

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## New Drugs for Ovarian Cancer

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### **H&O** What insights into the pathobiology of epithelial ovarian cancers have led to new treatment approaches?

**SK** One of the key insights is the understanding that the vascular endothelial growth factor (VEGF) family of growth factors is a particularly relevant element of the pathophysiology of epithelial ovarian cancer. The normal ovary, in its development, expresses VEGF. Ovarian cancer, which is characterized by early invasion and spread across the peritoneal cavity and the development of ascites, is associated with high levels of expression of VEGF and related growth factors. High levels are linked to poor outcomes, and, in experimental models, inhibition of VEGF delays, slows, and stops disease progression and reduces ascites. Therefore, the new antiangiogenic, anti-VEGF drugs are likely, it is thought, to have as great an effect in ovarian cancer as in any other epithelial cancer (with the possible exception of renal cancer). Single-agent bevacizumab (Avastin, Genentech), which is an antibody against VEGF, is clearly active in this setting.

### **H&O** What are the clinical findings with bevacizumab in patients with ovarian cancer?

**SK** In patients with advanced disease, significant tumor shrinkage and control of ascites has been observed with the administration of bevacizumab. In two phase II trials, adding together rates of clinical response and meaningful stable disease, over 50% of patients have benefited from the use of this agent. Both trials included patients with relapsed ovarian cancer and used a regimen of 15 mg/kg of bevacizumab every 21 days. The study

by Burger and associates enrolled 62 patients and was restricted to patients who had received one or two prior chemotherapeutic regimens, but the patients could be platinum-sensitive or -resistant. The study by Cannistra and colleagues enrolled 44 patients who were platinum-resistant, as well as resistant to either liposomal doxorubicin (Doxil, Ortho Biotech) or topotecan; patients could have received no more than three prior chemotherapeutic regimens. Bevacizumab demonstrated objective response rates of 21% and 16%, respectively. Additionally, 32 (52%) and 27 (64%) of cases, respectively, achieved stable disease, with median progression-free survival of 4.4 and 4.5 months. The concern, however, was that the study by Cannistra and colleagues was stopped early due to bowel perforation, which is an established serious side effect of bevacizumab, usually in no more than 3–4% of patients. In this study, bowel perforations occurred in 11% of patients, and the trial was therefore ended early. Researchers are worried that bowel perforation resulting from treatment with bevacizumab is more likely to occur if the ovarian malignancy is very close to the bowel wall. Still, the explanation and mechanism of the bowel perforation is unclear at present. It is thought that patients with very advanced disease quite close to the bowel wall should not presently be treated with bevacizumab.

As a result of these single-agent trials, three large randomized trials are ongoing, two assessing bevacizumab in combination with chemotherapy, and one assessing bevacizumab as a continued maintenance treatment. The placebo-controlled Gynecology Oncology Group 218 trial intends to enroll 2,000 patients with stage III and IV disease and randomly assign them to one of three arms: paclitaxel and carboplatin, with or without bevacizumab (15 mg/kg every 21 days) for six courses, with a third arm continuing bevacizumab for an additional 48 weeks. The Gynecological Cancer Intergroup ICON 7 trial mandates

that patients should not be candidates for further interval debulking or delayed primary surgery. It is not placebo-controlled, uses a lower dose of bevacizumab (7.5 mg/kg every 21 days), and is a two-arm trial. This trial plans to enroll 1,520 patients and randomly assign them to receive either conventional paclitaxel plus carboplatin (six cycles) alone or with bevacizumab every 3 weeks during chemotherapy and continuing for an additional 36 weeks. The third trial is for platinum-sensitive relapsed ovarian cancer patients (GOG 213). It is a two-arm trial, with paclitaxel-carboplatin together with concurrent and maintenance bevacizumab compared to PC alone, in 1,600 patients. If these trials are positive, as trials of bevacizumab in breast and gastrointestinal cancers have been, the findings could lead to regulatory approval of this agent for the treatment of patients with advanced ovarian cancer. It is important to note that in breast, colon, and lung cancer, single-agent bevacizumab did not demonstrate activity, as it has in ovarian cancer.

### **H&O** What other agents targeting VEGF are under investigation in this setting?

**SK** There are several small-molecule tyrosine kinase inhibitors of VEGF that vary according to their selectivity for the VEGF family, as some inhibit other tyrosine kinase growth factors as well. There is one phase II study of pazopanib (GlaxoSmithKline) that showed activity in the setting of ovarian cancer. Large-scale randomized trials of tyrosine kinase inhibitors in relapsed disease are planned to answer the question of whether small-molecule inhibitors of VEGF can change the treatment paradigm. The next step could be a combination of a monoclonal antibody and a small-molecule tyrosine kinase inhibitor. In ovarian cancer, bevacizumab has been combined with sorafenib (Nexavar, Bayer/Onyx). This combination showed impressive levels of efficacy but also high rates of toxicity. VEGF-Trap, which binds to the VEGF receptor, is another active and well-tolerated agent, but there is no evidence thus far that it is more effective than bevacizumab. It is unknown whether the risk of bowel perforation is lower with this agent. VEGF-Trap will be evaluated in the future, I believe, in combination with other agents. There is still a good deal of room for increasing our knowledge about these approaches to treating ovarian cancer. Over the next few years, thousands of women will be enrolled on randomized clinical trials of drugs, either monoclonal antibodies or small molecules, that target the VEGF pathway.

### **H&O** What other targets are under investigation?

**SK** The main challenge ovarian cancer poses to clinicians is drug resistance. Although good results are often

achieved initially with paclitaxel and carboplatin, most patients eventually develop resistance to these drugs, followed by death 2–3 or more years after relapse. The focus of research is understanding the mechanism of resistance, which may well be multifactorial. One important factor could be overexpression of the key signaling pathway Pi3k/Akt. This overexpression may lead to the rational use of a novel agent to be added to chemotherapeutic regimens to inhibit Pi3k/Akt. This pathway is associated with increased cell survival by decreasing apoptosis. Increased expression of Pi3k/Akt or mutations or amplification of oncogenes in that pathway can be a mechanism of drug resistance. Additionally, mammalian target of rapamycin (mTOR), which is downstream of Pi3k/Akt, may be active in ovarian cancer. Overall, it is estimated that 40% of patients have overactivity in this pathway, possibly linked to drug resistance. There are drugs that have been shown experimentally to enhance the activity of carboplatin and paclitaxel significantly—such as a Pi3k inhibitor under development by Genentech, an Akt inhibitor under development by GlaxoSmithKline, and the mTOR inhibitor temsirolimus (Torisel, Wyeth)—beginning to be investigated clinically, initially as monotherapy. Another agent, which targets heat shock protein (HSP) 90, is important because this protein is required for several of these pathways to function properly in the cell. If this chaperone protein is inhibited, it is hypothetically possible to inhibit a number of signals simultaneously; it has been shown that paclitaxel can be enhanced with an agent that inhibits HSP-90. In coming years, combinations of these agents with standard chemotherapy will be investigated. Ovarian cancer is thought to be one of the best settings for the evaluation of agents that interfere with the Pi3k/Akt pathway, including HSP-90, because we already understand this pathway to be the mechanism of resistance to paclitaxel and carboplatin in the disease—and because the pathway is overexpressed in a significant percentage of patients with ovarian cancer.

### **H&O** Could you discuss the role of cell damage repair in drug resistance?

**SK** One mechanism of resistance occurs when a drug like carboplatin enters the cell and binds, as expected, to DNA, but the cancer cell then learns to repair the damage before the cell can be killed. The cell is thus resistant. In order for the cell to become sensitive to chemotherapy again, it is necessary to interfere with this repair process. Inhibitors of the repair process are under development. For example, poly (ADP-ribose) polymerase (PARP) inhibitors interfere with base-excision repair, which is one of the ways cells become resistant. On the other hand, cancer cells may become resistant to DNA-damaging drugs because they fail to recognize the damage, and this

apoptosis, or cell death, is not triggered. This failure may come about through the silencing by methylation of key damage recognition genes (eg, *hMLH1*). This process may be reversed by demethylating agents that assist the cell in recognizing the damage caused by carboplatin, causing genes otherwise silenced by methylation to reawaken, so to speak, and, in turn, signal cell death. This mechanism is under investigation in a randomized phase II study of carboplatin and decitabine (Dacogen, MGI Pharma). Increasingly, researchers are using blood and tissue samples taken from patients during trials to investigate the mechanisms linked to resistance, and the finding of free DNA in the blood led to the hypothesis behind demethylating agents.

Additionally, gemcitabine (Gemzar, Lilly) can be relevant in this setting. Gemcitabine has been combined with carboplatin in attempts to overcome drug resistance. This agent is a cytotoxic and, in a way, an antifolate that depletes cells of nucleotides. One argument for combining gemcitabine with carboplatin is that when the nucleotides are depleted from the cell, it becomes more sensitive to carboplatin. This combination, which has empirical roots unlike the combination of carboplatin and decitabine, is now used commonly in ovarian cancer.

### **H&O** What does the future hold for the treatment of ovarian cancer?

**SK** The key question to ask is whether a novel agent can be effective as monotherapy or only in combination with a cytotoxic. Targeting VEGF should be considered the most promising approach, and it is possible that in coming years targeting VEGF will be shown to be a useful maintenance approach. Second, using agents that inhibit Pi3k/Akt or mTOR in combination with chemotherapy is a quite interesting approach, but research is not developed to the degree that these agents can yet be readily used clinically. Third, I believe PARP inhibitors will offer an exciting approach.

Our recent data on the uses of an oral PARP inhibitor administered as monotherapy in the setting of ovarian cancer is particularly interesting. Some ovarian cancers are inherited and, as such, are related to mutations of the *BRCA1* or *BRCA2* genes. These mutations cause the

gene to be dysfunctional. The normal function of *BRCA* is to repair DNA damage. When mutations are present, the cell cannot repair damage caused by homologous recombination, which is one of several different repair pathways. *BRCA* mutations alone are not enough to cause cell death, but if the cell is exposed to a drug that affects another repair process, it becomes exquisitely sensitive and the cell dies. This potential for exquisite sensitivity is unique to cells with mutations of *BRCA1* or *BRCA2*. A PARP inhibitor can be the additional drug needed to effect the sensitivity, as demonstrated experimentally in the laboratory. A clinical trial in over 40 patients treated with a PARP inhibitor has shown activity in this setting, as reported at the American Society of Clinical Oncology annual meeting in 2007 by Dr. Tim Yap. It is possible that the efficacy of PARP inhibition may not be confined only to women with *BRCA1* or *BRCA2* mutations but may also be seen in women with serous ovarian cancer in which *BRCA* function may be lost through other mechanisms, adding up to approximately one third of women with this form of the disease. Further research is needed to confirm this hypothesis. One reason this treatment approach is exciting is that it is based on a molecular signature, for which patients can be tested up-front. Selecting patients who may benefit from novel agents is increasingly appealing, and the major drawback of agents that target VEGF is that no test is available to identify patients with ovarian cancer for whom these agents offer benefit.

### **Suggested Readings**

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