This issue of our newsletter highlights gynecologic cancer research and clinical trials at the Chao Family Comprehensive Cancer Center.

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

UCI-led research results in FDA approval of drug for ovarian cancer

UC Irvine Chao Family Comprehensive Cancer Center researchers have been at the forefront of testing to determine whether the drug bevacizumab — popularly known by the brand name Avastin® — could help women with reproductive system cancers.

In June, the U.S. Food and Drug Administration approved bevacizumab for front-line and maintenance therapy for advanced ovarian cancer based on an earlier UCI-led study. Bevacizumab — an angiogenesis inhibitor, meaning that it prevents new vessels from forming to supply blood to tumors — already had been approved for those uses in Europe because of the same study, Gynecologic Oncology Group Protocol 0218, which was developed at UCI by Dr. Robert A. Burger and published in the New England Journal of Medicine in 2011.

Adjunct therapy with bevacizumab added an average 3.7 months of survival for women with advanced cervical cancer, according to another UCI study led by gynecologic oncologist Dr. Krishnansu S. Tewari and published in 2014 in the New England Journal of Medicine.

In Tewari's most recent study, which was presented to the American Society of Clinical Oncology (ASCO) conference in June in Chicago, the question was whether bevacizumab improved the overall survival of women with ovarian cancer. The results provided a check on big hopes for the drug.

Bevacizumab did lengthen the time women enjoyed freedom from ovarian cancer, Tewari said, but even so, "it did not improve overall survival time."

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These findings give oncologists a more complex issue to ponder when prescribing drug regimens for their patients. Although their patients will have more months without progression of the disease, they will not live longer.

Still, the FDA has evolved over the years and has recognized the value of progression-free survival, which is why the agency recently approved bevacizumab for ovarian cancer.

"It's important to understand that there is no overall survival benefit," Tewari said. "There are significant side effects with this drug. It is also expensive. And we do not have a biomarker for this treatment to tell us if it will work particularly well for a certain person or kind of tumor."

The drug costs thousands of dollars a month to administer — a six-month, front-line cycle of chemotherapy plus bevacizumab typically costs about $70,000, he said — and though its patent will end in a few years, it's uncertain whether that will lead to generics with significantly lower prices.

Meanwhile, side effects can include gastrointestinal perforation in about 1 percent of patients, Tewari said, as well as bleeding or blood clots.

This study and UCI's previous trials on bevacizumab were funded by the National Cancer Institute, Tewari noted, giving them "a very high degree of integrity."

"I'm excited that research that originated at UCI led to phase 3 randomized trials in two different cancer types," said Tewari.

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"And both led to FDA approval. But we also want to be fair and balanced about the findings."

Tewari is working on two new studies. He is the global chair and principal investigator of a phase 3 trial of checkpoint inhibition immunotherapy in recurrent/metastatic cervical cancer. He also is the local principal investigator on a nationwide study to determine whether adding immunotherapy to a combination of chemotherapy plus bevacizumab improves outcomes for patients with newly diagnosed, advanced ovarian cancer.

Both studies are open to patient enrollment at the Chao Family Comprehensive Cancer Center.

For more information on his trials, contact Dr. Krishnansu Tewari at ktewari@uci.edu.

Doctors with patients who may qualify for any of these trials are encouraged to contact the Chao Family Comprehensive Cancer Center's clinical research line at 877-UC-STUDY (877-827-8839) or by emailing ucstudy@uci.edu

The value of early in situ chemotherapy

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a promising treatment for patients with advanced ovarian cancer, allowing them to receive their first chemo dose along with their surgery, instead of as much as 10 weeks later.

Immediately after surgery to remove all visible ovarian tumors or lesions, a heated chemotherapy solution is pumped into the patient's abdominal cavity. The patient is then rocked back and forth for one to two hours on the operating table to spread the drug throughout the abdomen.

Because HIPEC is a regional rather than systemic treatment, it can be performed before the typical waiting period after surgery. The hope is that quick and direct treatment kills any cancer cells remaining after surgery and increases survival time without recurrence — and perhaps overall survival time as well.

But cisplatin, the chemotherapy drug typically used, can have serious side effects, says Dr. Leslie Randall, a UCI Health gynecologic oncologist who has been conducting extensive clinical studies on HIPEC.

"Cisplatin can be absorbed into the bloodstream relatively quickly," she said. "That means the patients can develop serious side effects while they're in a fragile, post-surgical state."

Immediate risks include renal toxicity, neutropenia (low levels of infection-fighting white blood cells) and thrombocytopenia (low levels of blood-clotting platelets). Randall and her team set out to find the optimal dose — the maximum dose with tolerable side effects — of a different chemotherapy drug, carboplatin, which is not as easily taken into the bloodstream. She reported on her study results at the 2018 American Society of Clinical

Oncology annual meeting in Chicago in June.

"We found that giving carboplatin for HIPEC was very safe and tolerable," she said. "There were very few severe side effects in contrast to what has been reported with cisplatin."

HIPEC has been used for some conditions since the 1980s, Randall said. Various concerns have limited its application, including side effects like those with cisplatin, and the potential danger of exposing operating-room staff to a chemotherapy drug. Improvements over the years in drug delivery to the abdominal cavity have alleviated many of those concerns.

Another issue is that adding HIPEC just after surgery increases the amount of time a patient is on the operating-room table and under anesthesia by an average of 2.5 hours.

> "We found that giving carboplatin as HIPEC was very safe and tolerable."

However, HIPEC has been shown to be effective in treating peritoneal mesothelioma. And while her recent results are promising, Randall said it is too early to tell whether HIPEC will lengthen survival time for ovarian cancer patients.

Few studies of HIPEC for ovarian cancer have included untreated control groups, but a recent European randomized, controlled trial reported in the New England Journal of Medicine found an improved overall survival rate with HIPEC using cisplatin, especially when neoadjuvant chemotherapy is given prior to surgery.

Before HIPEC with carboplatin can be adopted as standard care, Randall says her team's findings require confirmation. She said she is developing a confirmatory U.S. study, and that her team is planning a follow-up HIPEC-carboplatin study, which would assess the efficacy of HIPEC using the drug at the maximum dosages found to be safe.

For more information about her clinical trials, contact Dr. Leslie Randall at lrandall@uci.edu.

In Memoriam

UCI mourns the passing of Philip J. DiSaia, MD, former chair of the Department of Obstetrics and Gynecology and one of the nation's leaders in gynecologic cancer research and treatment.

DiSaia, co-author of Clinical Gynecologic Oncology, the most widely read textbook on the subject and which is currently in its ninth edition, spearheaded practice-changing clinical trials that established the standard of care for practically all gynecologic cancers over the course of his long career.

He served as president of the Society of Gynecologic Oncology and the American Board of Obstetrics & Gynecology, and led the National Cancer Institute's Gynecologic Oncology Group for four consecutive terms.

The grandson of Italian immigrants, DiSaia was born in Providence, R.I., in 1937. He graduated from Brown University in Providence with a bachelor's in science and earned a medical degree at Tufts University in Medford, Mass., followed by a residency in obstetrics and gynecology at Yale University in New Haven, Conn. He completed a fellowship in gynecologic oncology at MD Anderson Cancer Center in Houston, Tex.

In 1976, DiSaia joined UCI as chair of the Department of Obstetrics & Gynecology, and went on to establish four research-driven divisions in Gynecologic Oncology, Maternal-Fetal Medicine, Reproductive Endocrinology and Infertility, and Urogynecology.

Over the course of his 42 years at UCI, DiSaia cured and eased the suffering of thousands of women who struggled with gynecologic malignancies. He also was a beloved mentor to innumerable residents and fellows who carry his legacy in their hearts today.

DiSaia, who was surrounded by his family when he passed away peacefully at home on Sept. 27, is survived by his wife, Patti DiSaia, their four sons and daughters-in-law, and numerous grandchildren.

A celebration of his life will be held at 12:30 p.m. on Nov. 4, 2018, at the University of California Irvine Hills Community Center.

Evaluating cost and efficacy of ovarian cancer treatments

Because of the high recurrence rate of advanced ovarian carcinoma after successful first-line chemotherapy, maintenance therapy plays an important role in follow-up treatment.

But which therapies are the most effective, both in terms of their ability to prolong survival without any progression of the cancer and the overall cost of using them?

A team led by Dr. Juliet Wolford, a third-year gynecologic oncology fellow at UCI Health, and Dr. Krishnansu Tewari sought the answer, using a cost-effectiveness model based on existing studies of medication effectiveness, then compiling comprehensive lists of associated costs, including the medication price, the cost of providing treatment (infusions, for example, are more expensive than taking a medication orally), and any costs to manage side effects.

The study, which received a merit award from the American Society of Clinical Oncology (ASCO), was selected for the 2018 Best of ASCO program and Wolford was invited to present her team's findings at the society's June meeting in Chicago.

The study examined six different medications. The first three are niraparib, olaparib and rucaparib, all of which are PARP inhibitors, a targeted therapy that prevents cancer cells from repairing damaged DNA, thereby leading to their death. The others are the anti-angiogenic bevacizumab, which starves tumors by preventing them from connecting to blood vessels; the chemotherapy drug paclitaxel, and the immunotherapy agent pembrolizumab.

"It is unprecedented to have potentially six targeted therapies for maintenance strategies," Wolford said. Several of the treatments she studied have only become available since 2014.

Of the six, the PARP inhibitors were by far the most expensive, with two of them each costing more than $500,000 before progression. There are a couple of reasons, Wolford said: The medication is taken daily instead of monthly. The most effective PARP inhibitor was niraparib, which was the second-most expensive at more than $515,000 prior to progression. Because it had the most success at holding off the progression of cancer, it was taken longer, which raised the price.

Because PARP inhibitors are oral medications and tend to be well tolerated, with fewer side effects, the non-medication costs tend to be lower. In other words, most of the expense lies in the medication itself.

However, bevacizumab, a far less expensive medication, performed nearly as well as niraparib in terms of survival without cancer progression — 19.8 months at a total cost of about $176,000, Wolford said.

The most expensive of the six drugs, olaparib, costs more than $564,000 before progression, Wolford and her team found. Yet, at 19.1 months, the survival period without progression was lower than that for patients treated with the bevacizumab, which costs less than one-third as much.

The least expensive medication, paclitaxel, costs a little more than $25,000, with an 18.9-month progression-free survival period — extremely close to the results for the most expensive treatment. That makes it seem to be the most cost-effective treatment.

"You have to be careful when you are looking at cost-effectiveness studies," Wolford cautioned. "Even though paclitaxel appears to be the most cost-effective, the patients being treated with it were first-line and thus tended to be healthier and have a better response" than patients using the other therapies examined for the study, she said.

Moreover, drug prices are very fluid. Before the Taxol drug patent expired in 2000, paclitaxel was far more expensive. Now that generic versions are available, "The cost is about one-sixth what it used to be," she said.

Wolford said her team's work clarifies outcomes and prices in ways that might help patients and their oncologists in the decision-making process. "As providers we should never withhold medications that could be beneficial because of cost," she said. "But we also need to be aware of the burden it might place on our patients. We must be mindful when treating patients with extremely expensive therapies that will have only marginal benefit."

For more information about her research, contact Dr. Juliet Wolford at jwolford@uci.edu

Contact Us

To learn more about our cancer clinical trials or determine whether we have one that might meet your patients' needs, call the Chao Family Comprehensive Cancer Center at 877-827-8839 or email us at ucstudy@uci.edu

Open clinical trials

These gynecologic cancer clinical trials are among many now accepting patients:

Immunotherapy Trials

GOG 3015: A Phase 3, Multicenter, Randomized Study of Atezolizumab versus Placebo Administered in Combination with Paclitaxel, Carboplatin, and Bevacizumab for Patients with Newly-Diagnosed Stage III or Stage IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.

This study tests whether adding atezolizumab to paclitaxel, carboplatin and bevacizumab is more effective than those drugs alone for advanced ovarian, fallopian tube or primary peritoneal cancer.

GOG 3016: An open-label, randomized, Phase 3 clinical trial of REGN2810 versus therapy of investigator's choice chemotherapy in recurrent or metastatic platinum-refractory cervical carcinoma.

This study compares overall survival between immunotherapy and chemotherapy in recurrent or metastatic cervical cancers after treatments with platinum-based chemotherapy.

UCI 18-19: (endometrial cohort): An Open-Label, Phase Ib Multicenter Study of IBI308 in Subjects with Advanced/ Metastatic Solid Malignancies.

The study's objective is to evaluate preliminary anti-tumor activity of IBI308 monotherapy in subjects with advanced and metastatic solid tumors with high tumor mutational burden and subjects with advanced or metastatic endometrial cancer.

Chemoradiation Trial

NRG GY006: A Randomized Phase 2 Trial of Radiation Therapy and Cisplatin Alone or in Combination with Intravenous Triapine in Women with Newly Diagnosed Bulky Stage IB2, Stage II, IIIB, or IVA Cancer of the Uterine Cervix or Stage II-IVA Vaginal Cancer.

This trial tests radiation therapy and cisplatin combined with a tumor-growth blocker compared to standard radiation therapy and cisplatin alone in newly diagnosed stage IB2, II, or IIIB-IVA cervical cancers or stage II-IVA vaginal cancer.

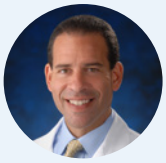
Intraoperative Imaging Trial

UCI 17-111: A Phase 3, Randomized, Single Dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection (OTL38) for Intra-operative Imaging of Folate Receptor Positive Ovarian Cancer.

This study tests the efficacy of imaging agent OTL38 combined with fluorescent light to detect folate receptor-positive cancer lesions not seen under normal light during primary surgical cytoreduction, interval debulking or recurrent ovarian cancer surgery.

For more information about these and our other gynecologic cancer trials, please call 877-UC-STUDY (877-827-8839) toll-free or email ucstudy@uci.edu

Meet our gynecologic oncology specialists



Robert E. Bristow, MD, MBA
rbristow@uci.edu

Fabio Cappuccini, MD
fcappucc@uci.edu

Kristine R. Penner, MD
kpennerk@uci.edu

Leslie M. Randall, MD
lrandall@uci.edu

Krishnansu S. Tewari, MD
ktewari@uci.edu

Jill H. Tseng, MD
jillt2@uci.edu

About us:

Chao Family Comprehensive Cancer Center

UC Irvine Chao Family Comprehensive Cancer Center is Orange County's only National Cancer Institute-designated comprehensive cancer center. It is a vital resource for the people of Orange County and surrounding areas, generating and disseminating new knowledge about the causes, prevention and treatment of cancer, as well as training the next generation of cancer providers and caregivers, and alleviating the overall cancer burden on our population.

Based on the campus of UC Irvine Medical Center in the heart of Orange County, the Chao Family Comprehensive Cancer Center integrates research, prevention and the most advanced diagnostics, treatment and rehabilitation programs to provide the best possible care for patients and their families. The cancer center also offers treatment, chemotherapy and infusion services, as well as access to clinical trials, at UCI Health Cancer Center – Newport.

Our cancer center researchers form disease-oriented teams that bring together patient-centered basic, translational and clinical investigators to facilitate the movement of discoveries through the pipeline into the clinical arena.

With a world-class, multidisciplinary team of surgeons, radiation oncologists, medical oncologists, pathologists, nurses, rehabilitation therapists, pharmacists, social workers and dietitians, the Chao Family Comprehensive Cancer Center is able to address cancers of all types and degrees of severity.

Contact us

For more information about cancer clinical trials at the Chao Family Comprehensive Cancer Center, call 877-827-8839 or email ucstudy@uci.edu