkers is likely to be area of active research in future studies[3].

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(Dr R K Bikramjit Singh, Sr Resident (DM); Dr Lalit Kumar, Professor, Dept of Medical Oncology, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi)

PERSPECTIVE

MOLECULAR GENETICS OF OVARIAN EPITHELIAL CARCINOMAS

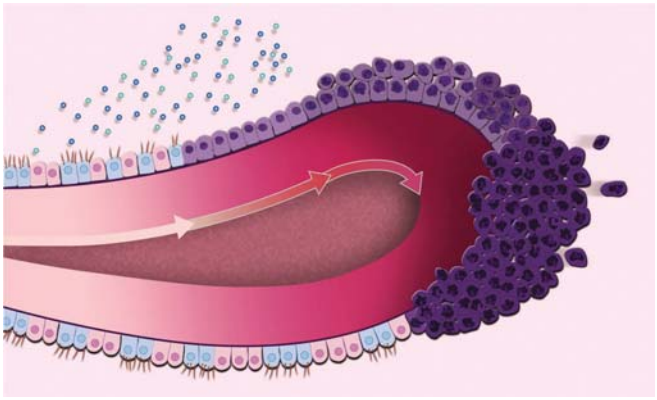
Introduction

Ovarian carcinogenesis is a complex, multistep polychromosomal process. Each histologic subtype of ovarian cancer is characterized by distinct histogenetic signatures and a unique complement of chromosomal abnormalities. Dysregulation of cell cycle control, in particular G1-S-phase transition, is implicated in the pathogenesis of most human cancers, including ovarian epithelial cancers (OEC). However, the prognostic significance of aberrant cell cycle gene expression in OEC remains mostly unclear. Hopefully, a better understanding of the molecular mechanisms underlying the tumorigenic process of ovarian carcinoma will lead to earlier diagnosis, novel therapies and ultimately better outcomes.

OEC, the most common ovarian malignancy, is a heterogeneous disease with several histologic subtypes that show characteristic cytogenetic features, molecular signatures, oncologic signaling pathways, and clinical-biologic behavior. Based on light microscopy and molecular genetics, ovarian carcinoma is subdivided into at least five main subtypes which, in descending order of frequency, are high-grade serous carcinomas (HGSC), clear cell carcinomas (CCC), endometrioid carcinomas (EC), mucinous carcinomas (MC) and low-grade serous carcinomas (LGSC). Clear cell, endometrioid, low-grade serous, and mucinous ovarian carcinomas typically present as indolent low-grade neoplasms [type I tumors]. HGSC [type II tumors] differs from type I tumors both for its aggressive nature and because it harbors unique genetic alterations. Somatic mutations in *K-ras, BRAF, erb-B2, PTEN, CTNNB1,* and *PIK3CA* characterize type I tumors and in *TP53* and the DNA-damage repair genes *BRCA1* and *BRCA2* in HGSC.

Serous Carcinomas

Serous carcinomas account for 60% of the ovarian malignancies. Owing to the stark differences in tumor phenotype and genetic aberrations, it has been recognised that LGSC and HGSC are fundamentally different tumor types. Because of their frequent association with cortical inclusion cysts or low-grade precursor lesions (borderline tumors) in the ovarian cortex, LGSC [type I tumors] are thought to develop from ovarian surface epithelial (OSE) cells. In contrast, HGSCs are not associated with serous borderline tumors and recent studies suggest that >50% HGSC likely arise from fallopian tube epithelium, specially the fallopian tube secretory epithelial cell (FTSEC). Females predisposed to HGSC (harboring inherited *BRCA*1/2 mutations) contain putative serous carcinoma precursor lesions, termed p53 signature, in the FTSECs at the fimbriated end. The precursor 'p53 signature', is defined as ≥12 consecutive FTSECs that appear morphologically benign in H&E-stained sections but exhibit intense nuclear p53 immunostaining. Many p53 signatures share identical somatic *TP53* mutations with coexisting serous tubal intraepithelial carcinomas and HGSCs, suggesting that all three entities have a common origin.



(*Illustration of stepwise progression of normal fallopian tube epithelium to invasive serous carcinoma: DNA damage → p53 mutation → clonal expansion of normal looking FT cells (**'p53 signature'**) → further genetic hits → proliferative capacity → tubal intraepithelial carcinoma → progress to serous carcinoma and/or exfoliation to ovarian surface)*

High-Grade Serous Carcinomas (HGSC): HGSCs constitute 90% of all serous carcinomas. Most *BRCA*-related hereditary ovarian cancers (57%–100%) are HGSCs. In contrast to LGSCs, these tumors show more than 3-fold variation in nuclear size. Most HGSCs have abnormalities of *BRCA1* or *BRCA2* (germline or somatic mutation or, in the case of *BRCA1*, promoter methylation and loss of expression) and *TP53*(mutation or deletion). These changes occur early during oncogenesis and result in loss of ability to repair DNA double strand breaks, which in turn lead to chromosomal instability. Serous ovarian carcinomas are characterized by high proliferative activity (PI Ki-67 = 30.0 +/- 0.3%), TP53 and p16 overexpression and low expression of p21. The frequency of TP53 mutation in early-stage

ovarian carcinomas of serous histology is comparable to that reported for advanced-stage tumors, and it is therefore likely to occur early in the progression of serous carcinoma.

Low-Grade Serous Carcinomas (LGSC): LGSCs are uncommon and account for less than 5% of all cases of ovarian carcinoma. The uniformity of the nuclei is the principal criterion for distinguishing between LGSC and HGSC, with less than 3-fold variability. LGSCs are characterized by frequent mutations of K-*ras*, *BRAF*, and *erb*-B2 (HER-2) genes. K-*ras* and *BRAF* mutations are found in 60% of serous borderline ovarian tumors (BOTs) and 68% of LGSCs. In addition, coexisting benign and borderline epithelia are frequently seen in patients with LGSC. Thus, LGSCs most likely arise by means of an adenoma–borderline carcinoma progression characterized by alterations in the RAS-RAF pathway. *PAX2*, a member of the paired-box gene family, is preferentially expressed in serous BOTs and LGSCs, possibly indicating a cell lineage from the secondary müllerian system. *PAX2* positivity is also linked to platinum chemoresistance; the development of therapies that target *PAX2* may be useful in the treatment of LGSCs.

Endometroid Carcinoma

Endometrioid carcinoma is the second most common ovarian cancer (10%–20% of cases). Endometrioid carcinomas affect peri- or post-menopausal women and are frequently associated with endometriosis, with up to 42% being associated with ipsilateral pelvic or ovarian endometriosis. Concurrent endometrial carcinoma is seen in up to 15%–20% of patients. Endometrioid carcinomas are characterized by specific genetic mutations; *CTNNB1* mutations (38%–50% of cases), *PTEN* mutations (20%), and microsatellite instability (up to 19%) are commonly seen. A low incidence of TP53 accumulation, a high incidence of c-myc overexpression (70%) and a low median Ki-67 labeling index is observed in endometroid phenotypes. Mutations involving the *CTNNB1* and *PTEN* genes and microsatellite instability are commonly seen in low-grade early-stage endometrioid carcinomas that originate in a stepwise fashion from borderline tumors or endometriosis, with a resultant excellent prognosis. Overexpression or mutation of TP53 is seen exclusively in patients with de novo development of high-grade endometrioid carcinomas with a poor prognosis.

Clear Cell Carcinoma

Clear Cell Carcinomas (CCCs) constitute less than 10% of all OECs. CCC has the strongest association with pre-existing ovarian endometriosis (49% of cases). Activation of the PI3K/AKT pathway and its downstream pathways with concomitant inactivation of tumor suppressor genes, such as *PTEN* and *mTOR* have been observed in endometriosis as well as CCCs and endometrioid carcinomas associated with endometriosis. Mutations involving the *PIK3CA* gene lead to activation of the PI3K/AKT pathway, resulting in improved cell survival and invasion. Hepatocyte nuclear factor (HNF)–1b is a homeobox transcription factor that plays a major role in embryologic organogenesis involving the derivatives of meso- or metanephros. Small molecule inhibitors that target the PI3K/AKT pathway are being developed and tested in clinical trials; they may play a greater role in the management of advanced-stage or recurrent ovarian CCC, one of the most lethal subtypes of ovarian cancer. Recent studies have found that the *HNF* gene is upregulated in reactive or atypical endometriosis as well as in CCCs associated with endometriosis. CCC reveal such trends as low expression of both TP53 and cyclin A and significantly increased expression of both p21 and cyclin E compared with the other histologic subtypes.

Mucinous Carcinoma

Mucinous carcinoma of the ovary accounts for 7% to 14% of all primary OECs. Distinction of primary ovarian epithelial tumors from metastatic adenocarcinomas is challenging for tumors exhibiting mucinous, endometrioid, or mixed endometrioid/mucinous differentiation. Large size (>13 cm) and unilaterality are features suggestive of a primary MC, while metastases are typically smaller and bilateral. Mucinous ovarian tumors are often heterogeneous. Benign appearing, borderline, non-invasive carcinoma and invasive patterns may coexist within an individual neoplasm. *KRAS* mutations are common in mucinous ovarian carcinomas and are an early event in mucinous tumorigenesis. These characteristic mutations are increasingly found in tumors that progress according to the adenoma-carcinoma sequence, including 55.7% of mucinous cystadenomas, 73% of borderline tumors, and 85% of mucinous carcinomas. HER-2 is amplified in 15–20% of ovarian carcinomas of mucinous type. Anti-HER-2 therapy may be effective in patients with tumors associated with gene amplification. Cervical

adenocarcinomas metastatic to ovary are positive for HPV and show strong diffuse positivity for p16. Mucinous and endometrioid carcinomas are largely characterized by p16 downregulation and the gene promoter hypermethylation. Lack of p16 is associated with TP53 wt (wild type) and is typical of mucinous and endometrioid tumors.

Transitional Cell Carcinoma

Ovarian transitional cell carcinoma (TCC) is a malignant ovarian tumor whose histopathologic features are similar to those of other types of TCC. However, the immunophenotype of ovarian TCC is reminiscent of that of OEC. TCCs account for 6% of all ovarian cancers. Ovarian TCCs are usually positive for HNF-1b. The specific cytogenetic features and oncologic pathways of ovarian TCCs have not yet been clarified.

Conclusion

Elucidation of the pathogenesis of serous carcinoma is important in that it may clarify an important aspect of response to chemotherapy. LGSC is not as responsive to conventional (taxane-based and platinum-based) chemotherapy as HGSC. PAX2, PI3K/ AKT pathway, CTNNB1 and PTEN genes have emerged as targets for novel therapy. The understanding of tumorigenesis in LGSC and mucinous carcinomas and cell of origin in HGSC, differentiating ovarian mucinous carcinoma from metastatic cervical adenocarcinoma has also been facilitated by the study of underlying molecular mechanisms.

(Dr Damandeep Kaur, Sr Resident; Dr Anurag Mehta, Director Laboratory Services)

ROBOTIC SURGERY AT RGCI&RC

Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC) has started Robotic Surgical Services in the field of oncology since February 2011. The first Robotic Radical Prostatectomy was done by Dr Sudhir Rawal, Director, Surgical Oncology and Chief of Genito-Uro Oncology on 28th February 2011and since then various surgeries like Radical Prostatectomy, Radical Cystectomy, Radical Hysterectomy, Radical Nephrectomy and VEIL have been performed for cacinoma of prostate, urinary bladder, cervix, uterus, kidney and penis respectively. Robotic Surgery gives the advantage of smaller incision, less pain and early recovery to the patient.

GLOBE SCAN

Ovarian Cancer Survival in UK

Ovarian cancer is the fifth most common cancer in women in the UK. Survival from ovarian cancer has almost doubled over the last 30 years, according to new figures from Cancer Research UK. The overall five-year survival rate for early ovarian cancer has increased from 21% in the early 1970s to 41% today. Based on data from the East of England Cancer Registry, survival rates for women diagnosed with stage III ovarian cancer, the majority (45%) of women still lag behind with just over 20% surviving five years and this falls to less than 6% of women with stage IV disease. These latest figures show that improvement in treatment are making a difference in helping more women surviving ovarian cancer, particularly those who are diagnosed earlier. To tackle the issue of late diagnosis, a pivotal trial of ovarian cancer screening is ongoing to detect the disease earlier and save many more lives. Moreover, new treatments in the pipeline could help keep the disease under control for longer.

(UK: Cancer Research UK, Mar 9, 2011)

Progress Against Ovarian Cancer

New treatment options have led to steady progress against ovarian cancer. National Comprehensive Cancer Network (NCCN) Ovarian Cancer Guidelines have added a new treatment option-dose-dense paclitaxel-for the first line treatment of stage II, III or IV epithelial ovarian cancer. In a Phase III open label randomized controlled trial, researchers have reported that dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer resulted in a significant survival advantage. The current guidelines emphasize that intraperitoneal chemotherapy (IP) should be used in stage III patients and that IP can also be used in optimally debulked (tumor no greater than 1cm) stage II patients. IP regime is very toxic, so it should be done in a centre that has experience with this regime. The NCCN panel also recognized that data for first-line and maintenance bevacizumab are becoming available in the clinical trials. Modest improvements in progression-free survival were observed in Phase III trials GOG 218 and ICON7. The panel prefers to await mature results of these trials prior to recommending the routing addition of bevacizumab to carboplatin/ paclitaxel.

(US: Medscape Medical News, Mar 14, 2011)

RESEARCH & DEVELOPMENT

BRCA Mutations and Impact on Survival

Researchers have reported that women with ovarian cancer who have the BRCA2 gene mutation are more likely to survive the malignancy than women with the BRCA1 mutation, or women without either mutation. Previous studies have been somewhat conflicting because of their small size and methodological limitations. This study clearly shows that this survival difference is real. The study also provides the first solid evidence that BRCA1 and BRCA2 mutations do not have the same impact on ovarian cancer survival. The researchers evaluated 3,531 cases of epithelial ovarian cancer, including 1,178 women with BRCA1 mutations, 367 with BRCA2 mutations and 1,986 with neither mutation. After adjusting for baseline characteristics, the five-year survival of women without mutations was 36%. Survival for BRCA1 or BRCA2 mutation carriers was 46% & 61%, respectively. This information may lead to improvements in clinical management of patients with these mutations. Further study is needed to explain why women with BRCA2 mutations had better survival than BRCA1 carriers, or those without either mutation.

(Am Assoc for Cancer Research, Apr 5, 2011)

Secondary Cancer in Ovarian Cancer Patients

A study presented at ASCO 2011 Annual Meeting, has reported multiple cases of squamous cell carcinoma (SCC) of the oral cavity in patients treated with long term pegylated liposomal doxorubicin (PLD) for relapsed ovarian cancer. Researchers monitored a cohort of patients on this therapy for side effects and secondary malignancies. They reported four patients receiving long term PLD for advanced stage ovarian cancer to have developed malignant and/or premalignant lesions of the tongue and/or oral cavity. All four patients had received maintenance therapy with PLD for periods of at least three years. Three patients were diagnosed with SCC of the tongue and/or oral cavity, and one with sublingual mucosa high-grade dysplasia. Noteworthy was a patient with three separate SCCs of the oral cavity. Three of the four patients had deleterious BRCA mutations. None of the patients were former smokers. These findings of secondary cancer of the oral cavity following long term PLD treatment of patients with recurrent ovarian cancer have implications for surveillance and preventive measures for such population.

(NYU Langone Medical Center, June 7, 2011)

Sunitinib in Ovarian Clear Cell Cancer

A group of international researchers has recently reported therapeutic response to the angiogenesis inhibitor sunitinib (sutent) in ovarian clear cell cancer (OCCC), which is a rare form or subtype of epithelial ovarian cancer that is generally refractory to platinum based chemotherapy. The researchers emphasized the growing realization that OCCC is molecularly and clinically distinct as compared to other forms of ovarian cancer, and noted significant common scientific characteristics possessed by both OCCC and renal clear cell cancer. The researchers identified specific overexpression of the IL6-STAT3-HIF in OCCC tumors, as compared with high-grade serous ovarian cancers. They reported sustained clinical and functional imaging responses in two OCCC patients with chemotherapy-resistant disease who were treated with sunitinib, thereby showing significant scientific parallels with renal clear cell cancer. Researchers highlighted the importance of specific therapeutic targets in the treatment of OCCC and suggested that more extensive clinical trials with sunitinib in OCCC patients are warranted.

(Clinical Cancer Res, Feb 22, 2011)

Turning Back the Clock on Ovarian Cancer

Researchers have found in initial tests that a type of regulatory RNA called miR-429 may be successful in inducing metastatic cells to convert back to a less metastatic, non-invasive form where traditional chemotherapy can better do its job. In the trial, they used two ovarian cancer cell lines, one with epithelial characteristics, like primary tumor cells, and the other with mesenchymal traits, like metastasizing cancer cells. They used miR-429 to see if it could turn the mesenchymal cancer cells back into epithelial cancer cells. They found that when they introduced miR-429 into the highly metastatic ovarian cancer cells, it was highly successful in helping cells turn back the clock. The cells became less invasive, less migratory and more like the cancer cells associated with primary tumors. They are testing to see if cells treated with miR-429 that change from mesenchymal to epithelial cancer cells are more susceptible to chemotherapy than metastasizing cells that have not undergone this change.

(Georgia Institute of Technology, Feb 3, 2011)

NEW TECHNOLOGIES

IMRT for Advanced Ovarian Cancer

Intensity-modulated whole abdominal radiotherapy (WAR) provides a new promising option in the consolidation treatment of ovarian carcinoma in patients with a complete pathologic remission after adjuvant chemotherapy. Recurrences of the disease occur mostly intraperitoneally. Ovarian cancer is a radiosensitive tumor and use of WAR as a consolidation therapy would appear to be a logical strategy. WAR used to be the standard treatment after surgery before the chemotherapy era, however, it was almost totally excluded from the treatment of ovarian cancer during the past decade because of its high toxicity. Modern intensity-modulated radiation therapy (IMRT) has the potential of sparing organs at risk. Phase I study has shown for the first time the clinical feasibility of intensity-modulated WAR and pointed out promising results concerning treatment tolerance. Now the OVAR-IMRT-02 study, a Phase II trial, is evaluating consolidation whole abdominal IMRT in patients with advanced ovarian cancer stage FIGO III. Future studies would enable firm conclusions regarding the value of consolidation radiotherapy within the multimodel treatment of advanced ovarian cancer.

(BMC Cancer, Jan 28, 2011)

New Diagnostic Blood Test

Biotechnology company MabCure Inc. has recently completed study on the diagnosis of ovarian cancer utilizing its proprietary monoclonal antibodies against 54 different blood samples. The study results provide initial clinical proof of concept that MabCure's ovarian cancer antibodies are capable of distinguishing between ovarian cancer and benign tumors of the ovary with 100% specificity. This technology is based on re-engineered hybridoma methodology, designed to achieve significant quantitative and qualitative improvements. A large library containing more than 30,000 hybridomas, provides MabCure with ability to select only a handful of the most highly specific monoclonal antibodies against unique tumor specific antigens appearing on targeted cancer cells. MabCure intends to expand this study with follow-on study of more than 100 blood samples containing ovarian cancer and benign tumors of the ovaries.

(MabCure Inc, Mar 11, 2011)

OVA1-Test

OVA1 is the first test cleared by FDA for aiding in the pre-surgical evaluation of a woman's ovarian mass for cancer, and also is the first protein-based In Vitro Diagnostic Multi-Variate Index Assays (IVDMIA), a new class of state-of-the-art software-based diagnostics. The test utilizes five well-established biomarkers– Transthyretin (TT or prealbumin), Apolipoprotein A-1 (Apo A-1), beta2-Microglobulin (beta2M), Transferrin (Tfr) and Cancer Antigen 125 (CA 125 II)–and proprietary software to determine the likelihood of malignancy in women with ovarian mass for whom surgery is planned. OVA1 is indicated for women who meet the following criteria: over age 18, ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. It is an aid to further assess the likelihood that malignancy is present when the physician's independent clinical and radiological evaluation does not indicate malignancy. The test should not be used without an independent clinical/radiological evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of the OVA1 test carries the risk of unnecessary testing, surgery, and/or delayed diagnosis. OVA1 would identify more ovarian cancers than a physician's preoperative assessment alone. The study showed OVA1's value over the CA 125 test in evaluating women for likelihood of ovarian cancer prior to surgery.

(Quest Diagnostics, May 24,2011)

Trabectedin

Trabectedin (yondelis) is an intravenous drug that works by damaging the DNA in cancer cells, making the cells unable to grow and spread. New data from the randomized OVA-301 study shows that trabectedin in combination with pegylated liposomal doxorubicin (PLD) results in improved progression free survival and overall survival. A subgroup analysis indicate that in the subset of patients with platinum-free interval (PFI) of 6 to 12 months, the combined treatment resulted in a 6-month improvement in overall survival. In the patients who had received third-line treatment with a platinum agent, it was found that the survival was better in those who had received trabectedin and PLD. These results suggest that prolonging the PFI by a non-platinum-effective regimen improves the outcome with subsequent, third line platinum treatment.

(Int J Gynecol Cancer, May 2011)

WATCH-OUT

Gene Expression Profiling

Ovarian cancer remains the most lethal among the gynecologic malignancies and the ovarian serous papillary cancer represents the most common histological type of ovarian carcinoma. Board of trustees of the University of Arkansas (Little Rock, AK) has been assigned United States Patent No 7,927,795 entitled "Gene expression profiling in primary ovarian serous papillary tumor and normal ovarian epithelium". Early detection and development of effective therapy against chemotherapy resistant/recurrent ovarian cancer remains a high priority. The invention is drawn to a method of detecting ovarian serous papillary carcinoma based on overexpression of a group of genes as well as down-regulation of group of genes. The invention provides a foundation for the development of new type-specific therapies against this disease. In one embodiment, the invention provides a method of treating carcinoma by inhibiting the expression and function of tumor-associated calcium signal transducer 1 (TROP-1/Ep-CAM) gene by monoclonal chimeric/humanized antibodies, which may be beneficial in patients harboring chemotherapy-resistant ovarian serous papillary carcinoma. The invention also provides a method of treatment by delivering clostridium perfringens enterotoxins to ovarian tumor cells overexpressing claudin 3 or claudin 4 protein.

(USPTO, June 6, 2011)

Hepsin mRNA in Ovarian Cancer

The invention bearing Patent No US 2011086056 (A1), published on April 4, 2011, allows for the detection of ovarian cancer by screening for hepsin mRNA in tissue. Hepsin mRNA is indicative of the hepsin protease shown herein to be specifically associated with the surface of 80% of ovarian tumors. Proteases are considered to be an intergral part of tumor growth and metastasis, and therefore, markers indicative of their presence or absence are useful for the diagnosis of cancer. The present invention provides a hepsin protein variant or a fragment thereof that is useful as a marker for ovarian cancer cells. Furthermore, the present invention is useful for treatment (i.e. by inhibiting hepsin or expression of hepsin) for targeted therapy, for vaccination, etc. The present invention provides methods of vaccinating an individual against hepsin or producing immune-activated cells directed towards hepsin. It also provides methods of immunotherapy targeted towards hepsin in an individual.

(European Patent Office, June 2, 2011)

Targeted Therapy for Ovarian Cancer

With modern surgical interventions and contemporary chemotherapy, the majority of patients would eventually have a relapse and die of complications of cancer. The object of the present invention is to provide a method of inhibiting the growth of ovarian cancer. Inventors Wecinreich David M (US) et al have been assigned Patent No W02111038139 (A1), entitled "Treatment of Ovarian Cancer Using a Specific Binding Agent of Human Angiopoietin-2 in Combination with a Taxane". Angiogenesis is the formation of new blood vessels from existing ones, which can go awry in cancer Tie 2 receptor tyrosine kinase and its ligands; the angiopoietins (Ang) are involved in the regulation of angiogenesis. Numerous published studies have demonstrated vessel-selective Ang-2 expression in cancer states associated with angiogenesis. The present invention is directed in one embodiment to a method of treating ovarian cancer in a human patient by administering a therapeutically effective amount of an Ang-2 inhibitor and/or a Tie-2 inhibitor in combination with a taxane. In some embodiments, the taxane is paclitaxel, docetaxel, or a derivative thereof. The Ang-2 inhibitor of the present invention can be an antibody, Fc-peptide fusion protein (such as a peptibody), Fc-Tie-2 extracellular domain (ECD) fusion protein (a "Tie-2 trap"), or a small molecule inhibitor of Tie-2.

(esp@cenet, June 8, 2011)

SCREENING FOR OVARIAN CANCER

Introduction

Ovarian cancer remains the most deadly gynaecologic cancer. Because of the location of the ovaries and the biology, approximately 70% of epithelial ovarian cancers are diagnosed at an advanced stage. CA-125 protein test has not proved to be a reliable indicator for documenting the presence of early-stage ovarian cancer. In 2007, the Gynaecologic Cancer Foundation, the American Cancer Society, and the Society of Gynaecologic Oncologists came out with a consensus statement that "women experiencing bloating, pelvic or abdominal pain, difficulty in eating or feeling full quickly, or urinary symptoms (> 12 days/ month) for more than a few weeks should see their doctor. Recent data show that several markers including CA-125, HE4, mesothelin, B7-H4, decoy receptor 3 [DcR3], and spondin-2 do not increase early enough to be useful in detecting early-stage ovarian cancer. Pelvic examination is unlikely to discriminate an early or premalignant lesion from a normal ovary. In screening studies, a pelvic examination could distinguish a benign mass f rom a malignant mass with a pooled sensitivity of 58% and a sensitivity of 98%.

Tumor Markers

CA-125 is an epithelial marker derived from coelomic epithelium. It is elevated in 90% advanced and 50% of early ovarian cancers. CA-125 can be elevated in many benign conditions including pregnancy, leiomyomata, ovarian cysts, endometriosis, appendicitis, and diverticulitis. CA-125 can also be elevated in other cancers, such as uterine, colon, lung, or pancreas. CA-125 may help raise an index of suspicion but it is not sufficiently sensitive or specific for effective screening.

Imaging

Ultrasonography attempts to discriminate between benign and malignant adnexal masses on the basis of morphology, septations, echogenicity, and volume. Ultrasound has a pooled sensitivity of 82% to 91% and specificity of 68% to 81% at distinguishing benign from malignant masses. Doppler imaging has a sensitivity and specificity of 72% to 88% and 73% to 90% respectively. Using morphology and Doppler imaging together resulted in a pooled sensitivity of 86% and a specificity of 91%. A new approach uses a mathematical model, called the Risk of Ovarian Cancer Algorithm (ROCA) that combines trends in CA-125 blood test results, patient's age, and results from a transvaginal sonogram (TVS) and referral to a gynaecologic oncologist, as necessary. The specificity of ROCA followed by TVS for referral to surgery was 99.7%. A large scale study of ROCA is underway in the United Kingdom.

Advancing Technologies

Proteomic approaches include Ova-Check test developed by Correlogic Systems, Germantown, MD. Initial studies quoted a sensitivity of 100% and a specificity of 95% in distinguishing cancerous from normal ovarian tissues. However, the results were difficult to reproduce in independent evaluations. The OvaSure Yale Ovarian Cancer Test (Laboratory Corporation of America, Burlington, NC) was recently introduced as a commercially available blood test. The initial study combined six biomarkers (leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125) into a model that classified samples as cancer vs normal. The US Food and Drug Administration recently cleared the test OVA1 (Vermillion Inc, Fremont, CA) for ovarian cancer which measures five serum proteins. The test is used for surgical decision making and not intended as a screening tool.

High-Risk Populations

Hereditary syndromes account for 10% of ovarian cancers. The risk of developing ovarian cancer is 39% to 46% for patients with BRCA1 mutations, 10% to 20% for BRCA2 mutations, and 9% to 12% for those with Lynch syndrome. There is no evidence that biomarkers, such as CA-125, HE4, or mesothelin are more specific in high-risk populations.

Conclusion

At present, no validated testing modality is available with enough sensitivity, specificity, and positive predictive value to be used as a screening test for ovarian cancer. Moreover an effective screening program must be accessible to the general public, and trained personnel must be available to act on the results of the testing. Such a program will require training and costly investment that is essential to provide the necessary technology and personnel qualified to deliver reliable outcomes.

(Dr Shveta Giri, Consultant, Dr Rupinder Sekhon, Sr Consultant, Dept of Genito-Uro Oncology)

ROLE OF CHEMOTHERAPY IN OVARIAN CANCER

Introduction

Ovarian cancer is the third most common diagnosed cancer and 2nd leading cause of death among women in Delhi. The disease is termed "Silent Killer" as only 15% of ovarian cancer is localized to the ovary, 17% is regional, and 62% occurs as distant disease. It presents late with symptoms of pelvic/abdominal pain, urinary urgency/frequency, bloating, and early satiety. Adnexal mass on pelvic examination commonly initiates a diagnostic evaluation for ovarian cancer. Ultrasound examination is the most useful non-invasive diagnostic test. CA-125 is elvated in 80% of advanced and 50% of early epithelial ovarian cancer (EOC). It is highest in serous and lowest in mucinous EOC. Approximately 90% of ovarian cancer is epithelial in origin and typically occurs in postmenopausal women. The management of EOC encompasses a combination of surgical resection and chemotherapy and it poses significant therapeutic challenges due to the advanced stage of most patients with this disease.

Treatment of Early Stage (Stages I and II) EOC

All patients treated surgically for early-stage disease should be stratified into low or high risk groups depending upon histopathological risk factors. Patients with low risk disease should be observed clinically with no adjuvant chemotherapy. On the other hand, all patients with high risk disease require adjuvant combination chemotherapy.

Data from International Collaborative Ovarian Neoplasm trial 1 (ICON1) and Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) combined over 900 patients, showed that the hazard ratio for recurrence-free survival is 0.64 (95% confidence interval [95% CI], 0.50-0.82; P¼ 0.001) in favor of adjuvant chemotherapy, and the hazard ratio for overall survival (OS) is 0.67 (95% CI, 0.50-0.90; P¼ 0.008) in favor of adjuvant chemotherapy. This along with information from various GOG trials indicates that chemotherapy improves progression-free survival (PFS) for patients with stage IA or IB poorly differentiated disease, stage IC, or stage II disease, and these patients should receive adjuvant chemotherapy. Based on the results of GOG 157 trial, it is recommended 6 cycles of paclitaxel and carboplatin be given to patients with high-grade serous cancers and a minimum of 3 cycles to the rest.

Treatment of Advanced Stage (Stages III and IV) EOC

There are two approaches to the management of such patients: (1) Primary cytoreductive surgery followed by adjuvant combination chemotherapy - The "Gold Standard". (2) Use of neoadjuvant chemotherapy (NACT) - emerging paradigm in selected cases (stage IV, unresectable stage IIIc). NACT may be used in unresectable pelvic and abdominal disease and stage IV patients. It comprises 3 cycles of upfront chemotherapy, then interval cytoreducative surgery folowed by 3-4 cycles of adjuvant chemotherapy.

***Treatment of Optimally Debulked Disease*:** The long-term OS rate for women with optimally debulked stage III disease is approximately 25%. Thus, a small but appreciable cure rate is found in women treated with aggressive initial surgery followed by platinum-based chemotherapy. Based on the results of GOG protocol 158, systemic treatment with carboplatin and 3-hour paclitaxel is equivalent to cisplatin and 24-hour paclitaxel, with an improved toxicity profile. Carboplatin and paclitaxel thus have widespread acceptance as initial chemotherapy for ovarian cancer. Scottish Randomized Trial in Ovarian Cancer (SCOTROC) study established docetaxel/carboplatin was an alternative first-line chemotherapy regimen for ovarian cancer

***Intravenous (iv) vs Intraperitoneal (ip)*:** Three randomized trials comparing iv with ip chemotherapy have shown a clinical benefit for use of the ip approach. The first trial, led by the Southwest Oncology Group, used iv cyclophosphamide in combination with cisplatin administered either ip or iv. This study showed a survival advantage for the group receiving ip cisplatin (49 months vs 41 months; P=0.02; relative risk [RR] = 0.76), and there was a significant reduction in sensory neuropathy with ip therapy. The second study compared a standard iv paclitaxel and cisplatin regimen with 2 cycles of high-dose carboplatin iv at an area under the curve (AUC) of 9 followed by 6 cycles of iv paclitaxel and ip cisplatin. This study showed a significant improvement in PFS (28 months vs 22 months) and OS (63 months vs 52 months) for the ip regimen. The third study compared the same standard iv paclitaxel and cisplatin regimen with an intensive regimen of iv paclitaxel with ip cisplatin and ip paclitaxel. This study also showed marked improvement

in PFS (24 months vs 18 months) and OS (66 months vs 50 months) for the ip regimen.

The latter 2 studies showed increased toxicity for the ip regimen. Current efforts are focusing on ways to improve the tolerability of ip administration using contemporary supportive care measures, modification of the treatment regimens, and use of carboplatin in place of cisplatin. Suboptimally debulked and stage IV disease patients should receive iv systemic therapy.

***Treatment of Suboptimally Debulked Disease*:** Evidence clearly demonstrates that chemotherapy prolongs survival in these patients. Although there are many active agents for the treatment of ovarian cancer, the standard of care is combination therapy that includes a taxane and a platinum compound, usually carboplatin and paclitaxel (GOG 111, EORTC).

Maintenance Therapy: Trials have focused on the prolonged use of single-agent chemotherapy, ip chemotherapy, hormonal therapy, and vaccines. So far, none of these interventions has shown an improvement in OS. A Phase III SWOG/ GOG trial sparked controversy because it showed that a maintenance strategy of 12 monthly cycles of single-agent paclitaxel delivered to women who attained a complete response to primary platinum-paclitaxel chemotherapy, significantly improved PFS, compared with delivery of 3 cycles of the same treatment regimen. The trial was unable to demonstrate an OS advantage, although a subset of the patients with a low CA-125 baseline did exhibit an improvement in survival. Bevacizumab has emerged as an attractive choice as a maintenance strategy in a Phase III GOG trial with improved PFS. Mature survival data is awaited.

Recurrent EOC

It may be suspected by the development of new symptoms, the radiographic detection of an asymptomatic disease recurrence by CT scans, or a rising serum concentration of CA-125, which may predate radiographic disease progression by many months. All symptomatic patients must be treated. The optimal timing of second-line therapy in asymptomatic patients (typically detected because of rise in the serum level of CA-125) has been controversial.

Platinum Sensitive EOC: It is defined by recurrence 6 or more months after the completion of initial chemotherapy. The management plan is as under:

- Consider secondary cytoreductive surgery for appropriate patients
- Platinum retreatment is the standard of care
- Platinum-based combinations improve PFS and, in some cases, OS compared with platinum alone
- Prior and persistent toxicities should be considered when choosing therapy

***Platinum-Resistant EOC*:** It includes patients who progress while receiving initial chemotherapy (sometimes called platinum-refractory) or within 6 months of completing initial platinum-based chemotherapy. They have particularly worse prognosis. Drugs with single agent activity in Phase II trials include Topotecan (9-20%), liposomal Doxorubicin (12-26%), Gemcitabine (11-17%), Etoposide(6-32%) and Altretamine. Hormone therapy with tamoxifen, aromatase inhibitors (eg letrozole), or fulvestrant is associated with low objective response rates (10%) and used in advanced cases. Commonly used regimens are mentioned below:

- Topotecan daily x 5 d, every 3 wk
- Topotecan wkly on d 1, 8, and 15, every 4 wk
- Pegylated liposomal doxorubicin every 4 wk
- Gemcitabine on d 1 and 8 every 3 wk or d 1, 8, and 15 every 4 wk
- Etoposide orally 14/21 d or 14-21/28 d
- Paclitaxel wkly on d 1, 8, and 15 every 4 wk or d 1, 8, 15, and 21 every 4 wk
- Docetaxel every 3 wk

Biological and Newer Agents

Bevacizumab, an anti-VEGF monoclonal antibody, has demonstrated 16-21% single agent efficacy in Phase II studies. However, there is concern of increased risk of perforation. Phase III combination and maintainance studies are ongoing. Aflibercept (also known as VEGF Trap) in a Phase II trial showed 11% response rate. Sorafenib, Cediranib and Poly ADP-Ribose Polymerase (PARP) inhibitors are in Phase II/III trials.

Conclusions

Early diagnosis and multidisciplinary approach is the cornerstone of management of ovarian cancer. Recurrent ovarian cancer is challenging, and despite the many advances in therapeutic options for this disease, vast scope for improvement remains.

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WORKSHOP ON MEDITATION

A workshop on Meditation was organized by Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC) with 'The Art of Living Foundation' from June 13th to 15th at Pushpa Devi Bagrodia Dharamshala (Ashray), Rohini, Delhi. RGCI&RC invited patients along with their attendants and hospital staff to benefit from this workshop. The Art of Living Foundation is a multi-faceted organization with one of the largest volunteer bases in the world. It is a not-for-profit, educational and humanitarian non-government organization engaged in stress-management and service initiatives. Talks were delivered and practical training on meditation was also given. It was pointed out that a mind that is calm, without hesitation and anticipation is meditation. Meditation is not an action, it is an art of letting go without any effort. So, one should Relax-Relax more-Relax more and more and then meditation happens with effortlessness.

Meditation offers innumerable benefits.One can seek calmness, peace of mind, joy, vibrant health, greater energy, positive relationships and fulfillment in life. Meditation prevents stress from getting into the system and releases accumulated stress that is in the system.With meditation, the physiology undergoes a change and every cell in the body is filled with more prana (energy). This results in joy, peace and enthusiasm as the level of prana in the body increases. Meditation lowers high blood pressure. It decreases tension, headaches, insomnia, muscle and joint problems and improves mood and behavior. It improves the immune system and increases the energy level, as one gains an inner source of energy.

With regular practice of meditation: Anxiety decreases, Emotional stability improves, Creativity increases, Happiness increases, Intuition develops, Clarity and peace of mind is gained, Problems become smaller and Meditation sharpens the mind. Meditation makes one aware that one's inner attitude determines happiness.

Other benefits of meditation include: Emotional steadiness and harmony which cleanses and nourishes from within and calms oneself, whenever one feels overwhelmed, unstable, or emotionally shut down. With the assimilation of meditation into daily life, the consciousness evolves and in time, is able to experience the higher and refined states of consciousness and the disturbances in your life become negligible. Anger and disappointments become fleeting emotions that occur momentarily and then vanish. One starts living in 'the moment' and let go of 'the past'. Meditation can bring about a true personal transformation.

The volunteers made the audience familiar with various types of meditation. Most types involve being still and quiet, but some involve movement, such as tai chi, chi gong or walking meditation. **Mindfulness meditation** means being aware and present in each moment. One sits still in a comfortable position in a restful place. In some types one brings the mind back to his breathing. Mindfulness meditation helps to cope better and be more at ease in life. In **focused meditation**, one uses an object, such as a flower or candle flame, to focus the attention on. This can help the mind to concentrate better, which is an important part of meditation. In **visualisation,** one creates specific images in one's mind. One focuses the imagination to create pictures or images for a specific reason, such as to relieve symptoms of cancer or help to relax. In **guided meditation**, the meditation teacher, or the voice on the tape or CD, guides the imagination with the aim of relaxing. **Transcendental meditation** method involves repeating a specific word or mantra given to a person by the transcendental meditation teacher. It aims to increase the energy and lower the stress level. It also helps to develop concentration and focus the mind. In **prayerful meditation**, the aim is to develop one's spirituality to open you up to God or a higher power and to develop positive qualities, such as compassion and wisdom.

Some scientific evidence shows that meditation can help to relieve particular symptoms and improve your quality of life. It can improve the mood and the ability to concentrate, reduce severe depression (mindfulness based stress reduction), boost the immune system and help to control pain. However, there is no evidence to suggest that meditation can help to prevent, treat or cure cancer or any other disease. When one has been introduced to a type of meditation practice, one can do it oneself at home.To experience the benefits of meditation, regular practice is necessary. Once imbibed into the daily routine, meditation becomes the best part of the day.

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