Since the use of platinum and a taxane became standard treatment for ovarian cancer over a decade ago, few if any major changes to this regimen have been made. In recent years a focus on non-traditional drugs and altered routes of administration has resulted in new hopes for women with ovarian cancer. The resurgence of intraperitoneal chemotherapy administration and the addition of biologic agents, including antiangiogenesis agents and immune-based therapy, are examples of the promise of improved disease control.

For over fifteen years, researchers have been studying intraperitoneal (IP) chemotherapy in ovarian cancer, since it is a disease often confined to the abdominal cavity. Despite promising results, IP therapy was not routinely used in the past because it is difficult for patients to tolerate. In January 2006, the National Cancer Institute issued an announcement urging clinicians to consider administering adjuvant IP chemotherapy to select Stage III ovarian cancer patients. This recommendation is based on the results of several key studies published over the last ten years. The patients who received IP therapy showed a dramatic improvement in overall survival. Although IP therapy has more early side effects than IV therapy, it has proven to be a successful “new” method of chemotherapy administration in the adjuvant setting for ovarian cancer. Researchers in our division participated in the trials leading up to the NCI announcement and we are currently offering this state-of-the-art therapy.

Biologic therapies are becoming widely used in many cancers. A promising subset of biologic therapy is antiangiogenesis inhibition. Angiogenesis, the formation of new blood vessels, is essential to cancer growth and spread. Research is underway to find anti-angiogenesis agents that block the formation of these new blood vessels, in effect stopping the cancer. One of these agents, Avastin® (bevacizumab), was recently approved by the FDA for use in colon cancer and is currently being studied in other disease sites, including ovarian cancer. The UW gynecologic oncology team is participating in one such study comparing different combinations of carboplatin, paclitaxel and Avastin.

Lastly, one of the main interests of our translational research lab program is to achieve a better understanding of the interactions of the immune system and ovarian cancer. The “featured protocol” in this edition of our newsletter utilizes an antibody (cytokine fusion protein, KS-IL2) that was developed in UW Cancer Center labs. We are excited to see this therapy go from our lab bench to the bedside of women with gynecologic cancers. It is our hope that any or all of these novel strategies will help future patients who suffer from this deadly disease.
**Our Featured Protocol**

**CO 04702: Phase I Dose-Escalation Study of the Safety, Tolerability, Pharmacokinetics, Biological and Clinical Activity of EMD 273066 Administered with Low-Dose Cyclophosphamide to Subjects with Epithelial Cell Adhesion Molecule (EpCAM) Positive Advanced Cancers**

A healthy immune system is known to contribute to cancer prevention as well as to the success of cancer therapy. Activating the body’s immune system to identify and eliminate malignant cells is the primary goal of tumor immune therapy. Numerous strategies have been utilized to produce such immune activating results. These have included variations on vaccination strategies with the infusion of passive anti-tumor immunity via antibody- or laboratory-activated immune cells, as well as treatment with immune activating cytokines. Interleukin 2 (IL-2) is one of the most potent activating cytokines of the human immune system. It is responsible for the activation of several immune cell lines, including T lymphocytes and natural killer cells, which both have the capability of identifying and destroying tumor cells. Maintaining a local tumor bed environment with high levels of IL-2 is a necessary component of this type of therapy. In the past, IL-2 has been given systemically to generate such local tumor bed activation. Unfortunately, the systemic toxicities, such as renal insufficiency and vascular leak syndrome, have limited its use in most solid tumors.

Genetically engineered monoclonal antibodies, in contrast, can target therapies directly to tumor cells, which express specific antigens. These antibodies have been used to direct chemotherapeutic drugs, radiotherapeutic isotopes, and more recently, immune activating cytokines to the intended cells.

Immunocytokines are genetically engineered fusion proteins consisting of a humanized mouse monoclonal antibody linked to two intact cytokine molecules. KS-IL 2 is one such fusion protein recognizing the cell surface adhesion molecule EpCAM. EpCAM is expressed in low levels in most normal epithelial tissues but is over expressed on cancer cells, including many epithelial ovarian cancers. KS-IL 2 therapy utilizes this over expression of EpCAM to target IL-2 to the local tumor beds. In theory, antibody-delivered IL-2 will activate immune cells locally within the tumor bed, enhancing its anti-tumor properties. The localization of IL-2 by the antibody negates the necessity of high dose IL-2 and its associated toxicities.

Recently, significant attention has been brought to the presence of immunosuppressive T cells in patients with malignancies. T regulatory cells have the ability to suppress the tumorcidal activity of activated lymphocytes. Of interest, low dose cyclophosphamide has been shown in several studies to preferentially reduce circulating numbers of immunosuppressive T regulatory cells, relatively sparing the cytotoxic T cells. In order to capitalize on this effect, our current phase I trial is designed to assess the safety and patient tolerability of escalating doses of immunocytokine KS-IL 2 after pre-treatment with low dose cyclophosphamide (300 mg per m$^2$). In theory, this combination of therapy has several advantages:

1. Preferential suppression of T regulatory cells will allow for development and prolonged life of stimulated T cells.
2. Significant tumor bed IL-2 stimulation can be achieved with minimal systemic toxicities.
3. Initial tumor lysis resulting from KS-IL-2 binding can trigger broad-spectrum tumor antigen, generating long lasting anti-tumor memory.

The trial to date is treating patients in the third dose cohort of 1.5 mg per m$^2$ of immunocytokine. The planned treatment will escalate in cohorts of three patients with a maximum dose of 6 mg per m$^2$. The primary objective of this dose-escalating phase I study is to determine the tolerability and safety of immunotherapy in patients pretreated with low dose cyclophosphamide. Secondary objectives include 1) assessment of immune system activation via monitoring of a panel of lymphocytes throughout therapy (including sequential measurement of T regulatory cells) 2) tumor response to therapy and 3) assessment of the pharmacokinetics of this regimen.

Eligible patients must have a tumor sample available for EpCAM testing prior to being considered for enrollment (see Protocol Eligibility). Any tumor type that is found to be EpCAM positive is eligible for study participation. Patients are treated with immunocytokine for three consecutive days as inpatients on our General Clinical Research Center.

**Protocol Eligibility**

**Inclusion Criteria**

- 18 years or older
- Any EpCAM positive tumor by immunohistochemistry
- Karnofsky Performance Status 70%
- Subject-specific measures of objective tumor response

**Exclusion Criteria**

- Uncontrolled hypertension or hypotension
- Presence of medically significant third space fluids
- Previous diagnosis of an autoimmune disease

*Select eligibility requirements*
Our Current Protocols

Ovarian

CC 04703  Pre-clinical Studies of Glycoconjugate MUC16 in the Diagnosis and Response to Immunotherapy in Epithelial Ovarian Cancer

CO 04702  Phase I Dose-Escalation Study of EMD 273066 (See opposite page)

CO 04706  Phase III Randomized Trial of Gemcitabine/Cisplatin versus Paclitaxel/Cisplatin followed by Elective Paclitaxel Consolidation in Primary Epithelial Ovarian, Peritoneal or Fallopian Tube Cancer

GOG 199  Prospective Study of Risk-Reducing Salpingo-Oophorectomy and Longitudinal CA-125 Screening among Women at Increased Genetic Risk of Ovarian Cancer

GOG 212  A Randomized Phase III Trial of Maintenance Chemotherapy Comparing Single Agent Paclitaxel or Xyotax Versus No Treatment Until Relapse in Women with Advanced Ovarian or Primary Peritoneal Cancer

GOG 218  Phase III Trial of Carboplatin and Paclitaxel Plus Placebo Versus Carboplatin and Paclitaxel Plus Concurrent Bevacizumab in Women with Newly Diagnosed, Suboptimal, Advanced Stage Epithelial Ovarian and Peritoneal Cancer

GOG 220  Pelvic Mass Study to Develop Serum Proteomic Profiles (Signatures) for Epithelial Ovarian Cancer Diagnosis and Prognosis

Uterine

GOG 129-P  A Phase II Evaluation of Ixabepilone in the Treatment of Recurrent or Persistent Endometrial Cancer

GOG 130-E  Phase II Evaluation of Gemcitabine and Docetaxel in the Treatment of Recurrent or Persistent Carcinoma of the Uterus

GOG 299  Randomized Phase III Trial of Doxorubicin/Cisplatin/Paclitaxel and G-CSF versus Carboplatin/Paclitaxel in patients with Stage III & IV or Recurrent Endometrial Cancer

GOG 210  A Molecular Staging Study of Endometrial Carcinoma

GOG 239-B  Phase II Evaluation of Thalidomide in the Treatment of Recurrent or Persistent Carcinosarcoma of the Uterus

GOG 232-B  Phase II Evaluation of Paclitaxel and Carboplatin in the Treatment of Advanced, Persistent, or Recurrent Uterine Carcinosarcoma

Cervical

CO 02702  Preservation of Ovarian Function via Laproscopic Ovarian Transposition in Patients with Locally Advanced Squamous Cell Carcinoma of the Cervix

GOG 204  Randomized Phase III Trial of Paclitaxel/Cisplatin versus Vomilion/Cisplatin versus Gemcitabine/Cisplatin versus Topotecan/Cisplatin in Stage IB, Recurrent or Persistent Carcinoma of the Cervix

GOG 9918  Phase I Trial of Tailored Radiation Therapy with Concomitant Cetuximab and Cisplatin in the Treatment of Patients with Cervical Cancer

Vulvar

GOG 205  Phase II Trial of Radiation Therapy and Weekly Cisplatin Chemotherapy for the Treatment of Locally-Advanced Squamous Cell Carcinoma of the Vula

For more information about these clinical trials at the UW Comprehensive Cancer Center, contact CancerConnect, (800) 622-8922 or (608) 262-5223 in the Madison area.

A complete listing of all clinical trials at the UW Comprehensive Cancer Center is also available on our website, www.cancer.wisc.edu.

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Coretta Scott King died of ovarian cancer in January 2006.

Over 70% of women with ovarian cancer are not diagnosed until the disease has spread beyond the ovary, making it difficult to treat successfully.

The average age for developing ovarian cancer is 61 years old.

Ovarian cancer is the leading cause of gynecologic cancer deaths in the U.S.

One woman out of every 55 will develop ovarian cancer.

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