Gynecologic Cancers

In addition to breast cancer, women face the threat of gynecologic cancers, particularly malignancies of the ovaries and cervix. Researchers from Australia presented data on what they feel should become the new standard for patients with partially platinum-sensitive relapsed ovarian cancer. In an informational session, Dr Jack Cuzick discussed the need for widespread vaccination against the human papillomavirus to eliminate cervical cancer.

Researchers Propose Standard of Care for Patients with Partially Platinum-Sensitive Ovarian Cancer

Many clinicians continue to puzzle over the best way to treat patients with ovarian cancer who relapse 6 to 12 months after treatment with a platinum-based chemotherapy regimen. These women are typically categorized as “partially” platinum-sensitive. Some researchers in the United States were hopeful that trabectedin (Yondelis), which has demonstrated activity in this patient group, would help fill this gap in therapy options, but the FDA declined to approve the drug this month, requesting additional information.

Paul Vasey, MD, consultant medical oncologist and associate professor of medicine, University of Queensland, Australia, discussed results from the CALYPSO trial. This phase III international study is the largest ever to focus on platinum-sensitive patients whose ovarian cancer has relapsed more than 6 months after initial treatment.

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–Paul Vasey, MD

CALYPSO looked at the effectiveness and safety of carboplatin plus pegylated liposomal doxorubicin (PLD) compared with standard therapy consisting of carboplatin and paclitaxel (Taxol). Earlier results showed the regimen was active and well tolerated by platinum-sensitive patients. Today’s analyses considered the subset of patients with partial platinum sensitivity. “Not only was the combination of carboplatin and PLD shown to be no inferior to carboplatin-paclitaxel in these patients, it was also shown to be significantly superior,” Dr Vasey said.

Median progression-free survival (PFS) associated with the PLD regimen was 1.4 months longer than median PFS in the paclitaxel group (9.4 mo vs 8.8 mo, respectively; P = .004). The PLD regimen also had less toxicity, and women receiving the combination demonstrated significantly lower rates of peripheral neuropathy, hypersensitivity reactions, and alopecia compared with the paclitaxel-arm.

“The lower incidences of peripheral neuropathy and hypersensitivity reactions observed in the carboplatin and PLD study group are important because these side effects can be dose-limiting and often lead to treatment discontinuation,” according to Eric Pujade-Lauraine, MD, PhD, professor, Université de Paris Descartes in France. Dr Pujade-Lauraine heads Group d’Investigateurs Nationaux pour l’étude des Cancers Ovariens, which took part in the multinational study. He recommended the combination of PLD and carboplatin as the “preferred therapeutic option for patients with partially platinum-sensitive relapsed ovarian cancer.” For more information on the CALYPSO study, visit the Website at www.calypsosow.org.

Irinotecan Prodrug Performs Well in Early Stage Testing Against Resistant Ovarian Cancer

The results of two studies presented in Berlin provide optimism that a new technology can improve the pharmacokinetic properties of existing oncologic agents in patients with ovarian cancer. One of the new therapies is NKTR-102, a PEGylated produg of irinotecan being developed by Nektar Therapeutics.

The first study presented was preclinical, and tested NKTR-102 in a mouse model engineered with platinum-resistant ovarian cancer. Nektar scientists compared 3 differently weekly doses of NKTR-102 (50 mg/kg, 100 mg/kg, and 150 mg/kg) with irinotecan to determine their effect on tumor progression. All mice treated with NKTR-102 demonstrated complete or partial tumor regression; in comparison, none of the mice treated with irinotecan demonstrated complete response and only 1 demonstrated partial regression. The investigators concluded that response to NKTR-102 was dose-dependent, with 9 of 10 mice given the highest 150 mg/kg dose of NKTR-102 experiencing complete response.

The second study was a dose-escalation phase I trial that included 76 patients, 5 of whom had ovarian cancer. Of these 5, researchers said 2 were evaluable for response. One patient received 145 mg/m² of NKTR-102 every 3 weeks and the other, 73 mg/m² of NKTR-102 every 3 weeks. Both experienced partial responses of up to a 35% reduction in tumor volume. In the patient receiving the higher dose, CA-125 concentrations decreased by 80%. The investigators evaluated the pharmacokinetics of the active irinotecan metabolite, SN38, and found that exposure was considerably higher in patients receiving NKTR-102 compared with patients who received irinotecan.

Company scientists said Nektar’s polymer conjugate technology platform significantly improves the half-life of a chemotherapy agent such as irinotecan, which may help account for these promising results. A phase II study is underway in patients with platinum-resistant ovarian cancer who typically have poorer outcomes. Nektar plans to apply this technology to other small-molecule chemotherapy molecules.


Clinical Benefit Seen with Everolimus in Endometrial Carcinoma

A multicenter phase II study enrolled 22 patients (median age, 64 y) with treatment refractory endometrial carcinoma who were not candidates for surgical treatment or radiotherapy. An earlier study had shown antitumor activity with everolimus (Afinitor) in patients with recurrent endometrial carcinoma, and investigators decided to investigate the drug for safety and efficacy.

Everolimus is an mTOR inhibitor, and patients in this single-arm trial received 10 mg of everolimus per day until evidence of tumor progression or intolerance. Patients were evaluated at 3 months for progression and toxicity. Endometrial carcinoma of various histological subtypes were represented in the study, with the majority of patients (64%) having endometrioid disease. Common sites of metastases included lymph nodes, lung, bone, pelvic, and peritoneal. Prior to treatment with everolimus, 68% of patients had undergone 1 course of chemotherapy, and 32% received 2 courses.

The median duration of treatment with everolimus was 72 days (range, 4–119). The most commonly reported toxicity of any grade was fatigue, experienced by 88% of participants. A total of 60% of patients experienced hematological toxicities (all grades), and 50% reported diarrhea, with another 50% reporting nausea or vomiting. Other adverse effects, reported by less than 50% of patients, included dyspnea, rash, and anorexia.

Common grade 3–4 toxicities included fatigue (36%), anorexia (13%), and anemia (11%). Grade 3–4 dyspnea, nausea, diarrhea, pneumonitis, and infection were each reported in 4% of patients. While there were no drug-related deaths, 6 patients required dose reduction and 23% had treatment interruption due to adverse events. At 3 months’ follow-up, 8 patients had stabilized disease and 1 had partial response. Patients with poorly differentiated carcinoma were more likely to have progressive disease than patients in other subgroups.

The investigators concluded that everolimus demonstrated clinical benefit in these women with pretreated recurrent endometrial carcinoma refractory to chemotherapy. They plan to enroll another 2 patients, excluding those with poorly or nondifferentiated tumors.

Can HPV Vaccination Eradicate Cervical Cancer?

Widespread adoption of vaccination programs has nearly eliminated life-threatening diseases like smallpox and polio from many parts of the world. Jack Cuzick, MD, believes the same could be done with cervical cancer. Dr Cuzick is the John Snow Professor of Epidemiology and department head at the Cancer Research UK Centre for Epidemiology, Mathematics, and Statistics, Wolfson Institute of Preventive Medicine, and a well-known figure in oncology.

Dr Cuzick told an attentive audience that he believes new human papillomavirus (HPV) vaccines on the horizon, which are effective against 9 strains of HPV, coupled with a shift to molecular HPV screening, could allow countries to eradicate cervical cancer within their borders. According to Dr Cuzick, HPV is responsible for more than 99% of cervical cancer cases. Currently approved vaccines Gardasil and Cervarix only immunize against HPV types 16 and 18, the strains responsible for approximately three-quarters of cases.

During the press conference, Dr Cuzick pointed out some obvious concerns with vaccination, the foremost being that it only works in younger women who have never been exposed to the virus through sexual activity. In sexually active unvaccinated women, he said it is “important to determine whether or not the virus is actually there” through screening. Another concern is the durability of the vaccine. Dr Cuzick said the speculation is that HPV vaccination provides lifelong protection, but it will take years of follow-up to establish this definitively. He suggested that to achieve herd immunity will likely require vaccinating boys as well as girls, and boys are only now becoming part of the HPV vaccination picture. Gardasil was approved for males only recently in the United States, and the Centers for Disease Control declined to recommend vaccination of boys against HPV.

While vaccination is a feasible approach for the next generation, Dr Cuzick said, “We mustn’t forget the current generation of women.” Many have already been exposed to HPV, which is why he advocates the use of more effective cervical cancer screening methods, like molecular HPV testing. Major European studies involving more than 30,000 women show HPV testing picks up 90% of precursor lesions, whereas cytology, “a technology that is over 50 years old,” he said, “only picks up half of them.”

Adopting HPV screening, an objective computerized test, is an important component of any campaign to eradicate cervical cancer. Dr Cuzick said only persistent HPV infection causes cancer and most cases of HPV will not progress to cancer if treated promptly. Although HPV testing is more expensive than cytology, he believes its higher accuracy rate and the need for less frequent screening will offset the increased costs of the test. “When you’re negative for the HPV test, the duration of protection is much longer than when you’re negative for a smear,” he explained. Dr Cuzick said women aged 25 to 30 years would likely only have to undergo HPV testing every 5 years; HPV-negative women older than 50 years could get re-tested every 8 years. He also said studies show “self-sampling works quite well for HPV testing,” which would obviate the need to visit a physician for screening.

Dr Cuzick encouraged European governments to take responsibility for educating the public on HPV vaccination because “people are, not surprisingly, a little skeptical of pharmaceutical-based education programs.” Clearly, he was speaking largely to the European audience because he did not address obstacles the United States has faced in implementing HPV vaccination programs. Groups continue to protest state or federal attempts to mandate HPV vaccination in minor females. Some people feel vaccinating girls against a sexually transmitted disease will encourage them to have premarital sex; others say they have concerns about the safety of the vaccines. These obstacles to adopting universally mandated vaccination for younger girls could seriously hinder attempts to eradicate cervical cancer in the United States.

Patients’ Histological Characteristics

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Ovarian Cancer Initiatives
http://tinyurl.com/yelwxhb

The CDC strives to expand our knowledge of ovarian cancer by initiating and conducting research projects with various private and national organizations. The primary efforts are aimed at identifying factors that help advance early detection of the disease, as well as improving treatment and addressing survivors’ needs. The site also explains risk factors for the development of ovarian cancer and presents information on incidence and death rates according to race, age, and ethnicity. Visitors to the site can read about the CDC’s ongoing studies and projects related to ovarian cancer.

Cervical Cancer Prevention (PDQ)
http://tinyurl.com/y9e596k

This National Cancer Institute information summary serves as a resource to help clinicians and health professionals provide comprehensive, peer-reviewed, evidence-based information about cervical cancer prevention to their patients. Regularly reviewed and updated, the PDQ also includes information on several cervical cancer topics, including incidence and mortality statistics, cervical cancer risk factors, and interventions for cervical cancer prevention. Other topics review dietary factors, reproductive behavior, human papillomavirus infection, and vaccines to prevent it.

Society of Gynecologic Oncologists
www.sgo.org

The Society of Gynecologic Oncologists (SGO) contains information for physicians who treat women with cancers of the reproductive system with a goal of promoting high quality comprehensive clinical care. Members have special options available to them, such as CME offerings, but even nonmembers will find the Website useful, with Webcasts from the 40th Annual Meeting on Women’s Cancer. The site has information available on clinical practice, including news on emerging therapeutic options and diagnostic techniques. It also provides coding information. The Website includes a bookstore with handbooks on chemotherapy options, staging, and surgery.

The Oncofertility Consortium
http://tiny.cc/ikdeK

This site has sections for physicians and patients. The physicians section is designed to aid in dealing with the difficult but important issue of preserving reproductive options for patients with cancer. This includes cancers that affect the reproductive organs like uterine and ovarian cancer. The Consortium “seeks out ways to encourage collaboration between oncologists and reproductive endocrinologists” and help them communicate with patients about fertility-preservation options. It includes video from a conference on the issue, a blog, and research initiatives. Login is required to access secure resources from the National Physicians Cooperative, affiliated with the site.

The Clearyt Foundation
www.clearyfoundation.org

Founded by Laura K. Shawver, a biotechnology entrepreneur treated for ovarian cancer, the Clearyt Foundation works with CLIA-certified diagnostic laboratories and helps pay for tests of formalin-fixed paraffin-embedded tumor samples for patients with ovarian cancer who cannot afford them. Physicians can visit the site and develop a patient profile to see whether their patients are eligible. The samples are sent to the appropriate facility for a battery of tests, with a basic panel taking approximately 4 days to complete. Physicians are mailed to the physician, typically in 4 weeks or less. The site also lists ongoing trials for patients with ovarian cancer based on the patients’ tumor biology.