Targeted therapy for gynecologic cancers: Toward the era of precision medicine

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Abstract
Recent advances in molecular biology of cancer have led to the development of targeted agents, mainly of monoclonal antibodies and small-molecule compounds. Unlike traditional drugs that inhibit DNA synthesis and mitosis, these agents target the signaling pathways of cancer cells, stroma, and vasculature in tumor tissues. For gynecologic cancers, drugs targeting angiogenesis such as anti-VEGF antibody have been used in the treatment of advanced or recurrent ovarian and cervical cancers, and the drugs targeting homologous recombination deficiency such as PARP inhibitors have been approved for maintenance after chemotherapy in platinum-sensitive ovarian cancer. In addition, novel immunotherapy using the immune checkpoint inhibitors such as anti-PD-1 antibody has received much attention for modulation of local immunity, resulting in the durable response of platinum-resistant ovarian cancer. In the precision medicine era, further understanding of cancer genomics and identification of predictive biomarkers are essential to ensure better health for women with gynecologic cancer.

KEYWORDS
Anti-PD-1 antibody; Anti-VEGF antibody; FIGO Cancer Report; Gynecologic cancer; Immune checkpoint inhibitor; PARP inhibitor; Precision medicine; Targeted therapy

1 INTRODUCTION

Despite recent advances in cancer treatment, the number of deaths from gynecologic cancers remains substantial worldwide. In 2012, there were an estimated 527,624 new cases of cervical cancer and 265,672 deaths, 319,605 new cases of endometrial cancer and 319,605 deaths, and 238,719 new cases of ovarian cancer and 151,917 deaths.1 Cervical cancer is preventable through a combination of vaccination against HPV and systematic screening, but even then it remains the leading cause of cancer death for women in low-resource countries.2 Regarding ovarian cancer, although combination of cytoreductive surgery and standard chemotherapy using paclitaxel and carboplatin is effective, 70% of patients experience relapse and long-term survival remains poor. Thus, development of a novel treatment strategy is needed. Targeted therapy is a novel medical treatment for cancer—different from traditional cytotoxic chemotherapy—and inhibits the growth of cancer cells by interfering with specific molecules needed for their pathway of carcinogenesis and progression. As such, targeted drugs are expected to be less harmful to normal cells.

More importantly, if the driver oncogene and the main signaling pathway for cancer growth and survival are identified, the targeted drug is greatly effective owing to the "oncogene addiction" of the tumor cells. Epoch-making drugs are inhibitors of growth factor receptors and tyrosine kinases, such as trastuzumab for high-risk breast cancer and imatinib for chronic myeloid leukemia (CML).3 Another recent example is EML4-ALK lung cancer. In 2007, Soda et al.4 identified the fusion oncogene EML4-ALK in a subset of non-small-cell lung cancer (NSCL) with poor prognosis, and showed that an ALK kinase inhibitor, crizotinib, was effective and dramatically improved the survival of patients with this tumor. Although the definite drivers have...
not been identified in most gynecologic cancers, extensive research has disclosed that anti-angiogenic drugs and those interfering with DNA repair are effective in ovarian cancer. In addition, recent advances in knowledge of the local immune microenvironment of cancer have made it possible to use the immune checkpoint inhibitors. The present article will review the history of development and the current and future perspective of targeted therapies, focusing on gynecologic cancer treatment.

2 | DRUGS FOR TARGETED THERAPY AND THEIR MECHANISM OF ACTION

One of the earliest and most extensively used molecular targeted drugs is tamoxifen, a selective estrogen receptor (ER) modulator. This hormonal therapy competitively antagonizes ER in breast tissue, and has been widely used to prevent recurrence of ER-positive breast cancer. In the era of precision medicine, new drugs target more complex mechanisms, and are divided into two categories. The first is monoclonal antibodies that do not penetrate the cell membrane but bind with the ligands and receptors of the specific growth factors. The second is low molecular organic compounds that can enter the cytoplasm and act on targets such as tyrosine kinases, PI3K/AKT/mTOR pathways, and DNA repair mechanisms.

2.1 | Monoclonal antibodies targeting ligands and receptors

Hybridoma technology developed by Köhler and Milstein in 1975 made it possible to produce large quantities of monoclonal antibodies directed against specific human antigens. Monoclonal antibodies can induce the killing of tumor cells through antibody-dependent cell-mediated cytotoxicity, induced by the stimulation of monocytes, macrophages, natural killer (NK) cells, killer T cells, and granulocytes. Monoclonal antibodies are immunoglobulin G molecules that comprise two identical light chains and two identical heavy chains, and have antigen-binding domains (Fab) linked to an effector domain (Fc). Monoclonal antibodies bind to the targeted antigen expressed on the tumor cells at the Fab domain. The Fc domain binds to the Fc receptors expressed on NK cells, monocytes, or macrophages, which are the effectors of cell-mediated immunity. Such bridging by monoclonal antibodies between the tumor cell and the effector cells induces cytotoxicity by the NK cells and phagocytosis by the macrophages, thus causing lysis of the tumor cells. Monoclonal antibodies can also kill tumor cells by inducing the complement cascade, resulting in complement dependent cytotoxicity.

Epidermal growth factor receptor (EGFR) is a cell surface transmembrane receptor, which stimulates multiple pathways involved in cell proliferation, metastases, and angiogenesis. Binding of EGF to EGFR activates the signaling pathways through tyrosine kinase activity. Monoclonal antibodies can bind to the EGFR receptors and modulate signaling to normalize cellular growth rates and improve responsiveness to the cytotoxic agents. Human epidermal growth factor-2 (HER2/neu) is overexpressed in about 15%–20% of early stage breast cancers and is associated with poor prognosis. Trastuzumab is a humanized monoclonal antibody that selectively binds to the HER2 receptors and is indicated in metastatic breast cancer expressing HER2 receptors. Cetuximab is another EGFR blocker used in the treatment of head and neck cancer, colorectal cancer, and NSCLC. Although these monoclonal antibodies were tried in gynecologic cancers, their efficacy was found to be limited.

Angiogenesis, the formation of new blood and lymphatic vessels from existing vasculature, is a crucial process involved in solid tumor growth and progression. Vascular endothelial growth factor (VEGF) generated from the cancer cells plays a central role in angiogenic signals, stimulating endothelial cell migration, endothelial cell proliferation, and microvessel formation. The activated endothelial cells release matrix metalloproteinases to break down the surrounding extracellular matrix to promote blood vessel formation. The anti-VEGF monoclonal antibody, bevacizumab, can neutralize the VEGF receptors and inhibit the signaling pathways of angiogenesis, and has been approved for patients with cancer of the colon, lung, breast, kidney, and brain. Bevacizumab is an important targeted drug for gynecologic cancers, as described later.

2.2 | Tyrosine kinase inhibitors

Abnormal phosphorylation of tyrosine kinase leading to increased proliferation, angiogenesis, and anti-apoptosis is a major cause of tumorigenesis. The first selective tyrosine kinase inhibitor to be approved for cancer treatment was imatinib mesylate in 2001. Philadelphia chromosome is characteristically seen in CML and is related to BCR-ABL tyrosine kinase overexpression. Imatinib is a 2-phenylaminopyrimidine that inhibits the activated BCR-ABL tyrosine kinase and suppresses the growth of Philadelphia chromosome-positive CML.

Tyrosine kinase inhibitors can also target the EGFR. Gefitinib is an EGFR tyrosine kinase inhibitor that prevents cell proliferation, stimulates apoptosis, and increases levels of the cyclin-dependent kinase inhibitor p27, which leads to G1 cell cycle arrest. Gefitinib is approved for the treatment of advanced NSCLC. Erlotinib is another EGFR tyrosine kinase inhibitor used to treat metastatic NSCLC. Lapatinib against both EGFR and HER2 is indicated in HER2-positive breast cancers refractory to trastuzumab. Although a subset of ovarian cancer shows the amplification and/or overexpression of HER2 or EGFR, the efficacy of these drugs is so far limited in gynecologic cancers. Tyrosine kinase inhibitors that inhibit the VEGF signaling pathways are sorafenib, sunitinib, and pazopanib. Pazopanib was tried in ovarian cancer patients, and some positive effects have been reported.

2.3 | PI3K/AKT/mTOR pathway inhibitors

The phosphatidylinositol 3-kinase (PI3K) signaling pathway is critical in development of cancer and mediates cell growth and proliferation. mTOR (mammalian target of rapamycin) acts within the canonical PI3K signaling pathway and is an important integrator of several targetable signaling cascades. There are several novel
agents that inhibit PI3K (pictilisib/GDC-0941, BMK120, MK-2206) and mTOR (temsirolimus, everolimus). mTOR inhibitors have been approved for astrocytoma, breast cancer, renal cell carcinoma, and also received attention for the novel treatment of endometrial cancer and a subtype of ovarian cancer with PTEN mutation or other gene abnormalities in this pathway.9

2.4 | Poly (ADP-ribose) polymerase (PARP) inhibitors

BRCA1 and BRCA2 are tumor suppressor genes involved in homologous recombination (HR) DNA repair when double-strand breaks occur in normal cells. BRCA1/2 germline mutations account for about 5%–10% of all breast cancers and about 15% of all ovarian cancers. PARP plays an important role in repairing the single-strand DNA breaks, and PARP inhibitors in tumors with BRCA1/2 mutations prevent DNA repair in the tumor cells and make them vulnerable to apoptosis. Clinical trials using PARP inhibitors have shown remarkable improvement in progression-free survival in patients with platinum-sensitive ovarian cancer, as described later.

2.5 | Immunoconjugates

Immunoconjugates are essentially monoclonal antibodies used to deliver cytotoxic drugs, cytokines, or radioisotopes directly to tumor cells. The concentration of drug in the tumor is increased significantly and the toxicity can be minimized. Cytotoxic agents that have been successfully delivered using monoclonal antibodies are those that block polymerization of tubulin or cause DNA damage. Monoclonal antibodies have also been used to deliver liposomal anticancer drugs such as doxorubicin or vincristine. However, the logistics of storage and administration of the immunoconjugates limit their use.

3 | MOLECULAR-TARGETED DRUGS FOR GYNECOLOGICAL CANCERS

Numerous agents that target specific gynecologic cancer-related molecules have been tried, mainly for patients with advanced or recurrent disease. Among them, anti-VEGF antibodies have now been used in the treatment of ovarian and cervical cancers, and PARP inhibitors have received attention as promising drugs that will change the natural course of ovarian cancer patients.

3.1 | Anti-VEGF antibodies

The anti-VEGF antibody, bevacizumab, is a recombinant humanized monoclonal immunoglobulin G antibody that binds to circulating VEGF and prevents it from binding to its receptors. This drug also normalizes tumor vessels that are structurally and functionally abnormal, leading to their reversal that may enhance the effects of chemotherapy. Clinical benefits have been reported in patients with colorectal cancer, NSCLC, and breast cancer. Adverse events are hypertension, proteinuria, and serious gastrointestinal toxicities such as perforation and fistula. Bevacizumab was expected to be effective in ovarian cancer, since VEGF plays an important role in the process of peritoneal dissemination and angiogenesis.10

Two phase II trials evaluated bevacizumab as monotherapy for ovarian cancer, and yielded favorable results with response rates of 16%–21%. Gastrointestinal perforation was observed in 11% of patients.11,12 Two phase III trials with bevacizumab for ovarian cancer were conducted (GOG218, ICON7), and in both trials, paclitaxel and carboplatin chemotherapy plus bevacizumab and maintenance with bevacizumab showed a significantly longer progression-free survival than chemotherapy alone (GOG218: 14.1 vs 10.3 months, P<0.001; ICON7: 19.8 vs 17.4 months, P<0.001).13,14 Although statistically significant improvement was not demonstrated in overall survival, the benefit in overall survival was obtained in higher-risk women with incomplete surgery or Stage IV disease (ICON7: 39.7 vs 30.2 months, P=0.03).

Two phase III trials were conducted to evaluate recurrent disease. In the AURELIA study for platinum-resistant recurrent ovarian cancer patients, significant improvement in progression-free survival but not in overall survival was obtained in the chemotherapy plus bevacizumab group.15 The benefit of bevacizumab in quality of life was consistent, especially in patients with ascites. The OCEANS study showed that, in platinum-sensitive recurrent ovarian cancer, chemotherapy with bevacizumab followed by its maintenance had a significantly longer progression-free survival but no difference in overall survival.16 Recently, however, a phase III trial GOG-0123 reported a significant overall survival improvement in recurrent, platinum-sensitive ovarian cancer.17 Following these studies, bevacizumab has been approved for ovarian cancer patients in both primary and recurrent settings. For cervical cancer, a phase III clinical trial was conducted in patients with metastatic, persistent, or recurrent disease, and showed overall survival improvement by addition of bevacizumab to chemotherapy. Fistula occurred in 15% of patients in the bevacizumab group.18

3.2 | PARP inhibitors

Poly (ADP-ribose) polymerase (PARP) is a key enzyme involved in repair of DNA single-strand breaks using the base excision repair pathway. In recent years, PARP inhibitors have emerged as one of the key targeted therapies in the management of ovarian cancer. Since preclinical evidence of the efficacy of PARP inhibitors in BRCA deficient cell lines, ovarian cancer—especially high-grade serous cancer (HGSC)—has been one of the major candidates for its clinical application owing to the high prevalence of BRCA1 and BRCA2 germine mutations. Functional BRCA deficiency leads to deficient DNA repair through the HR machinery. PARP inhibitors block the other major complementary and back-up DNA repair pathways, thereby leading to cell death—referred to as "synthetic lethality". In ovarian cancer, functional homologous recombination deficiency (HRD) exists in approximately 50% of HGSCs owing to BRCA germline mutation, BRCA somatic mutation, BRCA methylation, and epigenetic loss of other factors in the HR pathway; therefore, a significant proportion of ovarian cancers benefit from the use of PARP inhibitors.19 BRCA
deficiency and the extended spectrum of HRD phenotype, known as “BRCAness”, are also associated with improved platinum sensitivity and survival. The evolution of clinical trials of PARP inhibitors in ovarian cancer has contributed to a progression from its use only in patients with BRCA germline mutations to those with any platinum-sensitive recurrent ovarian cancer.

Based on the success in several landmark phase II/III clinical trials, including the NOVA, SOLO, and ARIEL series that showed significant improvement in the progression-free survival of patients after recurrence,20–23 three PARP inhibitors (olaparib, rucaparib, and niraparib) were approved for use in ovarian cancer between 2014 and 2016. Although the licensed indications, dosage, and adverse effects differ among them, the major advantages—especially as maintenance therapy in recurrent ovarian cancer—include the availability of oral formulations and that they are well tolerated, except hematological toxicities that are managed by dose reduction. Recently, there has been a move toward determination of HRD status to allow a more personalized approach, and assays for HRD to predict individuals who benefit from this agent have been explored enthusiastically.24

Other areas of recent clinical and translational research on PARP inhibitors in the maintenance setting include when to test for HRD. This is because there are several resistance mechanisms to PARP inhibitors, such as the phenomenon of revertant secondary mutations in the BRCA gene during recurrence leading to loss of HRD. Furthermore, the unmet need is treatment of the other 50% HR-competent or proficient ovarian cancers that are deemed to be chemoresistant. This has led to the emergence of several trials investigating the role of adding other agents, such VEGF inhibitors, immune checkpoint inhibitors, and HR inhibitors, as combination therapy with PARP inhibitors to either modify the HR function or the tumor microenvironment.

4 | NOVEL IMMUNOTHERAPY FOR GYNECOLOGIC CANCERS

Immunotherapy using immune checkpoint inhibitors has received much attention, since recent clinical trials demonstrated efficacy in a subset of patients with recurrent ovarian cancer.25 For years, various immunotherapy agents have been tried. These are classified as active or passive. Active immunotherapy for ovarian cancer includes CD4+ T cells targeting MUC1, or vaccination with p53 peptide, HER2-derived peptide, and WT-1 peptide. Passive immunotherapy has tested use of antibody against CA125, folate receptor, or EcCAM. Generally, the efficacy of such conventional immunotherapy is limited. However, for cervical cancer, trials with therapeutic vaccine targeting HPV oncoproteins E6 and E7 are under phase III.26

Recently, the mechanism of “escape from the host immune” in cancer has been described.25 An immune reaction to antigens, including cancer cells, is initiated with antigen recognition by dendritic cells (cognitive phase). These cells migrate to lymph nodes and present the antigens to T cells, which recognize the cancer cells and become activated. At the same time, a second signal is sent via interaction of specific molecules known as immune checkpoint molecules, i.e. B7, CD28, and CTLA-4. When the interaction between B7 and CD28 occurs, active immunity is initiated. If the interaction between B7 and CTLA-4 is stronger, the response is inhibited. Such pro- or anti-immune mechanisms also occur when T cells recognize the target (effector phase). If the interaction between PD-1 on T cells and PD-L1 on target cells is stronger, the immunologic attack will be attenuated. Cancer cells frequently express either CTLA-4 or PD-L1, which reduce the immune attack by T cells. Therefore, immunotherapy using anti-CTLA-4 antibodies for the cognitive phase or PD-L1/PD-1 antibodies for the effector phase is a novel targeted therapy against the immune checkpoint signals.

In 1999, clinical trials started using anti-CTLA-4 antibodies (ipilimumab, tremelimumab), anti-PD-1 antibodies (nivolumab, pembrolizumab), and anti-PD-L1 antibodies (atezolizumab, durvalumab, avelumab). Among these, nivolumab has been approved for treatment of melanoma, lung cancer, renal cancer, and gastric cancer. In 2010, Hamanishi et al.27 conducted the first clinical trial using nivolumab in patients with platinum-resistant, recurrent ovarian cancer; overall response rate was 15% and disease control rate was 45%. Interestingly, the response was durable, as two patients with complete response showed no evidence of disease three years after the treatment. Results of a trial using the anti-PD-L1 antibody, avelumab, for recurrent ovarian cancer were reported at the American Society of Clinical Oncology (ASCO) 2015: the overall response rate was 11%, whereas disease control rate was 55%.28 Adverse effects of immune checkpoint inhibitors are colitis, endocrinopathies affecting pituitary, adrenal, and thyroid glands, and pneumonitis. The advantage of using these drugs is the durability of response, including the possibility of cure. Thus, successful clinical trials with immune checkpoint inhibitors have opened a new window for cancer treatment. Recently, another PD-1 antibody, pembrolizumab, has been tried for advanced cervical cancer, and overall response rate was 17%.29

5 | FUTURE PERSPECTIVE FOR PRECISION MEDICINE

We are entering a new era of precision medicine, where treatment and prevention of disease takes into account individual variability in genes, environment, and lifestyle of each person. The final goal is increasing patient specificity so that the right treatment is given to the right patient at the right time. Comprehensive genomic analyses using next-generation sequencing (NGS) and gene expression profiling using DNA microarray are revealing the diversity of genome, epigenome, and expression profiles of cancer. Such data act as predictive biomarkers to select a specific therapy, and also to indicate accurate risk assessment, monitoring, and predicting resistance and tolerability to a treatment regimen for each patient.

For ovarian cancer, especially HGSCs, the Cancer Genome Atlas Network published complete molecular data from NGS and microarray analyses in 2011. It was shown that HGSC does not have the definitive driver, however, there are four subtypes in the gene expression profile
(differentiated, immunoreactive, mesenchymal, and proliferative), and that patients with the mesenchymal subtype showed the worst prognosis. Such novel classification is relevant for the difference in the microenvironment of cancer cells. Recent bioinformatics and clinicopathology approaches have shown that the mesenchymal subtype is more sensitive to paclitaxel and fits the dose-dense paclitaxel and carboplatin chemotherapy.\(^\text{30}\) Bevacizumab may also improve the survival of patients with mesenchymal and proliferative subtypes, but not those with the immunoreactive subtype.\(^\text{31}\) Thus, selection of drugs will be done according to molecular analyses. The high cost of the recent targeted drugs also leads to the unmet needs for development of predictive biomarkers. Further research is necessary to advance precision medicine for better prognosis and quality of life in each patient with gynecologic cancer.

**AUTHOR CONTRIBUTIONS**

PB, AM, and IK contributed equally to the design, planning, and writing of this manuscript.

**CONFLICTS OF INTEREST**

The authors have no conflicts of interest to declare.

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