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Editorial

How to start niraparib in real-world Asian ovarian cancer patients?

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- See the article "Phase 2 single-arm study on the efficacy and safety of niraparib in Japanese patients with heavily pretreated, homologous recombination-deficient ovarian cancer" in volume 32, e16.
- See the article "Phase 2 single-arm study on the safety of maintenance niraparib in Japanese patients with platinum-sensitive relapsed ovarian cancer" in volume 32, e21.

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Poly (ADP-ribose) polymerases (PARPs) inhibitors are the current standard treatment for ovarian cancer along with platinum-based chemotherapy.

Niraparib has proven to have clinical activity as a maintenance therapy in newly diagnosed ovarian cancer (PRIMA study) and platinum-sensitive recurrent ovarian cancer (NOVA study) after platinum-based chemotherapy as well as more than the fourth-line recurrence therapy in recurrent ovarian cancer (QUADRA study) [1-3].

Niraparib monotherapy in the QUADRA study showed response rates of 27% and 26% in BRCA-mutated platinum-resistant recurrent disease and homologous recombination deficiency (HRD)-positive platinum-sensitive recurrent disease, respectively [3]. While most PARP inhibitors have been studied only in BRCA mutant ovarian cancer, the clinical outcomes of niraparib in HRD-positive and BRCA wild-type ovarian cancer compared to the other PARP inhibitors are promising. The efficacy of niraparib in HRD-positive and BRCA wild-type of ovarian cancer was also consistent. However, in terms of toxicity, grade ≥3/4 thrombocytopenia occurred in 42% of patients in the QUADRA study and 33.8% of patients in the NOVA study [2,3]. Therefore, individual doses were identified by adjusting the dose level through dose modification during treatment irrespective of the dose findings in the phase 1 study [4].

Based on the exploratory analysis of the NOVA study, the PRIMA study was amended to introduce the individualized starting dose (ISD) based on baseline body weight and platelet counts during the study. For patients with a body weight <77 kg or platelet counts <150,000/mL at baseline, 200 mg was used as the starting dose. Based on a retrospective analysis of the PRIMA study, this ISD did not compromise the efficacy of niraparib in first-line maintenance therapy in the PRIMA study [5].

However, in case of Asian patients there was no chance to participate in clinical trials of niraparib, and so it is necessary to evaluate whether this ISD is applicable to Asian ovarian cancer patients and whether niraparib's efficacy is consistent, especially in HRD-positive Asian ovarian cancer patients. In this issue, Okamoto et al. [6] evaluated clinical outcomes of niraparib in HRD-positive platinum-sensitive recurrent ovarian cancer as more than

fourth-line therapy and Takehara et al. [7] evaluated the safety of niraparib at a starting dose of 300 mg (fixed starting dose) as a maintenance therapy in Japanese patients with platinum-sensitive, recurrent ovarian cancer.

The response rate of niraparib monotherapy was 35% (17.7%–55.8%) in Japanese HRD-positive platinum-sensitive recurrent ovarian cancer, similar to that of the QUADRA study [6]. However, the frequency of dose reduction and interruption occurred at 75% and 70%, respectively, which was relatively higher than that of the QUADRA study [6]. This is thought to be because ISD was not applied to Japanese ovarian cancer patients with a relatively low average body weight. As maintenance therapy, Takehara et al. [7] reported that 14 of 19 patients (73.6%) reduced the dose to 200 or 100 mg at the start of cycle 2 and 14 of 19 patients (78.9%) interrupted niraparib in 30 days. The incidence of grade ≥3 thrombocytopenia was lower than the incidence in patients with body weight <58 kg in the NOVA trial. However, it is thought to be due to early dose modification and a short follow-up period. At the time of the data cutoff, 14 patients (73.7%) started the second cycle, and only 5 (26.3%) started the third cycle, which is shorter than 4 months at the end of dose adjustment in the NOVA study [7]. It is necessary to analyze whether additional dose adjustment occurred during subsequent cycles and whether further safety issues occurred during the maintenance period because relatively low average body weight of ovarian cancer patients. Therefore, long term follow-up studies about real-world safety and efficacy of niraparib maintenance therapy in Asian patients are needed.

Recently, a randomized double-blind phase 3 trial (NORA) for the ISD of niraparib maintenance treatment in platinum-sensitive recurrent Chinese ovarian cancer patients was reported. In the trial, grade ≥3 thrombocytopenia occurred in only 11.3%, which relatively low compared to 21.3% of the subgroup of ISD in the RIMA study [5]. Predictive risk factors for thrombocytopenia such as mean body weight of the enrolled patients and detailed data of mean dose intensity need to be analyzed [8].

Actually, this hematologic toxicity of the PARP inhibitor originates from the PARP trapping potency of the PARP inhibitor [9]. This PARP trapping potency is variable among PARP inhibitors and is known to affect the dose-limiting toxicity (DLT) of PARP inhibitors. Niraparib has high PARP trapping compared to olaparib. In a phase 1 dose escalation study, the maximum tolerated dose (MTD) of niraparib was determined to be 300 mg based on 21 days of DLT evaluation [10]. There was no occurrence of DLT in the first stage with 10 patients in the 300 mg group. However, for an additional 40 patients in a 300 mg dose expansion cohort, 33% of patients needed to reduce the dose due to hematologic toxicity in a subsequent second cycle [10]. The cumulative hematologic toxicity of continuous maintenance therapy may be accumulated during treatment. Therefore, after the determination of MTD based on the phase 1 clinical trial, which is determined based on short-term safety, additional dose finding analysis is needed in the course of further clinical trials. In the case of talazoparib, the single dose MTD was 1 mg [11]. However, in the multidose assessment, PARP inhibition of PBMC occurred when the dose of talazoparib was 0.6 mg or more according to the results of serial evaluation of PBMC PARP inhibition [11].

Quality of life (QOL) including safety as well as efficacy have been identified as an important issue in long-term maintenance therapy in recurrent ovarian cancer. Previous maintenance chemotherapy including paclitaxel monotherapy, nintedanib, etc., showed limited clinical outcomes because of the detrimental effect on QOL by cumulative toxicities and loss of

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chemotherapy holiday, resulting in no improvement of overall survival by the confounding effect of subsequent treatment.

In addition to safety, it is necessary to analyze the efficacy of ISD in Asian ovarian cancer patients. According to the QUADRA study, in the case of ovarian cancer with HRD-negative/unknown status, the response rate of niraparib was only 19% in the platinum-sensitive recurrent state [3]. Hazard ratios of progression free survival in maintenance niraparib therapy in HRD-negative and unknown ovarian cancer was only 0.68 and 0.85, respectively, in the PRIMA study [1]. Ovarian cancer with HRD-negative/unknown accounted for 51.8% of all ovarian cancer patients in the PRIMA study and 49.1% in the NOVA study [1,2]. Therefore, the efficacy of niraparib maintenance therapy may vary depending on the proportion of HRD-positive patients among platinum-sensitive ovarian cancer patients. The ethnic differences in molecular genetic status ovarian cancer patients could affect the clinical outcome of treatment. The AGO-OVAR 16 pazopanib maintenance study suggested that the uneven distribution of the BRCA mutation group in Asian ovarian cancer patients may affect the different clinical outcomes of pazopanib therapy compared to that of Western patients [12]. Therefore, to apply niraparib maintenance therapy to all platinum-sensitive patients, it is also necessary to analyze the proportion of HRD-positive patients among Asian platinum-sensitive ovarian cancer patients, considering the current limited availability of the Myriad HRD test. In addition, it may be necessary to evaluate whether the correlation between BRCA mutation and HRD score is consistent in Asian patients. Recently, it was reported that the epidemiologic data of Korean BRCA-mutated ovarian cancer may not be the same as that of the Western type [13].

In conclusion, PARP inhibitors have opened a new era in ovarian cancer treatment. However, there are some limitations to apply niraparib therapy to Asian ovarian cancer patients. Future studies of the molecular and genetic characteristics of Asian ovarian cancer patients and real-world long-term safety data should be considered.

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