Clinical Trials in Ovarian Cancer, Part 1

The American Cancer Society has estimated that in 2002 ovarian cancer will strike 23,300 women, and 13,900 women will die from the disease.[1] Five-year survival is about 80% for women with stage I disease, 50% for women with stage II disease, 25% for women with stage III disease, and 15% for women with stage IV disease. Among women with advanced-stage disease, optimal debulking surgery, as well as platinum/taxane-based adjuvant therapy prolongs disease-free and median survival.[2,3] Population-based data suggests that guidelines for therapy are not uniformly followed in community practice.[4] In addition, older patients appear to receive less aggressive treatment than younger patients.

Clinical Trials Referral Resource is designed to serve as a ready reference for oncologists to help identify clinical trials that might be suitable for their patients. We hope it will also enhance accrual to clinical trials by informing practicing oncologists of ongoing protocols. Currently in the United States less than 10% of eligible adult patients are entered into clinical trials. The result is a delay in answering important therapeutic and scientific questions and disseminating therapeutic advances to the general oncology community.

It should be emphasized that including a specific trial does not imply that it is more important than another trial. Among the criteria for selection are that the trial is addressing an important question and is not expected to close in the immediate future (less than 1 year), and that initial staging or laboratory tests required for patient eligibility are widely practiced and available. Information on other protocols can be accessed via Physician’s Data Query (PDQ).*

We emphasize that this is an attempt to encourage referral of patients to these trials. We are specifically not soliciting additional members for the cooperative groups, nor are we suggesting how practicing oncologists should be treating patients who are not in a study.

This month’s installment of Clinical Trials Referral Resource is devoted to current clinical trials of the Cancer Trials Support Unit, a National Cancer Institute pilot program.

For patient entry information, see the individual trials.

Part 1 of this two-part series will discuss prevention, screening, adjuvant treatment, neoadjuvant chemotherapy, and adjuvant chemotherapy trials for ovarian cancer. Part 2, to be published in next month’s issue of ONCOLOGY, will detail diagnosis and treatment trials for recurrent disease.
Epidemiology

About 5% of ovarian cancer appears linked to an inherited predisposition. The most common genetic syndromes are mutations at the BRCA1 and BRCA2 loci.[5] The risk of ovarian cancer is higher with BRCA1 mutations than BRCA2 mutations. Other known risk factors for ovarian cancer include northern European descent, nulliparity, and advancing age.[6] Protective factors include pregnancy, lactation, and use of hormonal contraceptives. In the United States, ovarian cancer is more common in the northern states than the southern states.[7] It has been hypothesized that higher levels of sun exposure in southern latitudes, resulting in increased vitamin D levels, may also be protective against the development of ovarian cancer.

Prevention Trials

There is no consensus yet as to the existence or the nature of premalignant ovarian neoplasia.[8] Reliable intermediate biomarkers for use in prevention studies have not been identified. Several prevention studies are underway evaluating retinoids/progestins, which appear to have activity in primate models.[9-11] Phase II studies are being conducted in women at high genetic risk for ovarian cancer, who have decided to undergo prophylactic oophorectomy (Gynecologic Oncology Group [GOG]-0190). The intervention is given during a defined window of opportunity between the decision to undergo surgical removal of the ovaries and the actual procedure.

Screening Trials

To date, an effective screening algorithm for ovarian cancer has not been identified. The best imaging modality for the adnexa, transvaginal ultrasound, lacks both adequate sensitivity and specificity for diagnosing early ovarian cancer.[12] The serum marker CA-125, which is used to monitor response to therapy among women with advanced ovarian cancer, similarly lacks both sensitivity and specificity[13]; up to 50% of women with early ovarian cancer have CA-125 levels in the normal range. Aggressive efforts are under way through the NCI’s Early Detection Research Network, Ovarian Cancer Specialized Programs of Research Excellence, Cancer Diagnosis Program (Diagnostic Research Branch, Program for the Assessment of Clinical Cancer Tests), and Center for Cancer Research, to identify more effective markers, marker combinations, and screening algorithms. Proteomics appear particularly promising in this regard.[14]

The NCI has recruited 74,000 women to the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), which is evaluating screening for prostate, lung, colon, and ovarian cancer.[15] In this trial, women are randomized to yearly monitoring of their CA-125 level and transvaginal ultrasound, or normal clinical care. They are to undergo such evaluation for 6 years, then are followed for an additional 7 years. The United Kingdom, under the leadership of Drs. Ian Jacobs and Usha Menon, has recently started an even larger screening trial (in 100,000 women), evaluating both transvaginal ultrasound and serial, individualized CA-125 levels.[16]

The NCI’s Cancer Genetics Network has recently undertaken a screening trial for women at high risk for familial ovarian cancer (Massachusetts General Hospital [MGH]-000084). The trial, led by Dr. Steven Skates, has already accrued 1,000 patients. Dr. Mark Greene, of the NCI’s Division of Cancer Epidemiology and Genetics and the GOG, has developed a complementary study to quantify the benefit of prophylactic oophorectomy in women at high familial risk (GOG-0199).

Primary Treatment Trials

Recent studies have documented the importance of surgery in the treatment of ovarian cancer.[17] Comprehensive surgical exploration, accompanied by systematic biopsies of intra-abdominal tissues and retroperitoneal lymph nodes, must be performed to accurately stage ovarian cancer. In addition, removal of gross disease via surgical debulking significantly improves outcome for women with advanced (stage III and IV) ovarian cancers.

Patients found to have stage IA/IB, grade 1 or 2 epithelial ovarian cancer may not require adjuvant
therapy. In general, women with stage I, grade 3, stage IC, and stage II ovarian cancer are recommended to undergo adjuvant chemotherapy. However, recent European data suggested that this treatment improves recurrence-free survival, but not overall survival in women with accurate surgical staging.[18] Adjuvant therapy is generally based empirically on regimens with documented activity in women with recurrent or advanced ovarian cancer. Most regimens are based on platinum or the combination of a platinum and taxane, generally for three to six courses. The GOG has completed a trial in which women with early-stage ovarian cancer were randomized to three vs six cycles of carboplatin (Paraplatin)/paclitaxel (GOG-0157). The current GOG trial randomizes the same population of women to three courses of carboplatin/paclitaxel with or without weekly low-dose paclitaxel (40 mg/m²) for 24 weeks, which is thought to have an antiangiogenic effect (GOG-0175).

For women with advanced (ie, stage III/IV) ovarian cancer, adjuvant chemotherapy generally consists of six to eight courses of intravenous platinum/taxane therapy. Although several trials suggest that concomitant intravenous and intraperitoneal therapy of the same agents may improve survival, intraperitoneal therapy has gone out of vogue in the community setting and is rarely employed.[19-21] Similarly, despite promising data associated with the use of whole abdominal radiation, radiation therapy is rarely, if ever, used in primary adjuvant therapy for epithelial ovarian cancer.[22]

Several trials are under way to evaluate the addition of another agent to the platinum/taxane combination. Despite advances in our understanding of the molecular biology of ovarian cancer, we have yet to define a comprehensive set of molecular targets or determine how best to optimize individual therapy based on the molecular characteristics of a patient’s cancer. The agents currently under evaluation in phase III trials are primarily cytotoxic agents that have demonstrated activity in women with recurrent, platinum-resistant ovarian cancer. Agents currently under evaluation include the topoisomerase I inhibitor topotecan (Hycamtin), gemcitabine (Gemzar), and two anthracyclines, epirubicin (Ellence) and liposomal doxorubicin.

As the response rate to adjuvant therapy has risen with the introduction of taxanes, the patient sample size for phase III trials has increased. Intergroup collaboration is often necessary to complete clinical trials in a timely fashion. The Gynecologic Cancer Intergroup (GCIG), which brings together international clinical trials Cooperative Groups conducting trials in gynecologic cancer, has worked to facilitate such collaboration. Among those trials developed under the umbrella of the GCIG is GOG-0182/International Collaborative Ovarian Neoplasm group (ICON) 5, a joint international study developed under the auspices of the GCIG, and led by the GOG. Clinical trials groups participating in GOG-0182/ICON 5 include the GOG, the Southwest Oncology Group (SWOG), the new Cancer Trials Support Unit (CTSU), the British Medical Research Council (MRC), the Australia-New Zealand GOG (ANZGOG), and the Italian ICON Study Group. Estimated accrual to this trial is 4,000 patients, making it the largest treatment trial yet conducted in ovarian cancer; accrual to date is 1,200 patients.

Other joint trials of primary chemotherapy in ovarian cancer are being conducted jointly by the German Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) and French Group d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens (GINECO) gynecologic cancer Cooperative Groups as well as the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), and Spanish Grupo Espanol de Investigacion en Cancer de Ovario (GEICO) Cooperative Groups.

Prevention

**Title:** An Exploratory Evaluation of Fenretinide (4-HPR) as a Chemopreventive Agent for Ovarian Carcinoma (active)

**Protocol Number:** GOG-0190

**Participating Institutions:** Gynecologic Oncology Group

**Contact:** Mary B. Daly, mb_daly@fccc.edu

Screening

**Title:** Screening Study for Ovarian Cancer in Women Who Are at High Genetic Risk for Developing
Ovarian Cancer (active)

**Protocol Number:** CRCA-FOCS, EU-20044, UKFOCSS  
**Participating Institutions:** Addenbrooke’s NHS Trust  
**Contact:** James Mackay, +44 (0) 207 905 2386

**Title:** Prospective Study of Prophylactic Salpingo-Oophorectomy and Longitudinal CA-125 Screening Among Women at Increased Genetic Risk of Ovarian Cancer (active)  
**Protocol Number:** GOG-0199  
**Participating Institutions:** Gynecologic Oncology Group  
**Contact:** Mark H. Greene, (301) 594-7641

**Title:** Screening Study for Ovarian Cancer in Participants Who Are at High Genetic Risk for Developing Ovarian Cancer (active)  
**Protocol Number:** MGH-000084  
**Participating Institutions:** Massachusetts General Hospital  
**Contact:** [http://epi.grants.cancer.gov/ovarian/](http://epi.grants.cancer.gov/ovarian/)

**Title:** Study of Clinical, Genetic, Behavioral, Laboratory, and Epidemiologic Characteristics of Individuals and Families at High Risk of Breast or Ovarian Cancer (active)  
**Protocol Number:** NCI-02-C-0212  
**Participating Institutions:** Center for Cancer Research (NCI)  
**Contact:** Mark H. Greene, (301) 594-7641

**Title:** Genetic, Clinical, and Epidemiological Study of Individuals and Families at High Risk of Cancer (active)  
**Protocol Number:** NCI-78-C-0039  
**Participating Institutions:** Division of Cancer Epidemiology and Genetics (NCI)  
**Contact:** Mark H. Greene, (301) 594-7641

**Title:** National Ovarian Cancer Early Detection Program: Screening and Genetic Study (active)  
**Protocol Number:** NCI-G00-1753, NU-99G7, NU-99G8  
**Participating Institutions:** Robert H. Lurie Comprehensive Cancer Center (Northwestern University)  
**Contact:** David A. Fishman, (312) 926-6606

### Adjuvant Treatment of Early-Stage (FIGO I/II)

**Title:** A Randomized Phase III Trial of IV Carboplatin (auc 6) and Paclitaxel 175 mg/m² q21 Days × 3 Courses Plus Low-Dose Paclitaxel 40 mg/m²/wk Versus IV Carboplatin (auc 6) and Paclitaxel 175 mg/m² q21 Days × 3 Courses Plus Observation in Patients With Early-Stage Ovarian Carcinoma (active)  
**Protocol Number:** GOG-0175  
**Participating Institutions:** Gynecologic Oncology Group  
**Contact:** Robert S. Mannel, (405) 271-7589

### Neoadjuvant Chemotherapy for Presumed FIGO Stage III/IV

**Title:** Phase III Randomized Study of Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery vs Upfront Cytoreductive Surgery Followed by Chemotherapy With or Without Interval Debulking Surgery in Patients With Stage IIIC or IV Ovarian Epithelial, Peritoneal, or Fallopian Tube Cancer (active)  
**Protocol Number:** EORTC-55971  
**Participating Institutions:** Gynecological Cancer Group  
**Contact:** Ignace B. Vergote, [ignace.vergote@uz.kuleuven.ac.be](mailto:ignace.vergote@uz.kuleuven.ac.be)

**Title:** A Phase II Evaluation of Neoadjuvant Chemotherapy, Interval Debulking Followed by Intraperitoneal Chemotherapy in Women With Stage III and IV Epithelial Ovarian Cancer, Fallopian Tube Cancer or Primary Peritoneal Cancer (active)
Adjuvant Chemotherapy for FIGO Stage III/IV

**Title:** Phase III Randomized Study of Carboplatin With or Without Gemcitabine in Patients With Advanced Ovarian Epithelial Carcinoma Who Failed Prior First-Line Platinum-Based Therapy (active)

**Protocol Number:** AGOSG-OVAR-2.5, CAN-NCIC-OV.15, EORTC-55005, EU-20064, NCI-V00-1601

**Participating Institutions:** AGO Ovarian Cancer Study Group

**Contact:** Jacobus Pfisterer, jpfisterer@email.uni-kiel.de

**Title—**A Phase III Randomized Trial of Paclitaxel and Carboplatin vs Triplet or Sequential Doublet Combinations in Patients With Epithelial Ovarian or Primary Peritoneal Carcinoma (active)

**Protocol Number—**GOG-0182

**Participating Institutions—**Gynecologic Oncology Group

**Contact—**Michael A. Bookman, ma_bookman@fccc.edu

**Title—**Phase II Evaluation of Intravenous Paclitaxel, Intraperitoneal Cisplatin, Intravenous Liposomal Doxorubicin and Intraperitoneal Paclitaxel in Women With Optimally-Debulked Stage III Epithelial Ovarian Cancer, Primary Peritoneal or Fallopian Tube Cancer (active)

**Protocol Number—**S9912

**Participating Institutions—**Southwest Oncology Group

**Contact—**Harriet O. Smith, hsmith@salud.unm.edu

**References:**


Source URL: http://www.diagnosticimaging.com/clinical-trials-ovarian-cancer-part-1

Links:
[1] http://www.diagnosticimaging.com/review-article