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Age Is a Risk Factor for Olaparib Dose Modification and Discontinuation in Patients With Ovarian Cancer

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Abstract. *Background/Aim: Olaparib, a poly (ADP-ribose) polymerase inhibitor, is widely used as maintenance therapy for ovarian cancer. Dose modification, such as dose reduction and treatment interruption, are frequently performed to manage adverse events (AEs) of olaparib. By identifying patients at high risk for dose modification before administration, interventions related to appropriate control of AEs can be implemented. This study aimed to evaluate risk factors of olaparib dose modification and its clinical usefulness. Patients and Methods: Sixty patients with ovarian cancer who received olaparib were included in this retrospective cohort study. Associations between patients' characteristics and dose modification were evaluated by multivariate logistic regression analysis. We also examined whether risk factors of dose modification were associated with treatment discontinuation due to AEs. Results: Twenty-five (41.7%) patients required dose modification. Patients who required dose modification were significantly older (p=0.018) and tended to be more underweight (p=0.078) than those who did not require dose modification. In multivariate analysis, increasing age was significantly associated with dose modification (odds ratio=1.056; 95% confidence interval=1.002-1.112; p=0.034). The optimal cutoff of age as a risk factor for dose modification, calculated from receiver operating characteristic curves, was 65.0 years. Patients aged 65.0 years and older were significantly more likely to discontinue olaparib owing to AEs (p=0.0437). Conclusion: Age is a risk factor of olaparib dose modification due to AEs. Older patients, who frequently require dose modification, are more likely to discontinue olaparib, suggesting that strict management of AEs is particularly necessary in this patient group.*

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The therapeutic approach to advanced ovarian cancer has undergone a considerable change with the advent of poly (ADP-ribose) polymerase (PARP) inhibitor therapy. Olaparib, a PARP inhibitor, has proven effective as a maintenance therapy in the initial treatment for advanced ovarian cancer, as well as for recurrent disease, and is currently used in clinical practice as standard care (1-4).

When chemotherapeutic agents are administered to patients, their adverse events (AEs) must be managed appropriately. Dose modification (dose reduction or treatment interruption) of chemotherapeutic agents are performed as appropriate in clinical practice for the purpose of managing AEs. Olaparib dose modification is also required to manage AEs, and its frequency has been reported to be 45% in patients with recurrent platinum-sensitive ovarian cancer with BRCA DNA repair-associated (*BRCA*) gene mutations (5).

Predicting in advance which patients are at high risk for requiring olaparib dose modification may help clinicians to manage AEs appropriately. Consequently, olaparib might be administered more safely to patients with ovarian cancer. Furthermore, avoiding unnecessary dose modification by predicting the risk of dose modification may lead to preserving the relative dose intensity (RDI) of chemotherapeutic agents, thus maintaining therapeutic efficacy. In fact, several reports have suggested that dose modification of chemotherapeutic agents reduces therapeutic efficacy (6-8). Adhering to the prescribed dose and avoiding unnecessary dose modification when administering chemotherapeutic agents is recommended.

There have been several reports on risk factors associated with dose modification of chemotherapeutic agents. The presence of thrombosis and postoperative residual tumor have been reported as risk factors of dose modification for

platinum and taxane combination therapy in ovarian cancer (9). In addition, when using niraparib, a PARP inhibitor, patients with ovarian cancer weighing less than 58 kg were at a higher risk of dose modification (10). Determining risk factors of olaparib dose modification would enable clinicians to provide safer and more effective treatment to patients with ovarian cancer, but as far as we are aware, no such study has been reported to date, and the risk factors of olaparib dose modification remain unknown.

In the present study, we evaluated the risk factors of olaparib dose modification and its clinical usefulness. We conducted a retrospective study in patients with ovarian cancer who were treated with olaparib.

Patients and Methods

Patients and study design. The Institutional Review Board of Saitama Medical University International Medical Center approved this single institution-based, retrospective cohort study (reference number: 2022-112). Informed consent was waived because of the retrospective nature of this study. The procedures of this study were carried out in accordance with the Declaration of Helsinki. Patients who were diagnosed histologically with epithelial ovarian cancer (EOC), fallopian tube cancer, or peritoneal cancer, who received maintenance therapy with olaparib from March 2018 to March 2022, were included in this study. The criteria for inclusion in this study were as follows: (i) patients who were older than 18 years old at the time of diagnosis; and (ii) patients who were diagnosed with epithelial ovarian, fallopian tube, or peritoneal cancer. The criteria for exclusion from this study were as follows: (i) patients with malignancies other than EOC; and (ii) patients whose clinical data available for analysis were insufficient.

Treatment and evaluation of adverse events. Olaparib was administered orally each day at a dosage of 600 mg. Olaparib dose modification was implemented according to the discretion of the attending physician to manage AEs, such as grade 3 hematological and non-hematological toxicities. In cases where AEs were unmanageable, the attending physician made the decision to discontinue olaparib. AEs were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (11).

Statistical analysis. Continuous variables are expressed as the mean±standard deviation. Patients were categorized according to whether they required dose modification. Patients' characteristics and the type and incidence of AEs in each group were compared. Chi-square test or Fisher's exact test were used for the comparisons of categorical variables. Multivariate logistic regression analysis was performed to estimate the odds ratio (OR) with 95% confidence intervals (CIs) for dose modification. The optimal cutoff values for age and weight for dose modification was calculated based on the Youden index from receiver operating characteristic (ROC) curves (12). The patients were divided into two groups using cutoff values, and the incidence of treatment discontinuation and clinically significant adverse event (CSAE) were compared between both groups. CSAE was defined as (i) grade 3-4 AEs, or (ii) AEs resulting in dose reduction, treatment interruption, or discontinuation (13). Statistical significance was defined as $p<0.05$. Statistical analysis was performed using JMP Pro 13 software (JMP Pro 13; SAS Institute, Cary, NC, USA).

Table I. *Patients' characteristics (n=60).*

Characteristic		Value
Age (years)	Mean±SD	60.9±11.1
BW (kg)	Mean±SD	54.0±10.8
BMI (kg/m^2)	Mean±SD	22.0±4.1
ECOG PS, n (%)	0	60 (100%)
	≥1	0 (0%)
FIGO stage, n (%)	I/II	11 (18.3%)
	III/IV	49 (81.7%)
Histological type, n (%)	HGSC	47 (78.3%)
	Non-HGSC	13 (21.7%)
Primary cytoreductive surgery, n (%)	Yes	27 (45%)
Interval cytoreductive surgery, n (%)	Yes	33 (55%)
Residual disease after surgery, n (%)	<1 cm	44 (73.3%)
	≥1 cm	16 (26.7%)
Previous chemotherapy regimens, n (%)	1	13 (21.7%)
	2	32 (53.3%)
	≥3	15 (25.0%)
Tumor treatment status, n (%)	Primary	12 (20.0%)
	Recurrent	48 (80.0%)
BRCA status, n (%)	Mutation	15 (25.0%)
	Wild-type	2 (3.0%)
	Unknown	43 (72.0%)
Comorbidity, n (%)	Hypertension	7 (11.7%)
	Diabetes mellitus	4 (6.7%)
	Thrombosis	12 (20.0%)

BW: Body weight; BMI: body mass index; *BRCA*: BRCA DNA repair-associated gene; ECOG: PS Eastern Cooperative Oncology Group performance status; FIGO: International Federation of Gynecology and Obstetrics; HGSC: high-grade serous carcinoma.

Results

Patient inclusion and characteristics. From March 2018 to March 2022, olaparib was administered to 62 patients who were diagnosed with EOC. One patient was excluded from this study because of failure to meet the eligibility criteria, and one patient was excluded owing to a lack of sufficient clinical data for analysis. Consequently, 60 patients were considered eligible and included in this study (Figure 1). The median follow-up was 20.0 months (interquartile range=14.0-30.0 months). Table I shows a detailed overview of the patients' characteristics. The mean age of the patients was 60.9±11.1 years. The mean weight of the patients was 54.0±10.8 kg. A total of 81.7% of the patients had stage III or IV ovarian cancer. In addition, 20% of the patients received olaparib at the time of initial treatment and 80% at the time of recurrence. A total of 25% of the patients had *BRCA* mutations, and the others had no mutations or unknown.

Dose modification and adverse events profile. The patients were categorized into groups with and without dose modification. Dose modification was required in 25 out of 60 (41.7%) patients. Table II shows the type and incidence

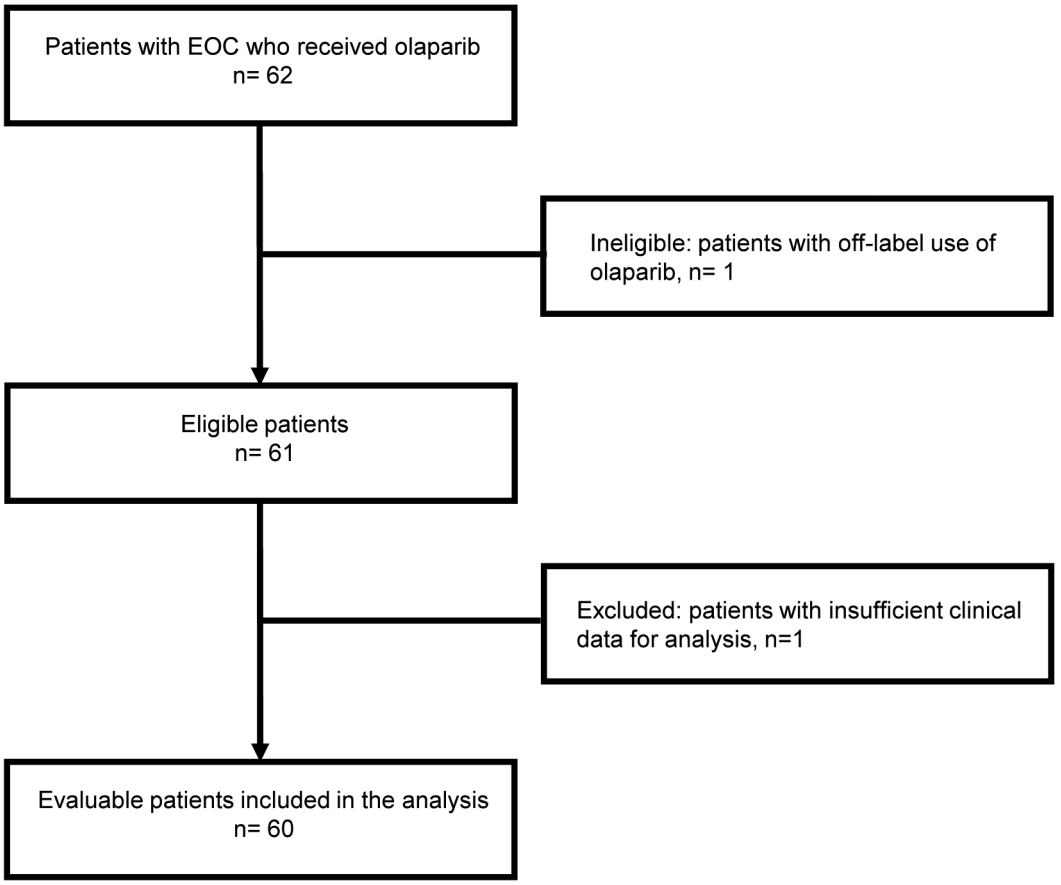

Figure 1. *Patient inclusion flowchart. Sixty-two patients with epithelial ovarian cancer (EOC) received olaparib. Of these, one patient was excluded because of off-label use of olaparib, and one patient was excluded because of insufficient clinical data for the analysis. Therefore, 60 patients were included in this study.*

of AEs in each group. The incidence of grade ≥3 anemia and nausea was particularly high in patients who required dose modification compared with those who did not.

Dose modification and patients' characteristics. We examined whether clinical parameters, such as age, weight, body mass index, treatment status, and comorbidities, were associated with dose modification. Patients who required dose modification were significantly older and tended to be underweight compared with those who did not require dose modification (p=0.018 and p=0.078, respectively, Table III). No other clinical parameters were significantly associated with dose modification. In addition, we examined the association between dose modification and patients' characteristics in the multivariate analysis. Increasing age was significantly associated with dose modification (OR=1.056, 95% CI=1.002-1.112; p=0.034, Table IV).

Association of treatment discontinuation with age and body weight. We calculated the optimal cutoff values for age and weight for dose modification based on the Youden index from ROC curves. The optimal cutoff value for age was 65.0 years, with a sensitivity of 64.0% and a specificity of 64.6%. The area under the curve (AUC) was 0.687 (Figure 2A). The optimal cutoff value for weight was 48.0 kg, with a sensitivity of 44.0% and a specificity of 76.0%. The AUC was 0.615 (Figure 2B). When we compared patients separately by the cutoff value, patients aged 65.0 years and older had significantly higher rates of treatment discontinuation and CSAE (p=0.043 and p=0.0018, respectively, Figure 3A). On the other hand, when we compared by the cutoff values for weight, there was no significant difference in the incidence of treatment discontinuation or CSAE between the two groups (p=0.712 and p=0.152, respectively, Figure 3B).

Discussion

In this study, we found that age was a risk factor of olaparib dose modification. Older patients with ovarian cancer were more likely to require dose modification, and in particular,

Table II. *Adverse event profile according to the dose modification status.*

	Patients without dose modification (n=35)		Patients with dose modification (n=25)	
Adverse event	All grades	Grade ≥3	All grades	Grade ≥3
Anemia	27 (77.1)	1 (2.9)	22 (88.0)	13 (52.0)
Neutropenia	10 (28.6)	0 (0)	12 (48.0)	3 (12.0)
Thrombocytopenia	17 (48.6)	0 (0)	14 (56.0)	1 (4.0)
Nausea	20 (57.1)	1 (2.9)	14 (56.0)	2 (8.0)
Vomiting	1 (2.9)	0 (0)	3 (12.0)	0 (0)
Decreased appetite	7 (20.0)	0 (0)	9 (36.0)	1 (4.0)
Fatigue	18 (51.4)	3 (8.6)	18 (72.0)	2 (8.0)
Diarrhea	2 (5.7)	0 (0)	3 (12.0)	0 (0)
Dysgeusia	6 (17.1)	0 (0)	5 (20.0)	0 (0)

Data are shown as n (%). Dose modification means dose reduction or treatment interruption of olaparib.

Table III. *Dose modification due to adverse events of olaparib and patients' characteristics.*

		Dose modification		
Characteristic		Without (n=35)	With (n=25)	*p*-Value
Age (years)	Mean±SD	58.1±10.7	64.8±10.4	0.018
BW (kg)	Mean±SD	56.1±11.4	51.1±9.3	0.078
BMI (kg/m^2)	Mean±SD	22.2±4.5	21.6±3.6	0.579
FIGO stage, n (%)	I/II	8 (22.9)	3 (12.0)	0.332
	III/IV	27 (77.1)	22 (88.0)	
Histological type, n (%)	HGSC	26 (74.3)	21 (84.0)	0.528
	Non-HGSC	9 (25.7)	4 (16.0)	
Residual disease after surgery, n (%)	<1 cm	26 (74.3)	18 (72.0)	0.999
	≥1 cm	9 (25.7)	7 (28.0)	
Previous chemotherapy regimens, n (%)	1	8 (22.9)	5 (20.0)	0.308
	2	16 (45.7)	16 (64.0)	
	≥3	11 (31.4)	4 (16.0)	
Tumor treatment status, n (%)	Primary	8 (22.9)	4 (16.0)	0.743
	Recurrent	27 (77.1)	21 (84.0)	
BRCA status, n (%)	Mutation	11 (31.4)	4 (16.0)	0.155
	Wild-type	2 (5.7)	0 (0)	
	Unknown	22 (62.9)	21 (84.0)	
Comorbidities, n (%)	Hypertension	2 (5.7)	5 (20.0)	0.117
	Diabetes mellitus	1 (2.9)	3 (12.0)	0.298
	Thrombosis	8 (22.9)	4 (16.0)	0.745

BW: Body weight; BMI: body mass index; *BRCA*: BRCA DNA repair-associated gene; FIGO: International Federation of Gynecology and Obstetrics; HGSC: high-grade serous carcinoma. Dose modification means dose reduction or treatment interruption of olaparib.

those aged 65 years and older had a significantly higher risk of treatment discontinuation due to AEs. Being underweight tended to be associated with olaparib dose modification, but this was not a risk factor for treatment discontinuation.

In this study, older patients frequently required dose modification owing to AEs from olaparib, which often led to treatment discontinuation. A few reports have examined the association between age and olaparib dose modification in

Table IV. *Multivariate analyses of the association between dose modification and patients' characteristics.*

Characteristic	Odds ratio	95% CI	*p*-Value
Age (years), continuous	1.056	1.002-1.112	0.034
BW (kg), continuous	0.959	0.904-1.017	0.146

CI: Confidence interval; BW: body weight.

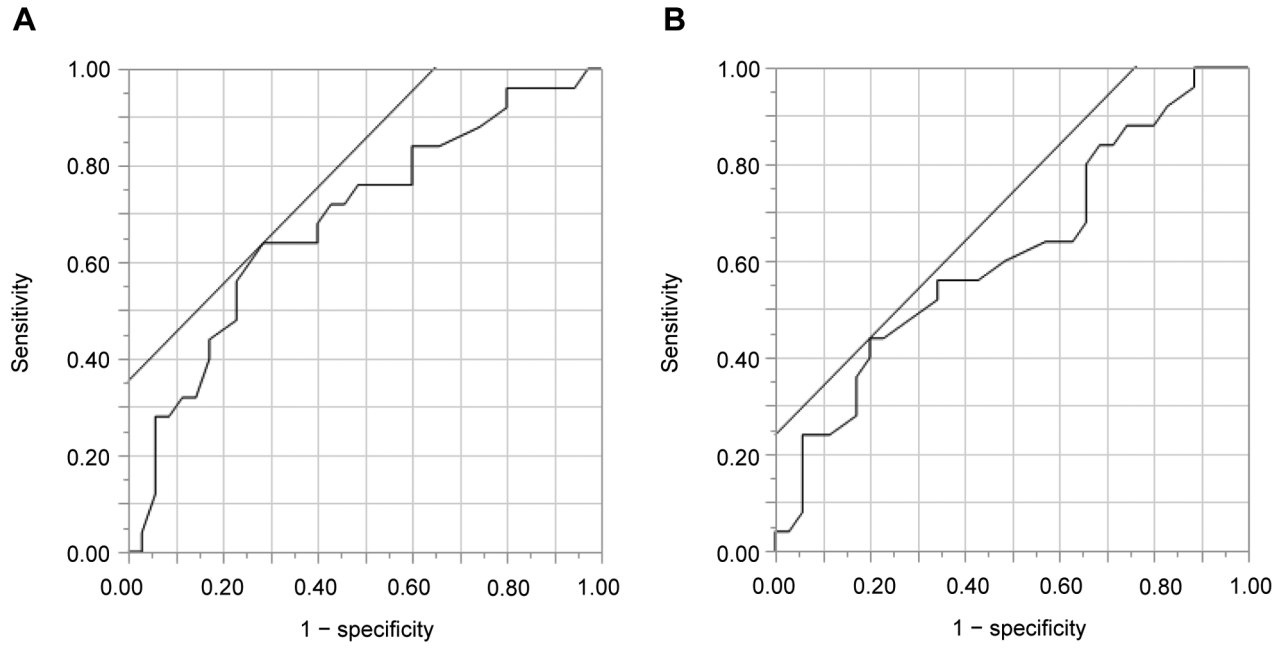

Figure 2. *Receiver operating characteristics (ROC) analysis of age and body weight predictive of the need for dose modification. (A) ROC curve of age for dose modification. The optimal cutoff value based on the Youden index was 65.0 years (sensitivity: 64.0%, specificity: 64.6%). The area under the curve was 0.687. (B) ROC curve of body weight for dose modification. The optimal cutoff value based on the Youden index was 48.0 kg (sensitivity: 44.0%, specificity: 76.0%). The area under the curve was 0.615.*

patients with ovarian cancer. The PAOLA-1 trial, which evaluated the benefit of maintenance therapy with olaparib and bevacizumab in the initial treatment of ovarian cancer, reported that the incidence of dose modification was not different between older and younger patients (14, 15). However, this report was on a study of olaparib therapy in combination with bevacizumab, not olaparib monotherapy as in our study. On the other hand, in a study of patients with ovarian cancer receiving olaparib monotherapy, Trillsch *et al*. reported no difference in patients who required dose modification between those older and younger than 65 years of age (5). However, this report was based on a limited population of patients with recurrent platinum-sensitive ovarian cancer with *BRCA* mutations. In our study, patients with initial treatment and patients without *BRCA* mutations were also included, and this difference in the clinical background of the included patients may be the reason for the different results between studies. To date, the risks of olaparib dose modification in older patients are unclear and require further investigation, but the present study suggests that more careful management of AEs is necessary in older patients.

In this study, being underweight tended to be associated with dose modification of olaparib therapy. To our knowledge, no report has yet demonstrated an association between olaparib dose modification and body weight. Berek *et al*. studied niraparib and its relationship with dose modification and body weight (10). They showed that patients who weighed <58 kg required more dose modification owing to AEs from niraparib and had more frequent treatment discontinuation than patients who weighed ≥77 kg. However, in our study of olaparib, being underweight did not lead to treatment discontinuation, although it tended to require dose modification. Our results suggest that olaparib is better tolerated than niraparib in underweight patients, but further studies on a larger number of patients are required.

To date, as far as we are aware, no reports have examined the risk factors of olaparib dose modification in patients with ovarian cancer. While dose modification is a cause of RDI reduction, Francis *et al*. reported that in their study, performance status (PS) was the only risk factor for an RDI ≤90% in multivariate analysis (16). In our study, PS was 0 for all patients, which caused difficulty in evaluating the relationship between PS and dose modification. On the other hand, age was not a predictive factor of a reduced RDI in their study (16). They only evaluated patients with *BRCA* mutations with recurrent platinum-sensitive disease, which is different from our study regarding the type of patients included. The difference in the clinical background of the patients may be the reason for the discrepancy between studies. However, our study included patients from a variety of clinical backgrounds, which may represent results in real-world practice.

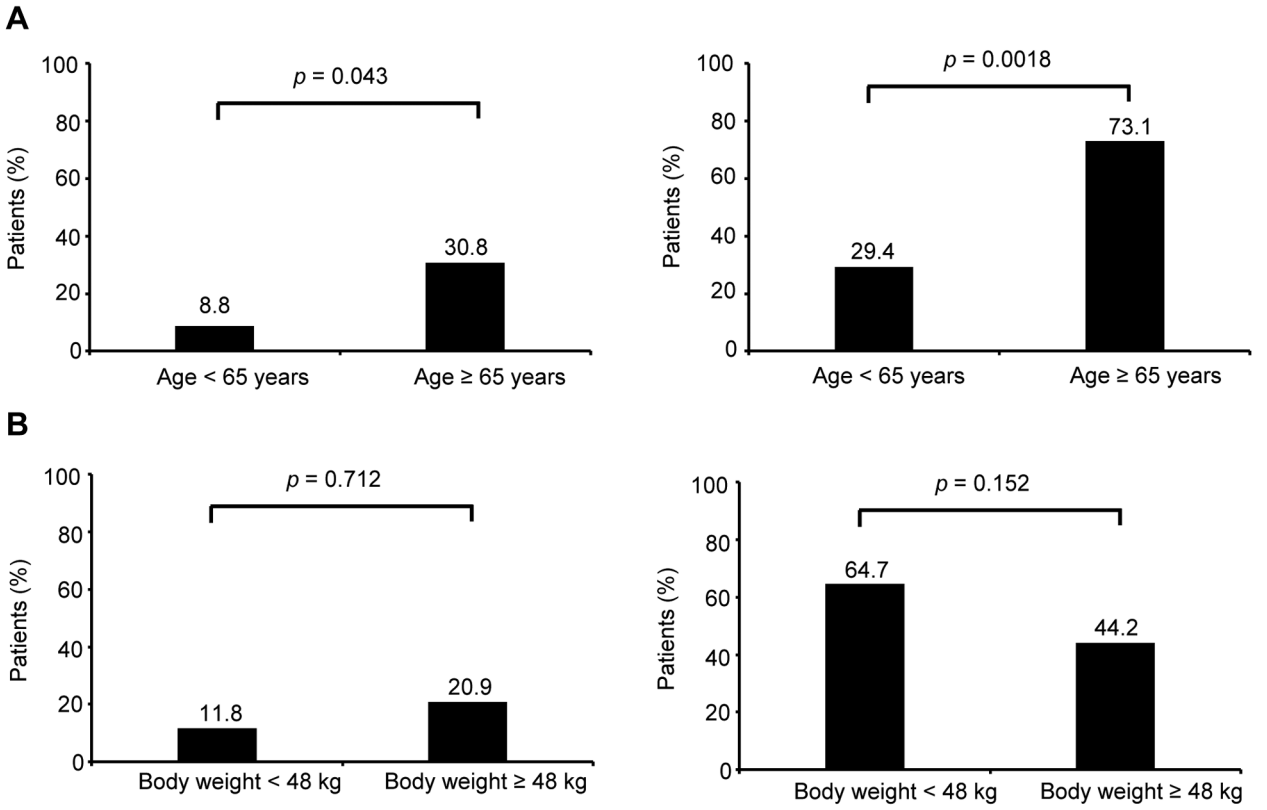

Figure 3. *Percentages of patients with treatment discontinuation owing to adverse events and clinically significant adverse events. (A) Treatment discontinuation according to age (≥65 and <65 years). (B) Treatment discontinuation according to body weight (≥48 kg and <48 kg).*

Study limitations. Firstly, this was a single-center study and retrospective in design. Secondly, the number of cases was relatively small. Thirdly, this study only evaluated the risk factors for dose modification and did not examine the relationship between dose modification and treatment efficacy. Little is known about the relationship between dose modification and the efficacy of olaparib therapy in patients with ovarian cancer. In the study by Francis *et al*. mentioned above, the authors compared the prognosis in patient groups with RDI >98%, 90-98%, and <90%, and reported no difference in progression-free and overall survival among the groups (16). However, their study only examined patients with *BRCA* mutations, who are more likely to benefit from olaparib, and whether a reduction in the RDI does not affect the prognosis in patients without *BRCA* mutations is unclear. Furthermore, in Francis *et al*.'s study, patients with an RDI <90% were evaluated collectively (16), but the effect of an even lower RDI on treatment efficacy is unknown. Therefore, whether olaparib dose modification affects the therapeutic efficacy is unknown. We will continue to study the effect of dose modification on treatment efficacy in a larger number of patients from various backgrounds at multiple institutions.

Conclusion

Dose modification is frequently performed to manage olaparib AEs. By identifying patients at high risk for dose modification before administration, interventions related to appropriate control of AEs can be implemented. Increasing age is a risk factor of olaparib dose modification due to AEs. Older patients are significantly more likely to discontinue treatment due to AEs, suggesting the need for particularly strict management of AEs in this patient group.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

HI designed the study and collected data. MS collected data. HY designed the study, performed the statistical analysis, and wrote the article. All Authors read and approved the final article.

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