Advancements in Ovarian Cancer Therapies

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The past decade has brought together substantial advances in analyses of cancer genomes enabling us to better understand the biology of tumors. Understanding the molecular biology of tumors mechanistic pathways in the context of contemporary drug development means that we can now predict sensitivity to treatments, and tailor target personalized therapies to patients.

Ovarian cancer, the second most prevalent gynecological cancer globally, affects nearly 225,000 women annually. Of all ovarian cancers, epithelial ovarian cancer (EOC) accounts for approximately 95% of ovarian cancer incidence, and is a leading cause of gynecologic cancer mortality worldwide.

Multi-modality therapy is the established standard of care worldwide. Regrettably, the majority of women (75%) are diagnosed at an advanced stage, and despite advancements in cytoreductive surgery and initial chemotherapy response, recurrence is common. While the 5-year survival rate for advanced ovarian cancer has seen some improvement (reaching 40-50%), most patients ultimately succumb to the disease.

Key advancements in the last five years, notably the introduction of targeted therapies in particular, and immunotherapy by using anti-angiogenic treatments and molecular inhibitors, is the focus of this mini review.

1. Anti-angiogenic therapies

A pro-angiogenic environment, characterized by increased levels of factors that promote blood vessel formation (vasculogenesis), is crucial in cancer development. While the vascular endothelial growth factor (VEGF) family is the most well-studied of these factors, others like fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and angiopoietins also play significant roles. Within the normal ovary, the VEGF family is essential for follicle development and ovulation. However, in ovarian cancers, overexpression of these pro-angiogenic cytokines and their receptors is observed and linked to tumor progression and a less favorable prognosis.

Bevacizumab (Avastin, Genentech/Roche), a monoclonal antibody against VEGF-A, is the most studied antiangiogenic agent in epithelial ovarian cancer (EOC) so far. Bevacizumab works by blocking the VEGF protein, which some cancer cells produce in large amounts. Blocking VEGF may prevent the growth of new blood vessels that tumors need to grow.

Four pivotal phase III studies have reported an improvement in progression-free survival (PFS) with the addition of bevacizumab to chemotherapy in both first-line and relapsed (platinum-sensitive and platinum-resistant) advanced ovarian cancer settings.

A significant challenge with bevacizumab treatment however, is the development of resistance. Clinically, it's observed that tumors adapt to angiogenesis inhibitors, finding ways to circumvent the therapeutic blockade. Research suggests this evasion primarily occurs through the activation and/or upregulation of alternative pro-angiogenic pathways, such as those involving PDGF and FGF, within the tumor. Additionally, the recruitment of bone marrow-derived pro-angiogenic cells and pericytes, which modify the tumor microenvironment, can bypass the necessity for VEGF signaling. Researchers are actively exploring strategies to overcome these potential

resistance mechanisms. One promising approach involves using tyrosine kinase inhibitors that target both VEGFR and other pro-angiogenic receptors, such as FGF (e.g., nintedanib, brivanib, dovitinib) and PDGFR (e.g., cediranib, pazopanib).

2. Poly (ADP-ribose) polymerase (PARP) inhibitors

PARP inhibitors represent a class of targeted therapy frequently employed in the treatment of breast, ovarian, and other cancers. These drugs focus on poly (ADP-ribose) polymerase (PARP), a crucial protein within cells responsible for DNA repair. While DNA damage occurs regularly in cells, it doesn't typically hinder growth and division as long as repairs are successful. However, PARP inhibitors disrupt this repair process. Dr. Jennifer Litton, Vice President of Clinical Research, explains that these inhibitors interfere with a cell's ability to fix damaged DNA. This interference is particularly impactful in cancers with pre-existing DNA repair deficiencies, such as those harboring BRCA gene mutations. Cancer cells with these mutations become overly reliant on PARP for DNA repair. As Dr. Litton notes, "When a cancer cell already has impaired damage repair, such as in patients with a BRCA mutation, the cancer cell cannot fix itself." Consequently, PARP inhibitors prevent these cancer cells from repairing their damaged DNA, halting their division and ultimately leading to cell death.

Common examples of PARP inhibitors include **olaparib, talazoparib, rucaparib, and niraparib.** Furthermore, these inhibitors can be combined with other treatments like immunotherapy or chemotherapy. Chemotherapy's mechanism of action involves damaging cancer cell DNA, ultimately leading to cell death. Because PARP inhibitors further hinder the cancer cells' ability to repair this DNA damage, combining them with chemotherapy can enhance the chemotherapy's effectiveness. In fact, the combination of PARP inhibitors with both immunotherapy and chemotherapy has demonstrated a reduction in the risk of disease progression for patients with advanced or recurrent endometrial cancer.

A common challenge with PARP inhibitors is the eventual development of resistance, diminishing their long-term effectiveness. At the research level, scientists are analyzing patient samples to decipher the mechanisms of PARP inhibitor resistance in cancer cells and to identify predictive biomarkers. Furthermore, researchers are investigating combination therapies, pairing PARP inhibitors with other targeted agents to overcome resistance and enhance treatment outcomes. One such promising combination involves PRMT inhibitors. PRMT (protein arginine methyltransferase) is another DNA-interacting protein within cells. Preclinical (in vitro and in vivo) studies have shown promising results with this combined approach, which is currently undergoing further investigation.

Anti-angiogenesis and PARP inhibition are the most promising, with positive randomized trial data in both cases.