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Clinical Treatment of Ovarian Cancer: First-Line Chemotherapy or Targeted Therapy for Recurrent Cases

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ABSTRACT

Ovarian cancer is the seventh most common gynecological cancer worldwide, ovarian cancer is the eighth leading cause of cancer death in women. In recent years, the number of ovarian cancer cases has been increasing in Japan, more than 9,000 women are diagnosed with ovarian cancer each year. The 5-year survival rate is 58%, the lowest among gynecological cancers, 4,758 ovarian cancer deaths in 2012. That is, it is reported that about one in two ovarian cancer patients has died. Because it is difficult to cure recurrent ovarian cancer, treatment is used to prolong life and improve quality of life. Because polyadenosine 5'-diphosphate ribose polymerase (PARP) inhibitors are oral targeted drugs that specifically act on cancer cells, they are expected to reduce the risk of disease progression and death while maintaining a good safety profile. In this way, the development of oral preparations has made it possible to avoid the burden on patients such as pain caused by conventional injections and the time constraints required for infusion. In this review, we discuss new treatments for ovarian cancer.

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Bevacizumab, an antibody to vascular endothelial growth factor (VEGF), is the first targeted drug to receive insurance coverage for gynecological cancer. Specifically, in November 2013, bevacizumab was approved for additional indications for ovarian cancer. Furthermore, in January 2018, olaparib, a polyadenosine 5'-diphosphate ribose polymerase (PARP) inhibitor, was approved for use as a maintenance treatment for platinum-sensitive recurrent ovarian cancer.

Representative clinical trials of bevacizumab in initial chemotherapy are the GOG218 and ICON7 clinical trials [1,2]. The GOG218 clinical trial is for ovarian cancer Stages III and IV, in arm 1, as a control group, 6 cycles of paclitaxel plus carboplatin combination therapy (TC therapy) plus placebo were administered from the second cycle of the TC method to the 15th month of treatment, in arm 2, bevacizumab 15 mg/kg was administered every 3 weeks from the second cycle of TC therapy to the end of TC therapy, in addition to 6 cycles of TC therapy, in arm 3, six cycles of TC therapy plus bevacizumab 15 mg/kg were administered from the second cycle to the 15th month of treatment.

The median progression-free survival (PFS) of TC therapy/bevacizumab combination therapy plus bevacizumab maintenance therapy (arm 3) was 14.1 months, compared with the control group (arm 1), PFS significantly prolonged the PFS at 10.3 months (HR = 0.72, 95% CI: 0.63-0.82). There was no significant difference in overall survival (OS) [1]. The ICON7 clinical trial was a randomized controlled trial conducted by GCIG clinical trial and was performed in ovarian cancer Stages I to IV. The ICON7 clinical trial is a two-arm design that does not use a placebo. In the control group, TC therapy was given, in the target drug group, TC therapy + bevacizumab group (bevacizumab 7.5 mg/kg for TC therapy) was administered every 3 weeks. After the end of TC therapy, bevacizumab was administered at the same

dose every 3 weeks for 36 weeks [12 cycles]. Compared to 17.3 months of PFS for TC therapy, the PFS of TC therapy plus bevacizumab group was 19.0 months, indicating a significant prolongation of PFS (HR=0.81, 95% CI: 0.70-0.94) [2].

In the OCEANS clinical trial for patients with platinum-sensitive relapse, gemcitabine + carboplatin (GC therapy) was considered as a control group. A randomized controlled trial was designed with GC/bevacizumab combination as the target drug group. PFS of GC/bevacizumab combination therapy was 12.4 months compared to 8.4 months of PFS for GC therapy, indicating a significant increase in PFS (HR=0.48, 95% CI: 0.39-0.61) [3]. Similarly, in the GOG213 clinical trial in patients with platinum-sensitive relapse, TC therapy was the control group, a randomized controlled trial was designed with TC/bevacizumab combination as the target drug group.

Regarding OS, one of the primary endpoints, the OS of TC/bevacizumab combination therapy was 42.2 months compared to 37.3 months of OS of TC therapy, and there was no significant difference (HR=0.829, 95% CI: 0.683-1.005). However, the results of a sensitivity analysis excluding 45 patients who were ineligible (platinum-resistant recurrence cases), compared with TC therapy, TC therapy/bevacizumab combination therapy showed a statistically significant increase in OS (HR=0.82, 95% CI: 0.680-0.996) [4].

In the AURELIA clinical trial in patients with platinum-resistant relapse, monotherapy chemotherapy (liposomal doxorubicin, weekly paclitaxel, topotecan) was considered as a control group. As a target drug group, single agent chemotherapy/bevacizumab combination therapy was designed as a randomized controlled trial. The PFS of monotherapy / bevacizumab combination therapy was 6.7 months, significant prolongation of PFS was demonstrated compared to 3.4 months for PFS with single agent chemotherapy (HR = 0.48, 95% CI: 0.38-0.60) [5].

The efficacy and safety of a PARP inhibitor (olaparib) as a maintenance treatment for platinum-sensitive recurrent ovarian cancer were studied in clinical SOLO2 clinical trial and Study19 clinical studies [6,7]. The SOLO2 trial is a randomized phase III trial of platinum-sensitive recurrent ovarian cancer with a germinal BRCA mutation. In the SOLO2 clinical trial, bevacizumab-free chemotherapy is given in advance of four or more courses. To investigate maintenance therapy for patients with a complete response (CR) or partial response (PR), cases were randomly assigned 2: 1 to the olaparib group (300 mg twice daily, oral tablet) and the placebo group. The median PFS for the olaparib arm was 19.1 months, significant prolongation of PFS was shown compared to 5.5 months in the placebo group (HR=0.30, 95% CI: 0.22-0.41) [6].

Study 19 is a randomized phase II study of platinum-sensitive recurrent serous ovarian cancer. To investigate maintenance therapy for patients who have had prior treatment with chemotherapy containing a platinum drug for two or more regimens and obtained a CR or PR with four or more prior cycles of chemotherapy, patients were randomly assigned to receive olaparib (400 mg twice daily, oral capsules) or placebo. The median PFS in the olaparib group was 8.4 months, indicating a significant increase in PFS compared to 4.8 months in the placebo group (HR=0.35, 95% CI: 0.25-0.49) [7].

A subgroup analysis of germinal BRCA mutation-positive patients showed a median PFS of 11.2 months in the olaparib group, which significantly increased PFS compared to 4.1 months in the placebo group (HR = 0.17, 95% CI: 0.09). -0.31) [7]. Analysis of patients with germinal BRCA wild-type/BRCA mutations of unknown significance showed a median PFS of 8.3 months in the olaparib group, indicating a significant increase in PFS compared to 5.5 months in the placebo group (HR = 0.50, 95% CI: 0.29-0.82) [7]. In addition, 13% of the olaparib maintenance therapy group continued olaparib maintenance therapy without progression for more than 5 years [7].

Bevacizumab showed an additional antitumor effect on initial treatment of ovarian cancer, platinum-sensitive relapse and platinum-resistant relapsed ovarian cancer. Treatment with olaparib improved PFS as a maintenance treatment for platinum-sensitive recurrent ovarian cancer. However, treatment with both drugs did not show prolonged OS. As characteristic serious adverse events resulting from treatment with bevacizumab: gastrointestinal perforation, thromboembolism, hypertension, delayed wound healing, bleeding, proteinuria, fistula, myelosuppression, infection, congestive heart failure, reversible retro leukoencephalopathy syndrome, shock, anaphylaxis, interstitial pneumonia, thrombotic micro Angiopathy has been reported.

The incidence of gastrointestinal perforation in a phase II study of ovarian cancer conducted overseas was 11% (5/44), and the study was discontinued due to its higher frequency than other carcinomas. A history of three regimens was reported as a significant risk factor for gastrointestinal perforation [8]. According to GOG218 clinical trial, patients with bowel obstruction and patients with a history of radiation therapy to the abdomen and pelvis were set

as exclusion criteria. The incidence of gastrointestinal adverse events (perforation, fistula, and bleeding) was 3.4% in the bevacizumab group and more frequent than in the placebo group (1.7%). History of treatment for inflammatory bowel disease, especially intestinal resection at the time of initial surgery, was a risk factor for gastrointestinal perforation [9].

When using bevacizumab in clinical practice, selection criteria for past clinical trials (PS 0-2, with appropriate bone marrow, liver, and kidney function), patients who meet the exclusion criteria (intestinal obstruction symptoms, history of abdominal/pelvic radiation therapy, abscess, surgery performed within 28 days, bleeding tendency, uncontrolled hypertension, history of myocardial infarction and unstable angina within 6 months, NYHA Grade 2 or higher heart failure, cerebrovascular disease within 6 months, clinically significant proteinuria), patients with little prior chemotherapy, patients without gastrointestinal complications; these patients were carefully selected, appropriate adverse event monitoring is required.

n the SOLO2 clinical trial using olaparib tablets, which were approved in Japan, Nausea (76%), anemia (43%), fatigue (38%), vomiting (37%), diarrhea (33%), asthenia (31%), dysgeusia (28%), headache (25%), Abdominal pain (24%), loss of appetite (22%), and constipation (21%) have been reported as the adverse events of olaparib 6). Grade 3 or higher anemia is observed in 20% of subjects, prior to and during the administration of olaparib, periodic blood tests should be performed to closely monitor the condition of the patient. Grade 3 or higher adverse events rarely occur in treatment with olaparib. Nausea and vomiting occur frequently, impairing the patient's QOL, as a result, treatment motivation is diminished, and treatment completion rates are adversely affected. Therefore, when olaparib is administered, sufficient measures are required for adverse events such as nausea and vomiting. In the treatment of several cancer types including ovarian cancers, the "oncogene test with an oncogene companion diagnosis" is already being performed as a standard test using cancer tissue to detect one or several gene mutations [10].

Conclusion

To date, only two molecular targeted drugs have been used in gynecological cancers. In ovarian cancer, combinations of PARP inhibitors with immune checkpoint inhibitors and/or VEGF signal inhibitors are being examined, and the results of these studies suggest that pharmacotherapy for ovarian cancer will change significantly in the next few years.

Footnote

The materials (manuscript and figures) are original research, has not been previously published and has not been submitted for publication elsewhere while under consideration.

Conflict of interest

All authors report no conflict of interest.

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