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

Shujie Yang¹, Xiangbing Meng¹,²*

¹Departments of Obstetrics and Gynecology, The University of Iowa, Iowa City, Iowa 52242; USA
²Holden Comprehensive Cancer Center, The University of Iowa, Iowa City, Iowa 52242; USA

*Corresponding author: Xiangbing Meng, Departments of Obstetrics and Gynecology, The University of Iowa, Iowa City, Iowa 52242, USA; E-mail: xiangbing-meng@uiowa.edu

Received Date: January 25, 2014, Accepted Date: February 22, 2014, Published Date: February 24, 2014


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/BRC2 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 pathobiology 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-crosslinking 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/recurrant 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/carboplatin/...
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.

Acknowledgement

We thank Eric Devor for assistance in manuscript preparation. This work was partially supported by NIH Grant R01CA99908-7, the Department of Obstetrics and Gynecology Research Development Fund.

Note

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

References


Submit your manuscript to a JScholar journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Immediate publication on acceptance
- Open access: articles freely available online
- High visibility within the field
- Better discount for your subsequent articles

Submit your manuscript at http://www.jscholaronline.org/submit-manuscript.php