ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Drugs in Ovarian Cancer

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H&O How has the prognosis for ovarian cancer changed in recent years?

GF Over the last decade, ovarian cancer prognosis has improved very modestly. According to the Surveillance, Epidemiology, and End Results program, the 5-year relative survival for ovarian cancer in the United States has only improved from 33.6% in 1975 to 45.2% in 2006, and the rate has not changed since. These advances are most likely from surgery and platinum-based therapy. Other than 2 very recent US Food and Drug Administration (FDA) approvals—for olaparib (Lynparza, AstraZeneca) and bevacizumab (Avastin, Genentech)—there have not been any new therapies approved for ovarian cancer in almost 10 years. Furthermore, neither olaparib nor bevacizumab is FDA-approved for frontline use.

H&O Could you describe these 2 drugs that were recently approved?

GF Bevacizumab was just approved in November 2014 for the treatment of women with platinum-resistant ovarian cancer, though it had been approved in the United States for other cancers and was previously approved for ovarian cancer in the European Union. Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A), thereby blocking angiogenesis and slowing tumor growth. Approval was based on AURELIA (A Study of Avastin [Bevacizumab] Added to Chemotherapy in Patients With Platinum-Resistant Ovarian Cancer), published in the *Journal of Clinical Oncology* in 2014. Patients were randomly assigned to chemotherapy with or without bevacizumab. The researchers found improvement in progression-free survival with bevacizumab vs chemotherapy alone (6.7 vs 3.4 months). The overall response rate was also significantly better (27.3% vs 11.8%, respectively); however, there was no significant change in overall survival (16.6 months vs 13.3 months, respectively). It is common in ovarian cancer for antiangiogenics to improve response rates and progression-free survival but not overall survival, and this has been the case for bevacizumab in frontline therapy and in platinum-sensitive recurrence. However, there was a trend towards improved survival in the platinum-resistant group, and the benefits were important enough that the FDA approved this agent.

The second recently approved drug is olaparib, which is indicated as monotherapy for women who have germline *BRCA* mutations and have been treated with 3 or more lines of previous chemotherapy. Olaparib is an inhibitor of the enzyme poly(adenosine diphosphate-ribose) polymerase (PARP). Approval in December 2014 was based on a trial by Kaufman and colleagues that included patients with ovarian cancer and germline *BRCA* mutations. The final publication included 193 patients with a median of 4 prior regimens; all were considered platinum resistant or not suitable for further platinum therapy. Using single-agent olaparib, the response rate was 31% with a 225-day median duration of response. Generally, toxicities were mild to moderate and included fatigue, nausea and vomiting, and anemia. One concern about olaparib is the potentially increased rate of myelodysplastic syndrome and acute myeloid leukemia (2% in this trial).

H&O Are there any more angiogenesis inhibitors in current or recent clinical trials?

GF Trebananib (AMG 386) is a peptide-Fc fusion protein that binds angiopoietin 1 and 2 to prevent their interaction with the Tie2 receptor, interfering with angiogenesis at a different point than the VEGF pathway inhibitors. This drug has some single-agent activity in the treatment of ovarian cancer. In a phase 3 trial called TRINOVA-1 (A Study of AMG 386 or Placebo, in Combination With Weekly Paclitaxel Chemotherapy, as Treatment for Ovarian Cancer, Primary Peritoneal Cancer and Fallopian Tube Cancer), women with relapsed ovarian cancer were randomly assigned to weekly paclitaxel with or without trebananib. Progression-free survival improved (7.2 vs 5.4 months, respectively) but an interim overall survival analysis showed no significant difference between the arms.

In addition, many VEGF receptor (VEGFR) tyrosine kinase inhibitors have been tested in ovarian cancer, and most seem to have some activity. However, when used in the frontline or maintenance setting these drugs generally appear to have the same problem as bevacizumab—they improve progression-free survival but not overall survival. For example, a study published in the *Journal of Clinical Oncology* in 2014 with the multikinase inhibitor pazopanib (Votrient, GlaxoSmithKline) found a 5.6-month improvement in progression-free survival when pazopanib was used as maintenance therapy in women who had a complete remission after frontline treatment. However, there was no improvement in overall survival.

There has been some recent interest in the combination of cediranib, an experimental VEGFR tyrosine kinase inhibitor, plus olaparib. A randomized phase 2 study published by Liu and colleagues found that in women with platinum-sensitive disease, this combination improved progression-free survival from 9.0 months to 17.7 months. Interestingly, improvement with the addition of cediranib was the most dramatic in women with wild-type or unknown *BRCA* mutation status (from 5.7 to 16.5 months). Overall survival data were not mature at the time of publication, but the 2-year overall survival rate was 65% in the olaparib alone group vs 81% in the olaparib plus cediranib group. The NRG oncology research group is expected to further explore this combination in an upcoming trial.

H&O Has there been any progress on immune therapies for ovarian cancer?

GF For ovarian cancer, immunotherapies—including vaccines, checkpoint inhibitors, or adoptive approaches—remain in early-stage testing. Although it is clear that the immune system is very important in ovarian cancer, we do not yet have advanced-stage trials of immune therapies.

Checkpoint inhibitors such as programmed death ligand 1 (PD-L1) inhibitors are currently stimulating lots of excitement. However, the initial trial reported in the *New England Journal of Medicine* in 2012 found that only 1 out of 17 ovarian cancer patients responded to a PD-L1 inhibitor. Similarly, a small study by Hamanishi and colleagues presented at the 2014 American Society of Clinical Oncology (ASCO) meeting reported that only 3 out of 13 patients responded to a programmed cell death 1 (PD-1) inhibitor. There are many ongoing trials of immunotherapy, including vaccines and adoptive T-cell therapy approaches. The Gynecologic Oncology Group recently completed a randomized trial (NCT01666444) of liposomal doxorubicin (Doxil, Janssen) with or without VTX 2337, a toll-like receptor agonist that may stimulate a variety of immune pathways. However, none of these therapies have reached advanced phase or appear likely to be approved for ovarian cancer in the immediate future.

H&O Have there been any studies on identifying subgroups of ovarian cancer patients?

GF Yes; one of the most promising developments is not a new drug, but the targeted use of the older drugs. Two studies were presented at the ASCO meeting last year that I think will become very valuable. In a study by Winterhoff and colleagues called ICON7 (A Randomised, Two-Arm, Multi-Centre Gynaecologic Cancer Intergroup Trial of Adding Bevacizumab to Standard Chemotherapy [Carboplatin and Paclitaxel] in Patients With Epithelial Ovarian Cancer), patients in a frontline setting with ovarian cancer were randomly assigned to carboplatin and paclitaxel with or without bevacizumab. Similarly to the trials I mentioned previously, bevacizumab treatment improved progression-free survival but not overall survival. Using a subset of these ovarian cancer patients, the researchers performed genomic assays and classified patients into the 4 groups that were defined by the Cancer Genome Atlas Project (TCGA): differentiated, immunoreactive, mesenchymal, and proliferative. They found that patients with serous carcinoma of the mesenchymal subtype obtained the most benefit from bevacizumab, with a progression-free survival improvement of 9.5 months. The differentiated, immunoreactive, and proliferative subgroups had smaller improvements in progression-free survival (5.8, 3.4, and 3.2 months, respectively).

In another study, Gourley and colleagues used their own molecular classification system. They divided patients into 3 subgroups—2 groups with angiogenic gene upregulation, and 1 group with angiogenic gene repression and immune gene upregulation. Although the

immune upregulation subgroup had superior survival overall, the addition of bevacizumab actually worsened progression-free survival and overall survival in that group. In the angiogenic upregulation groups, there was a nonsignificant improvement. Refining these molecular classifications should allow us to appropriately select patients who will truly benefit from bevacizumab and other antiangiogenic agents.

There is also an increased recognition that some of the less-common types of ovarian cancer do not respond well to standard cytotoxic therapy. Clear-cell ovarian cancers, low-grade ovarian cancers, and mucinous ovarian cancers are biologically different from the more common high-grade serous ovarian cancers. Although we do not yet have approved therapies that target these subtypes specifically, this is currently being studied. For example, MEK inhibitors are being tested for low-grade disease and have shown some benefit, and a trial of selumetinib in women with recurrent low-grade serous tumors showed a 15% response rate. Interestingly, retrospective reviews have also suggested that bevacizumab has activity in low-grade serous tumors. More than half of patients with clear-cell ovarian cancer have *ARID1A* mutations, making it a promising target; however, we currently do not have drugs to target this mutation.

H&O Is there any new research on drugs that are targeted to a specific mutation?

GF While there are a lot of mutations in high-grade serous ovarian cancers, there are not many recurrent mutations that are seen in large subsets of patients. Germline *BRCA* mutations are, of course, part of the current indication for olaparib. However, it is possible for ovarian cancers to have *BRCA* mutations or other defects in the homologous DNA repair pathway even in the absence of a germline mutations (called homologous recombination deficiency or HRD). These may predict sensitivity to PARP inhibitors, and can explain why some ovarian cancer patients who are not *BRCA* mutation carriers still respond to PARP inhibitors, unlike patients with other tumor types. Current trials are exploring which tumor alterations predict for response to PARP inhibitors in ovarian cancer patients who are not mutation carriers.

H&O What trends do you predict for the future of ovarian cancer drugs?

GF I think that we will have more targeted therapies for subgroups of patients, such as tumors with *BRCA* mutations, clear-cell or low-grade ovarian cancers, or genomic subsets such as those defined by the TCGA. One promising therapeutic area is the use of antibody-drug conjugates, for example cytotoxic compounds conjugated to anti-mesothelin antibodies or the anti-NaPi2b antibody. In addition, immunotherapy, although it has not yet been a home run in ovarian cancer, is still very promising.

Suggested Reading

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