REVIEW

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Targeted therapy of ovarian cancer including immune check point inhibitor

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Epithelial ovarian cancer is the eighth most common cause of cancer-related deaths in women because most patients present with advanced stage disease at the time of diagnosis. Although cytoreductive surgery and platinum-based chemotherapy remain the gold standards of treatment, the recurrence rate of ovarian cancer remains high. Attempts to improve this standard two-drug chemotherapy by adding a third cytotoxic drug have failed to affect either progression-free survival or overall survival and have resulted in an increase in toxic side effects. Some anti-angiogenic agents, poly(ADP-ribose) polymerase, and immune checkpoint inhibitors have shown efficacy in early stages of development for the treatment of epithelial ovarian cancer. As demonstrated in recent clinical trials, the use of bevacizumab, cediranib, pazopanib, olaparib, and rucaparib, either alone or in combination with conventional cytotoxic agents, improves progression-free survival. Trials on immune checkpoint inhibitors such as nivolumab have revealed prolonged responses in a small set of ovarian cancer cases but require further exploration. In this review, we discuss the role of targeted therapies against ovarian cancer, including the use of immune checkpoint inhibitors.

Keywords: Ovarian neoplasms; Molecular targeted therapy; Immunotherapy

INTRODUCTION

Epithelial ovarian cancer (EOC) is the eighth most common cause of cancer-related deaths in Korean women, with an estimated 1,021 deaths occurring annually nationwide in 2014 [1]. For the past decade, the standard treatment for women with advanced ovarian cancer has been optimal cytoreductive surgery and platinum-based chemotherapy. Although approximately 80% of patients respond to first-line chemotherapy, more than 70% of patients with advanced stage disease recur within 5 years and develop drug resistance [2,3]. Attempts to improve standard two-drug chemotherapy by adding a third cytotoxic drug have failed to affect either progression-free survival (PFS) or overall survival (OS) and have resulted in an increase in toxic side effects [4-7]. Advances in traditional cytotoxic chemotherapies, such as intraperitoneal administration and dose-dense therapeutic regimens, are improving response rates, as are novel agents such as bevacizumab or poly(ADP-ribose) polymerase (PARP) inhibitors [8,9]. Unfortunately, platinum-refractory advanced ovarian cancer does not show a proper response rate; therefore, more effective treatment strategies, particularly molecular targeting agents, are required to improve survival rates for patients with advanced ovarian cancer.

CURRENT TREATMENT MODALITIES

Optimal cytoreductive surgery is effective in most patients with ovarian cancer; however, in cases of advanced

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Table 1. Summary of efficacy data from randomized, controlled phase III trials of bevacizumab in advanced ovarian cancer

Study	Regimen	ORR (CR + PR), %	Median PFS, mon	Median OS, mon
GOG-0218 [21] (n = 1,873)	CP + placebo vs. CP + Bev vs. CP + Bev→Bev maintenance	-	10.3 vs. 11.2 vs. 14.1 (HR, 0.908; $p = 0.16$)[a] (HR, 0.717; $p < 0.001$)[b]	39.3 vs. 38.7 vs. 39.7 (HR, 1.036; $p = 0.76$)[a] (HR, 0.915; $p = 0.45$)[b]
ICON 7 [22,23] (n = 1,528)	CP vs. CP + Bev→Bev maintenance	48 vs. 67 ($p < 0.001$)	17.4 vs. 19.8 (HR, 0.87; $p = 0.04$)	44.6 vs. 44.5
OCEANS [24,27] (n = 484)	CG + placebo vs. CG + Bev	57.4 vs. 78.5 ($p < 0.0001$)	8.4 vs. 12.4 (HR, 0.484; $p < 0.0001$)	33.6c vs. 32.9[c] (HR, 0.960; $p = 0.736$)
AURELIA [28,29] (n = 361)	CTx (PLD, P, or Top) vs. CTx + Bev	11.8 vs. 27.3 ($p = 0.001$)	3.4 vs. 6.7 (HR, 0.48; $p < 0.001$)	13.3 vs. 16.6 (HR, 0.85; $p = 0.174$)

ORR, overall response rate; CR, complete response; PR, partial response; PFS, progression-free survival; OS, overall survival; GOG, Gynecologic Oncology Group; C, carboplatin; P, paclitaxel; Bev, bevacizumab; HR, hazard ratio; ICON, International Collaborative Ovarian Neoplasm; OCEANS, platinum-sensitive recurrent disease; G, gemcitabine; AURELIA, platinum-resistant ovarian cancer; CTx, chemotherapy; PLD, pegylated liposomal doxorubicin; Top, topotecan.
[a]CP + Bev vs. CP + placebo.
[b]CP + Bev→Bev vs. CP + placebo.
[c]Interim data.

stage ovarian cancer (International Federation Gynecology Obstetrics [FIGO] stage IIB-IIIC), platinum-based combination chemotherapy is recommended [10]. A modified carboplatin plus paclitaxel regimen with weekly paclitaxel results in improved long-term outcomes compared to the 3-weekly regimen in a phase III study on advanced ovarian cancer [11-14]. More than 80% of patients respond to first-line chemotherapy; however, approximately 70% of patients with advanced EOC recur within 5 years and develop drug resistance [2,3].

For recurrent EOC, there is no evidence of a survival benefit following early treatment of relapse on the basis of a raised cancer antigen 125 (CA-125) concentration alone [15]. The treatment options for recurrent EOC are based on the timing and nature of the recurrence and the extent of prior chemotherapy [16]. Patients responding to front-line platinum-based chemotherapy are very likely to respond to a rechallenge with platinum-based chemotherapy. However, patients relapsing after front-line platinum/paclitaxel chemotherapy have more side effects, especially neurotoxicity. Refractory ovarian cancer occurs in patients who have failed to achieve a response to therapy. Patients with platinum-resistant ovarian cancer do not respond to initial therapy or their disease recurs after a short (< 6 months) treatment-free interval [17]. The response rate in patients with platinum refractory status is below 10% [18]. Due to the number and diversity of active agents presently available for second-line treatment of ovarian cancer (i.e., pegylated liposomal doxorubicin, docetaxel, topotecan, vinorelbine, and belotecan), clinicians and patients often consider treatments beyond the second-line setting, assuming adequate organ function and overall performance status [17].

TARGETED THERAPIES

Vascular endothelial growth factor (VEGF) expression is higher in advanced stage tumors compared to those at an early stage [19]. Angiogenesis plays an integral role in the initiation and progression of ovarian carcinogenesis [20]. Given the association between increased angiogenesis and the progression of ovarian cancer, a number of anti-angiogenic agents are currently in development as potential treatment options for patients with advanced disease.

Bevacizumab

Proper efficacy data is currently available from four important phase III randomized trials in advanced ovarian cancer (Table 1). The first two trials tested bevacizumab in combination with carboplatin/paclitaxel in an adjuvant setting: the International Collaborative Ovarian Neoplasm (ICON-7) trial and the Gynecologic Oncol-

ogy Group (GOG) trial 218 [21-23]. The other two trials evaluated bevacizumab in recurrent cases of ovarian cancer: an ovarian cancer study comparing the efficacy and safety of chemotherapy and anti-angiogenic therapy in platinum-sensitive recurrent disease (OCEANS) and bevacizumab use in platinum-resistant ovarian cancer (AURELIA) [24-26].

ICON-7 enrolled 1,528 patients, 70% of whom had stage IIIc or stage IV ovarian cancer. At a median follow-up time of 36 months, patients in the bevacizumab arm showed a significant improvement in median PFS (2 months). The maximal effect of this trial was observed at 12 months but decreased after 24 months. A recently updated analysis showed similar PFS and OS benefits in the bevacizumab group [23].

GOG protocol 218 was a three-arm placebo-controlled study. In the standard treatment arm, patients were given carboplatin (area under the curve [AUC] 5 or 6) and paclitaxel (175 mg/m^2) every 3 weeks for six cycles. In the bevacizumab throughout arm, bevacizumab was given with chemotherapy for two to six cycles and then continued every 3 weeks for a total of 22 cycles. In the bevacizumab initiation arm, bevacizumab was given with chemotherapy for two to six cycles and then continued with placebo in cycles seven to 22. The dose of bevacizumab given intravenously (15 mg/kg) was double the dose given in ICON-7. The improvement in median PFS was significant in the bevacizumab throughout arm, but there was no significant difference in OS between the three arms (Table 1) [21-24,27-29].

The OCEANS trial was a randomized, multi-center, blinded, placebo-controlled phase III trial. Patients were randomly assigned to carboplatin plus gemcitabine combined with bevacizumab or placebo for six to 10 cycles. Bevacizumab or placebo was continued until disease progression. PFS for the bevacizumab arm was superior to that for the placebo arm (12.4 months vs. 8.4 months, respectively). In addition, bevacizumab therapy caused a significant improvement in the objective response rate (78.5% vs. 57.4%, respectively) and duration of response (10.4 months vs. 7.4 months, respectively). There was no OS benefit for patients who received bevacizumab compared to the placebo arm (33.6 months vs. 32.9 months, respectively) [24].

The AURELIA trial was the first randomized phase III trial to evaluate bevacizumab in combination with chemotherapy in platinum-resistant ovarian cancer [25,26]. Pegylated liposomal doxorubicin (40 mg/m^2) was given on day 1 every 4 weeks; weekly paclitaxel (80 mg/m^2) was administered on days 1, 8, 15, and 22 every 4 weeks; or topotecan (4 mg/m^2) was administered on days 1, 8, and 15 every 4 weeks or topotecan (1.25 mg/m^2) was given on days 1 through 5 every 3 weeks. Bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) was given until progression, unacceptable toxicity, or consent withdrawal. There was a 3-month prolongation of PFS with the addition of bevacizumab. The difference in OS was not significant (Table 1), but the overall response rate (ORR) was higher in the bevacizumab arm compared to without bevacizumab (11.8% vs. 27.3%, respectively).

Pazopanib

Pazopanib is an oral multi-target tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)-α and -β, and c kit. A phase II open-label study evaluated oral pazopanib monotherapy in patients with low-volume recurrent ovarian cancer with complete CA-125 response to initial platinum-based chemotherapy and subsequent elevation of CA-125. Patients were treated with pazopanib (800 mg once daily) until progressive disease or unacceptable toxicity. The ORR was 18% in patients with measurable disease at baseline [30]. The international Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom trial 16 (AGOOVAR 16) was a phase III randomized control trial that evaluated the role of pazopanib in maintenance therapy of ovarian cancer FIGO stages II-IV with no evidence of progression after primary therapy, consisting of surgery and at least five cycles of platinum/taxane chemotherapy; patients were randomized 1:1 to receive pazopanib (800 mg once per day) or placebo for up to 24 months. Maintenance pazopanib prolonged PFS compared to placebo (17.9 months vs. 12.3 months, respectively). Pazopanib maintenance therapy provided a median improvement of 5.6 months in PFS in patients with advanced ovarian cancer who did not progress after first-line chemotherapy. OS data did not suggest any benefit. Grade 3 or 4 adverse events of hypertension (30.8%), neutropenia (9.9%), liver-related toxicity (9.4%), diarrhea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%), and palmar-plantar erythrodysesthesia

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(1.9%) were significantly higher in the pazopanib arm. Treatment discontinuation related to adverse events was higher among patients treated with pazopanib (33.3%) compared to placebo (5.6%) [31].

Cediranib

Cediranib is an oral TKI of VEGFR-1, -2, and -3, and c-kit. Matulonis et al. [32] conducted a phase II study on cediranib for recurrent ovarian cancer. Cediranib was administered as a daily oral dose; the original dose was 45 mg and was lowered to 30 mg due to toxicity. The clinical benefit rate (complete response or partial response, stable disease > 16 weeks, or CA-125 non-progression > 16 weeks) was 30%. Eleven patients (23%) were removed from the study because of toxicity before two cycles. Grade 3 toxicities (> 20% of patients) included hypertension (46%), fatigue (24%), and diarrhea (13%) [32]. Cediranib was the first VEGFR TKI to show an OS benefit when used as maintenance therapy in recurrent ovarian cancer; this was demonstrated in the ICON-6 trial. The ICON-6 trial is a three-arm, three-stage, double-blind, placebo-controlled randomized trial in first relapse of platinum-sensitive ovarian cancer. Patients were randomized (2:3:3) to receive six cycles of carboplatin (AUC 5 or 6) plus paclitaxel (175 mg/m^2) with either placebo, cediranib (20 mg per day) followed by placebo, or cediranib (20 mg per day) followed by cediranib. Cediranib or placebo was continued for 18 months or until disease progression. The cediranib maintenance arm showed improvements in PFS and OS by 2.7 months. Although more adverse effects occurred in the cediranib arm, these were found to be tolerable [33].

PARP INHIBITORS

Olaparib

The first clinical illustration of synthetic lethality in cancer was from the development of PARP inhibitors for the treatment of cancers with defects in the BRCA1 (BReast CAncer gene 1) or BRCA2 tumor suppressor proteins, which are involved in the repair of DNA damage. Although this is a promising approach, multiple potential resistance mechanisms have been identified [34]. Ledermann et al. [35] conducted a randomized, double-blind, placebo-controlled phase II trial to evaluate maintenance treatment with olaparib in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who received two or more platinum-based regimens and had a partial or complete response to a platinum-containing regimen. Patients received olaparib (400 mg twice daily) or placebo. PFS was significantly longer with olaparib than with placebo (8.4 months vs. 4.8 months, respectively) [35]. According to the retrospective analysis of the phase II trial in advanced ovarian cancer with BRCA1/2 mutations, there was a significantly prolonged PFS in the olaparib group compared to the placebo group (11.2 months vs. 4.3 months, respectively). There was also a strong trend towards an OS advantage, although this was not statistically significant (34.9 months vs. 31.9 months, respectively). The OS benefit could not be shown because most patients received other post-progression therapies and lived for many more years. The most common grade 3 or worse adverse events in the olaparib group were fatigue (7% vs. 3%, respectively) and anemia (5% vs. < 1%, respectively) [36].

Two ongoing multi-center double-blind randomized phase III trials are Studies of Olaparib in Ovarian Cancer (SOLO) 1 and 2. These studies focus on the role of olaparib in the maintenance of high-grade ovarian cancer in patients with the BRCA mutation. SOLO 1 includes patients with newly diagnosed advanced ovarian cancer who have responded to first-line platinum therapy and SOLO 2 includes cases of recurrent ovarian cancer who have completed more than two lines of platinum therapy. Clinicians expect the maturated data from two important trials.

Rucaparib

Rucaparib is a potent oral inhibitor of PARP 1 and 2 according to Assessment of Rucaparib in Ovarian Cancer Trial 2 (ARIEL 2), which enrolled patients with platinum-sensitive recurrent EOC with the BRCA mutation. ARIEL 2 prospectively tested a novel next-generation sequencing-based homologous recombination deficiency (HRD) assay and algorithm to predict rucaparib sensitivity by assessing tumor BRCA status and genome-wide loss of heterozygosity (LOH). The patients received rucaparib (600 mg twice daily) in three pre-defined HRD subgroups: tumor BRCA^{mut}, BRCA^{wt}/LOH^{high}, and BRCA^{WT}/LOH^{low}. Efficacy data indicated ORRs of 69%, 39%, and 11%, respectively. Responses occurred in both

germline BRCA^{mut} (14/19, 74%) and somatic BRCA^{mut} (10/16, 63%) tumors [37]. The pivotal ARIEL 3 study compared the effects of rucaparib versus placebo.

PARP inhibitor in combination with anti-angiogenic drugs

The combination of olaparib and cediranib versus single-agent olaparib in a phase II study on patients with platinum-sensitive recurrent ovarian cancer showed better PFS in the combination arm compared to the single-agent olaparib arm (17.7 months vs. 9.0 months, respectively). A significant improvement in PFS occurred in germline BRCA wild-type patients receiving cediranib/olaparib. Grade 3 and 4 adverse events, including fatigue, diarrhea, and hypertension, were more common in patients who received cediranib/olaparib therapy [38].

IMMUNOTHERAPIES

The use of monoclonal antibody-based checkpoint blockade for the treatment of ovarian cancer is also being developed, as well as targeting cytotoxic T-lymphocyte associated protein 4 (CTLA-4) or the anti-programmed cell death ligand-1/programmed cell death-1 (PD-L1/PD-1) axis. The anti-CTLA-4 antibody being widely tested is ipilimumab. Hodi and colleagues [39] provided the first indication that this drug may be useful; they enrolled two ovarian cancer patients in an early trial and demonstrated a reduction in CA-125 in one patient and stabilization in another. PD-1 is a co-inhibitory receptor that is expressed on activated T cells and regulates anti-tumor immunity. Nivolumab is a fully humanized immunoglobulin G4 that blocks the engagement of PD-1 by PD-1 ligands. Nivolumab was administered every 2 weeks to patients with advanced or relapsed platinum-resistant ovarian cancer. Fifteen patients were treated with nivolumab (1 mg/kg, n = 10; 3 mg/kg, n = 5) and evaluated. The 1 mg/kg treatment cohort showed a 20% partial response rate and a 50% disease control rate, and tolerated the side effects well [40]. The expression of PD-L1 in the tumor microenvironment appears to be crucial for therapeutic activity, and initial trials have suggested that positive PD-L1 tumor expression is associated with higher response rates. However, subsequent observations have questioned the prospect of using PD-L1 as a biomarker for selecting patients for therapy, especially since many patients considered PD-L1-negative benefit from treatment. However, there is no definitive test for determining PD-L1 expression, and a cut-off reference for PD-L1-positive status has not yet been established.

CONCLUSIONS

Ovarian cancer remains the most challenging cancer to clinicians even though treatment options have improved over several decades. These improvements have relied on optimal surgery and platinum-based chemotherapies. Recently, the most considerable improvement in ovarian cancer treatment came from bevacizumab and PARP inhibitor therapies. Although ovarian cancer is a targetable tumor, its biology is unique and highly heterogeneous. Newer developed drugs, especially the PD-1/PD-L1 antibody, have shown promising results; however, we do not have a proper prognostic marker. Further research is required to understand the molecular mechanisms more fully and to develop targeting combination therapies to overcome resistance, which may help conquer this disease with minimal toxicity. More tailored treatments based on molecular characteristics are expected in the near future.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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