Ovarian Cancer Treatments on the Horizon

By Charlie Schmidt

ew treatments in ovarian cancer have been slow in coming. For nearly two decades, frontline therapies for newly diagnosed patients haven’t budged beyond paclitaxel and platinum-based drugs. And neither these nor additional options for second-line treatment, namely, gemcitabine and several other chemotherapies, have produced substantial advances in overall survival (OS). Median life expectancy for ovarian cancer patients remains stuck at barely 5 years, and roughly 80% of those diagnosed with the illness will eventually succumb to it.

Turning a Corner on Treatment

Against this intractable backdrop, participants at the 2011 American Society of Clinical Oncology’s (ASCO) annual meeting in Chicago enthusiastically received positive results for two new drug alternatives for treating ovarian cancer.

Two phase III clinical trials showcased one of these drugs, bevacizumab (Avastin), an angiogenesis inhibitor manufactured by Genentech in San Francisco. Both trials showed improvements in progression-free survival (PFS) but not in OS. This finding was good news for bevacizumab—the world’s best-selling cancer drug—which might soon lose its U.S. Food and Drug Administration approval for treating breast cancer. Mature data from the National Cancer Institute–sponsored ICON-7 trial showed that newly diagnosed women who received bevacizumab, paclitaxel, and carboplatin had a 15% relative improvement in PFS at 12 months, translating to an additional 1.5 months without disease progression. Likewise, the Genentech-sponsored OCEANS trial showed that second-line treatment with bevacizumab produced a median PFS of 12.4 months among relapsed platinum-sensitive patients (patients who relapsed more than 6 months after the final platinum treatment), compared with 8.4 months among control subjects, who received placebo. Patients in the treatment arm of this trial received bevacizumab combined with carboplatin and gemcitabine, followed by bevacizumab only (instead of placebo) as maintenance therapy.

The other new treatment, olaparib, which inhibits a DNA-repair enzyme known as poly (ADP–ribose) polymerase (PARP), also generated positive results in platinum-sensitive relapsed patients. In a phase II trial that the drug’s manufacturer, AstraZeneca, sponsored, olaparib given as maintenance treatment after second-line chemotherapy produced a median PFS of 8.4 months, compared with 4.8 months in placebo-treated control subjects, regardless of BRCA1 or BRCA2 status. According to principal investigator Jonathan Ledermann, M.D., at the UCL Cancer Institute, in London, that’s important because it means that a larger-than-expected group of cancer patients might benefit from PARP inhibitors. “And 50% of women in the treated group are still alive and taking olaparib, compared to 16% of the control patients,” Ledermann said.

Ledermann calls bevacizumab and olaparib the biggest developments to appear in ovarian cancer in years. These findings encourage Ledermann and other experts, not only because of the survival results but also because, in a first for ovarian cancer, targeted rather than chemotherapeutic drugs delivered the results. Bevacizumab inhibits vascular endothelial growth factor (VEGF), a protein that coordinates blood vessel formation, called angiogenesis. VEGF is also highly expressed in epithelial ovarian cancers, which account for roughly 80% of diagnosed cases.

Targeting Therapy

An important question now is how to determine precisely which patients might benefit most from bevacizumab, to avoid giving it to nonresponders who could suffer its side effects and who would still have to pay its exorbitant cost. Robert Burger, M.D., a professor of surgical oncology at the Fox Chase Cancer Center, in Philadelphia, said that patients with highly angiogenic tumors will logically make the best candidates. But how can one identify such tumors? Both healthy and cancerous tissues need blood vessels for survival. Steve Potts, CEO of Flagship Biosciences, in Flagstaff, Ariz., said the extent of a tumor’s angiogenic nature is associated with its microvessel density, defined as the number of blood vessels per unit of tissue in a histology slide. Flagship Biosciences develops automated tools for quantifying microvessel density, a parameter that, Potts said, could be used to select women for bevacizumab treatment and to monitor its effects.

Yet another option is to select patients on the basis of genetic information. Scientists have long known that ovarian cancer isn’t just one but rather several distinct illnesses, each with its own clinical profile and response to treatment. Clear cell ovarian tumors, for instance, don’t respond well to therapy, and neither do mucinous tumors that can spread to the ovaries from cancers elsewhere in the body. High-grade serous tumors, however—the most commonly diagnosed ovarian cancers—do respond to frontline treatment. Each tumor type has a different form, along with genetic and molecular differences.

The Cancer Genome Atlas at the NCI, along with a team headed by Richard Torrill, Ph.D., from the Peter MacCallum Cancer Centre, in Melbourne, Australia, are using molecular analyses to identify specific ovarian cancer genetic subtypes. And at ASCO last June, Charles Gourley, M.D., Ph.D., a leader in medical oncology at the UK’s University of Edinburgh Cancer Research Center, announced that he had detected three high-grade serous ovarian cancer subtypes. One expressed what he calls a “proangiogenic signal” dominated by genes involved in cell attachment and blood vessel formation. These results are pending publication. Gourley speculates that patients who express this proangiogenic signal could make optimal candidates for bevacizumab treatment. “These patients might derive larger...
The positive results reported at ASCO last June differ from negative findings reported earlier at the European Society for Medical Oncology’s 2010 annual meeting. That phase II study, from researchers at the Royal Marsden Hospital, in Sutton, UK, compared olaparib to pegylated liposomal doxorubicin (Doxil)—but only in patients with germline BRCA mutations, among whom it was thought the drug would work best. Response rates were not statistically improved in patients who took olaparib compared to patients receiving standard treatment. Results for the phase II study described at ASCO this year, which did generate statistically significant improvements in PFS, came from patients selected regardless of germline BRCA status. The data cutoff was too immature for OS analysis, the investigators claimed.

According to Ledermann, these results probably were positive when the earlier results were not because the germline BRCA selection criterion in the European study was too limiting. Epigenetic changes occurring during a patient’s life can impair BRCA function, and like germline mutations, they can also disable homologous recombination, leaving cancer cells vulnerable to the drug. Germline BRCA mutations were present in just 15% of Ledermann’s cohort, but they were among a larger 50% of the cohort that was deficient in homologous recombination for one reason or another. Thus, Ledermann’s phase II study contained a much larger percentage of potential responders, which may account for the differences observed with control subjects, who didn’t get olaparib. “This really is one of the most dramatic results we’ve seen yet in ovarian cancer,” Ledermann said. “It opens up an exciting way forward in treatment.”

OS, PFS, and FDA Approval
Still, neither olaparib nor bevacizumab produced observable differences in OS. At least for bevacizumab, that finding might not reflect the drug’s efficacy so much as that ovarian cancer patients are treated with so many drugs that ascribing OS improvements to any one of them is hard, said Carol Aghajanian, M.D., chief of gynecological medical oncology at the Memorial Sloan-Kettering Cancer Center, in New York, who presented OCEANS’ results at ASCO in June. “This becomes a real problem when we’re dealing with diseases like ovarian cancer that have a long time course,” she said. “We’re all grappling with this: how to measure OS benefits from specific drugs as cancers become more chronic.”

Meanwhile, recent problems with bevacizumab’s breast cancer approval could bode poorly for its indication in ovarian cancer, some experts said. “I hope it’s evaluated on its own merits and not in the context of an ongoing controversy,” Aghajanian said. “Ovarian cancer is a different disease with a different biology, and we know for certain that some medications work with some diseases and not with others. [Paclitaxel (Taxol)], for instance, does well in ovarian cancer, but it doesn’t work at all in colon cancer.”

OS issues could be critical when Genentech seeks FDA approval for bevacizumab in ovarian cancer later this year. Three trials currently show PFS benefits in the disease: OCEANS, ICON-7, and GOG-218, the last sponsored by the Gynecological Oncology Group in NCI’s Clinical Trials Cooperative Group Program. According to FDA spokesperson Erica Jefferson, OS is a “gold standard” that represents clear and direct benefits to patients because they live longer. “PFS of high magnitude may be acceptable in certain disease settings,” she wrote in an e-mail. “However, the magnitude of PFS that would be acceptable would be a review issue. Therefore, when [we consider] PFS as an endpoint for drug approval, the magnitude of PFS improvement must be substantial and it must outweigh the risk associated with the treatment.”