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Advances and Perspectives in the Treatment of High-Grade Serous Ovarian Cancer

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Ovarian cancer is the second most common gynecological malignancy but is, by far, the leading cause of death among gynecological cancers. Most ovarian cancer deaths (about 70%) happened in patients with advanced stage High-Grade Serous Ovarian Carcinomas (HGS-OC). Resistance to chemotherapy and metastasis are the main causes of treatment failure in HGS-OC. Combination treatment with platinum agents and paclitaxel is the standard therapeutic approach. The introduction of anti-angiogenic therapy and PARP-1 inhibitors induced synthetic lethality in HGS-OC with BRCA1/BRCA2 mutation is the most promising advance in the past 5 years [1,2].

With the development of new technologies, comprehensive genomic and epigenomic analyses of clinically annotated HGS-OC provides invaluable information to identify molecular mechanisms of pathbiology and to stratify patients for personalized treatment. An analysis of 489 high-grade serous ovarian adenocarcinomas from The Cancer Genome Atlas (TCGA) showed that these tumors typically have 50–70 somatic mutations [3]. Nearly all tumors (96%) have one or more TP53 mutations. Homologous Recombination (HR) repair defects including germline or somatic mutations (BRCA1/2, PTEN, ATM, ATR, CHK1/2, FANCA, FANCC, FANCD2, FANCF, FANCN/PALB2), amplification of C11orf30/EMSY or epigenetic silencing (Rad51C, BRCA1) has been identified in about 50% of the HGS-OC tumors. Mutations of BRCA1/2 genes greatly increase lifetime risk of breast and ovarian cancers. Fanconi Anemia (FA) is a rare genetic disorder marked by congenital defects, bone marrow failure, and cancer susceptibility. This condition is caused by genetic mutations in any one of the 15 cooperative proteins [4-6]. Tumors with FA pathway and other HR repair defects are highly sensitive to damage caused by DNA-cross-linking agents (platinum drugs) and ionizing radiation. Thus, HGS-OC patients with HR repair defects should be sensitive to PARP inhibitors or platinum agents. However, overall five year survival rate for ovarian cancer is still low. This suggests that some ovarian cancer patients with HR-defect are still resistant to platinum agents. One of the future key challenges is the development of resistance to PARP inhibitors. The presence of secondary somatic mutations in relapsed Epithelial Ovarian Cancer (EOC) and resistant cell lines that restore BRCA function may confer resistance to platinum as well as PARP inhibitors. Other mechanisms of resistance include tumor heterogeneity enhanced drug efflux and the reduction of the key mediators of DNA repair. Assays to quantify HR deficiencies in tumor samples and the measurement of γ-H2AX, Rad51 foci, BRCA1 foci are biomarkers currently being studied to stratify ovarian cancer patients sensitive to PARP inhibitors or platinum agents.

Angiogenesis-specific pathways are promising therapeutic targets in EOC. Most of the therapeutic agents developed for this purpose show only modest single-agent activity so this treatment strategy has been adapted to combine with chemotherapy. Bevacizumab (Avastin) is a humanized monoclonal antibody directed against Vascular Endothelial Growth Factor (VEGF). Bevacizumab binds and neutralizes VEGFA, the best known isoform of seven structurally related glycoproteins, thus disrupting VEGFR dimerization, phosphorylation and activation of the downstream MAPK PI3K /AKT and JAK/STAT signaling transduction pathways. Bevacizumab has shown moderate efficacy as mono therapy and combined with chemotherapy in both the relapsed/recurrent and first-line settings. The phase 3 placebo-controlled trial of frontline paclitaxel/carboplatin versus bevacizumab/paclitaxel/carboplatin with and without maintenance bevacizumab (the Gynecologic Oncology Group trial, GOG218), a progression-free survival benefit was seen in women who received concurrent and maintenance bevacizumab compared with chemotherapy alone [7]. A randomized phase 3 trial from the International Collaboration on Ovarian Neoplasms (ICON7) evaluated first-line paclitaxel/carbopl-

atin alone or in combination with bevacizumab followed by bevacizumab maintenance. This trial showed enhanced progression-free survival and overall survival in the bevacizumab arm versus chemotherapy alone with a significant decrement the health-related quality-of-life [8,9]. Bevacizumab has also been combined with other targeted agents, including mammalian target of rapamycin inhibitors (eg, everolimus, phase 2), poly(ADP-ribose) polymerase inhibitors (eg, veliparib, phase 1) and tyrosine kinase inhibitors (eg, sorafenib, phase 2) to overcome resistance by inhibiting multiple pathways simultaneously in several ongoing ovarian cancer clinical trials. Aflibercept or VEGF-Trap is a soluble decoy receptor modulating the availability of all isoforms of VEGF ligands. It is a recombinant fusion protein composed of two extracellular VEGFR ligand binding domains, domain 2 of VEGFR1 and domain 3 of VEGFR2 fused to the constant region of the human immunoglobulin IgG. AMG 386 is a peptide-Fc fusion protein neutralizing the interaction of Ang-1 and Ang-2 with the Tie2 receptor. Small molecule tyrosine kinase inhibitors (TKIs) that inhibit the activity of VEGF receptors, and other growth factor receptors including BIBF 1120, cediranib, vandetanib, sunitinib, sorafenib and pazopanib have also been used in SEOC clinical trials. Cediranib (AZD2171) is an inhibitor of multiple tyrosine kinases of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/PDGFR-β, FGFR-1, and c-kit. A phase 3 trial of cediranib plus carboplatin/paclitaxel ± cediranib maintenance for 456 women with ovarian cancer (ICON6)a, a three month overall survival increase was observed in the group with cediranib compared with placebo[10]. Whether patients resistant to bevacizumab can still respond to other antiangiogenic agents is a big challenge to these patients who are resistant to bevacizumab therapy. According to previous experience in renal cancer, the sequential approach can yield significant clinical benefit by using of alternative anti-angiogenic agents such as Cediranib or BIBF1120 sequentially or in combination with bevacizumab upon progression.

Another promising targeted therapy in ovarian cancer is to target the complex networks of inflammatory cytokines which regulate communication between malignant cells and supporting stroma within the tumor microenvironment. Chemokines can regulate migration, invasion, proliferation, and resistance to chemotherapy by affecting both tumor cells and the cells of the tumor microenvironment including leukocytes, endothelial cells and fibroblasts [11]. Chemokines such as CXCL12 (SDF-1) promote drug resistance, angiogenesis and metastasis of various cancers, including EOC. Activation of the CXCL12 (SDF1α) pathway is a potential mechanism of resistance to both targeted therapy and chemotherapy. High expression of chemokine receptor, CXCR4, was correlated with a significantly lower chemosensitivity to cisplatin, a poorer progression-free survival and a lower overall survival in a cohort of 124 EOC patients. Anti-CXCL12/CXCR4 agents (e.g., plerixafor) may act as sensitizers to targeted therapies or standard chemotherapies by targeting the CXCL12/CXCR4 pathway. Plerixafor has been approved for use in non-Hodgkin's lymphoma and multiple myeloma. Plerixafor also shows the ability to inhibit proliferation of pancreatic adenocarcinoma *in vitro* and in a xenograft mouse modelb. However, CXCL12 may also be activated via the CXCL12/CXCR7 pathway and cause resistance to plerixafor. Nox-A12, an aptamer against CXCL12 or the humanized hamster mono-clonal antibody l30D8 against CXCL12, which directly target both CXCL12/CXCR4 and CXCL12/CXCR7 may provide a better clinical benefit. Circulating CXCL12 levels are significantly correlated with progression of recurrent Glioblastoma Multiforme (GBM) and advanced Hepatocellular Carcinoma (HCC) [12,13]. Further study is required to test the correlation of circulating CXCL12 levels with diagnosis and prognosis of women with EOC. Although serum levels of CA125 and HE4 were previously proposed as early diagnosis markers for ovarian cancers, they were found not to be useful in certain cases of early- and late-stage ovarian cancer. For example, increased IGFBP-4 serum levels were recently detected in some patients without an increase of CA125 [14]. Therefore, combining other serum biomarkers could increase sensitivity for early SEOC detection. Serum microRNAs including miR-221 and miR-103 has been identified to be able to discriminate patients with high grade SEOC from age-matched healthy controls [15,16]. The addition of these serum biomarkers to current testing regimes may improve diagnosis for women with SEOC.

In conclusion, expansion of efforts to employ the invaluable resources of TCGA to identify genes and pathways involved in ovarian carcinomas and the application of such knowledge to the design of preclinical and clinical trials are urgently needed to increase the efficacy of therapeutic regimes to HGS-OC.

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Note

a) ICON6 ovarian cancer results may resurrect cediranib, AT THE EUROPEAN CANCER CONGRESS 2013. http://www.icon6.org

b) http://www.dailymail.co.uk/health/article-2534683/A-cure-pancreatic-cancer-available-ten-years-scientists-claim.html

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