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New Treatment of Advanced Ovarian Cancer: A Literature Review

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ABSTRACT

Epithelial ovarian cancer is one of the most common gynecological malignancies worldwide with an incidence of 225000 cases annually. For most patients, multimodality treatment including cytoreductive surgery and combination chemotherapy is an accepted standard of care. Despite the relatively favorable response to initial treatment, relapse free survival and overall survival are disappointing in patients with advanced ovarian cancer. Therefore, new treatment approaches have been proposed in recent years. The present review aims to describe the most relevant data published during the last four years on new approach to advanced ovarian cancer. Therefore, relevant studies were searched through Pubmed, Cochrane library and Scopus database published online until 2019. The most important changes studied in recent years have included the addition of new chemotherapy or targeted agent to first-line chemotherapy. Although combination of intravenous paclitaxel and carboplatin is currently accepted as the standard of care for treatment of advanced ovarian cancer, discussion around the intraperitoneal chemotherapy is still an important challenge. Additionally, much efforts have been dedicated to design an appropriate maintenance treatment as a goal of diminish the risk of recurrence. This review summarizes the results of most recent phase 3 trials surrounding optimal first-line chemotherapy, addition of a targeted agent including bevacizumab and maintenance treatment.

Keywords: Chemotherapy, Ovarian cancer, outcome

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Introduction

Epithelial ovarian cancer is the most common cause of death among patients with gynecologic cancers and the fifth common cause of cancer death in Europe **(1)**. Most patients with ovarian cancer present with advanced stage, which is defined by spreading the tumor outside the pelvis (FIGO stage III and IV) **(2)**. The incidence of ovarian cancer increases with age and the median age at the time of diagnosis is 63 years **(3)**. Unfortunately, majority of patients (75%) present with advanced stage and despite recent introduction of advanced strategies in treatment of ovarian cancer, relapse occurs in most cases **(4)**. The five-year survival rate for advanced stage epithelial ovarian cancer have improved only marginally over the recent decades ranging from 30 to 45 % **(5,6)**. Standard treatment of advanced epithelial ovarian cancer includes optimal cytoreductive surgery and platinum-based chemotherapy. Some important changes in schedule treatment such as neoadjuvant chemotherapy (NACT) or addition of new drugs to first-line therapy have developed. This review tries to introduce novel treatment strategies in advanced ovarian cancer.

First Line Chemotherapy in Advanced Ovarian Cancer

Primary debulking surgery followed by combination chemotherapy is currently considered as the standard care of treatment of advanced ovarian cancer **(3)**. However poor condition and high risk of morbidity and mortality of primary debulking surgery in patients with advanced ovarian cancer have proposed more effective new approaches in this subgroup of ovarian cancer **(7)**. Recently many studies have shown that neoadjuvant chemotherapy followed by interval debulking surgery may be associated with non-inferior survival outcome compared to primary debulking surgery **(8,9,10,11)**. Regarding to selecting who will benefit from NACT, more investigations are necessary. However, NCCN guideline recommended neoadjuvant chemotherapy followed by interval debulking surgery in some patients including bulky stage III or IV who are deemed unlikely to be completely cytoreduced to R0 and patients who are poor surgical candidates **(3)**.

Regarding to advanced stage of most ovarian cancer, majority of patients with epithelial ovarian cancer receive postoperative systemic chemotherapy. The standard chemotherapy regimen consists of a combination of paclitaxel 175mg/m2 and carboplatin AUC 5-6, both administrated intravenously every 3 weeks. This chemotherapy regimen has been the standard treatment from more than 15 years **(12)**.

Recently in attempt to improve outcome, alternative chemotherapy schedules have been evaluated as first

line chemotherapy in patients with ovarian cancer. In 2015, the Japanese Gynecologic Oncologic Group (JGOG) published results of a phase III study, which compared combination of weekly paclitaxel (80mg/m2) and carboplatin with the combination of three weekly paclitaxel (175mg/m2) and carboplatin. The study showed significant improvement in progression-free survival (PFS) and overall survival (OS) **(13)**. Also, Marchetti *et al.* reported a meta-analysis of comparing weekly versus three weeks chemotherapy. Although it did not show difference in OS and severe toxicity, the weekly paclitaxel administration significantly improved PFS **(14)**. However, in recent update of their meta-analysis, dose dense chemotherapy had no significant benefit on PFS. Therefore, they suggest that three weekly schedule should remain the standard of care for advanced ovarian cancer **(15)**. Furthermore, recent three phase ICON 8 trial has failed to show PFS and OS benefit of weekly compared to 3-weekly paclitaxel **(16)**. In conclusion, three weekly chemotherapy remains the preferred schedule unless further studies confirm definite superiority of weekly chemotherapy.

Although there is some controversy among clinicians about the numbers of cycles of chemotherapy, there is no evidence confirming that more than 6 cycles postoperative combination chemotherapy are beneficial for advanced ovarian cancer (**2,3**). A phase III trial assessed the value of addition of third agent to standard carboplatin/paclitaxel chemotherapy regimen. Compared with standard paclitaxel and carboplatin, addition of a third cytotoxic agent provided no benefit in PFS or OS after optimal or suboptimal cytoreduction **(17)**.

Intraperitoneal (IP) Chemotherapy

The rational for Intraperitoneal (IP) chemotherapy is to target the peritoneal cavity as a principle site of spreading and recurrence of ovarian cancer **(18)**. Administration of drugs directly into peritoneal cavity increases the dose intensity delivered to the tumor and reduces the systemic toxicity **(19)**. Although three large randomized trials have shown significant improvement in median survival with IP containing chemotherapy, there is much controversy surrounding the use of IP chemotherapy as a standard practice for patients with ovarian cancer. The reasons for this controversy are undefined optimal IP chemotherapy regimen, undefined optimal patient population and catheter-related complications **(20)**. However, IP containing chemotherapy may be considered in the first-line treatment of women with optimally debulked stage III epithelial ovarian cancer.

Anti-angiogenesis Agents

Bevacizumab, a humanized monoclonal IgG antibody that targets VEGF-R, has been one of the first and most investigated antiangiogenetic drugs in ovarian cancer. Bevacizumab is approved by FDA for the first-line treatment of stage III and IV ovarian cancer, fallopian tube, and primary peritoneal cancers due to the results of two randomized controlled Phase III trials. A phase 3 randomized trial (GOG 0218) compared combination of bevacizumab and carboplatin/paclitaxel with paclitaxel/carboplatin. The median PFS significantly increased in patients receiving upfront and maintenance bevacizumab (14.1 vs. 10.3 months $P<0.001$). Final OS which has been reported in JCO recently did not demonstrate a difference among groups in terms of OS **(21)**.

ICON-7 was another phase 3 randomized trial which evaluated bevacizumab in combination with carboplatin/paclitaxel as a frontline chemotherapy. Although PFS data confirm the finding of GOG 0218, benefits appear to be smaller (2.4 months increase in PFS). ICON-7 has suggested that OS increased in women with a poor prognosis but not in the whole study population **(3)**.

According to these studies postoperative chemotherapy combined with bevacizumab may be considered in patients with stage III and IV ovarian cancer.

Postremission Therapy

Majority of patients with ovarian cancer (>75%) will relapse after completion of primary treatment **(22)**. Several clinical trials have demonstrated the role of postremission therapy to reduce the risk of recurrence after response to first line chemotherapy.

Although multiple trials of cytotoxic and targeted agents such as paclitaxel, pazopanib and bevacizumab in the maintenance setting have shown PFS advantage, they were not associated with OS benefits **(23,24,25)**.

Recently a phase 3 study has been published which compared efficacy, safety and tolerability of pazopanib with placebo as maintenance therapy in women who have not progressed after first-line chemotherapy for advanced ovarian cancer. Although pazopanib as maintenance treatment prolonged PFS, this was not associated with median OS advantage **(26)**.

Based on GOG-0218 and ICON-7 trials, bevacizumab can be continued as maintenance therapy after primary treatment if an upfront chemotherapy/bevacizumab regimen was administrated.

Poly (ADP-ribose) Polymerase (PARP) Inhibitors

In 2014, both the United States Food and Drug Administration (FDA) and the European Medicine Agency (EMA) approved Poly (ADP-ribose) Polymerase (PARP) inhibitors for the treatment of ovarian cancer **(27)**. These agents are specifically active in epithelial ovarian cancers with deficient homologous recombination (HR) repair **(27)**. HR is an important pathway in repairing of double-stranded DNA breaks **(29)**. The Cancer Genome Atlas (TCGA) has demonstrated that about fifty percent of high grade serous ovarian cancers have aberrations in HR repair **(29)**. The first studied defects in HR repair are mutations in BRCA1 and BRCA2. PARP inhibitors

exhibit synthetic lethality when applied to BRCA1 or 2 mutated or other HR-deficient cells **(30)**.

Although previous approval of PARP inhibitors were to treat recurrent ovarian cancer as maintenance therapy, recently FDA approved olaparib for the maintenance treatment of patients with BRCA-mutated advanced ovarian cancer who have had complete or partial response to first-line platinum-based chemotherapy.

Conclusion

Most patients with epithelial ovarian cancer receive postoperative systemic chemotherapy. Recommendations regarding initial primary systemic therapy include intravenous with (or without) IP options. Neoadjuvant systemic chemotherapy may be considered for patients with bulky stage III or IV disease or high-risk surgical candidates. Bevacizumab may be considered as frontline treatment in combination with chemotherapy and followed by maintenance treatment.

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Conflict of Interest

Authors declared no conflict of interests.

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