

Factors Influencing Severe Hematologic Toxicity Following Niraparib Therapy in Patients With Ovarian Cancer

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Abstract

Background/Aim: Niraparib is a poly ADP ribose polymerase (PARP) inhibitor indicated for the maintenance therapy of ovarian cancer and the treatment of recurrent ovarian cancer. This study aimed to identify an indicator to predict severe hematologic toxicity after niraparib therapy.

Patients and Methods: We retrospectively included 32 patients with advanced ovarian cancer who were administered niraparib at Ogaki Municipal Hospital (Ogaki, Japan) between January 2020 and December 2024. Univariate analyses were performed to evaluate the relationship between the patients' baseline characteristics and the development of severe hematologic toxicity. Significant variables in the univariate analysis, as well as age, were entered into the multivariate logistic regression model. The optimal cutoff values for significant variables were determined using receiver-operating characteristic (ROC) curve analyses.

Results: Severe hematologic toxicity was independently associated with pre-treatment creatinine clearance (odds ratio=0.920; 95% confidence interval=0.823-0.998; $p=0.045$). The areas under the ROC curves of creatinine clearance at the time of the worst-grade hematologic toxicity before and during niraparib administration were assessed for their ability to predict severe hematologic toxicity. The area under the curves of creatinine clearance at the time of $\geq$ grade 3 hematologic toxicity during niraparib therapy showed high accuracy, with a value of 0.809 (95% confidence interval=0.659-0.958). The calculated cutoff value using the creatinine clearance curve was 47.0 ml/min.

Conclusion: Creatinine clearance is a risk factor for severe hematologic toxicity. A creatinine clearance value <47.0 ml/min may slightly increase the risk of this toxicity in patients with ovarian cancer receiving niraparib.

Keywords: Niraparib, ovarian cancer, severe hematologic toxicity, risk factor, odds ratio, creatinine clearance.

Introduction

Ovarian cancer (OC) is the leading cause of gynecological cancer-related deaths in women worldwide. The standard

of care for patients with newly diagnosed advanced-stage OC is surgical resection and first-line platinum-based chemotherapy, either alone or in combination with bevacizumab (1). Maintenance therapy with a poly



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ADP-ribose polymerase (PARP) inhibitor with or without bevacizumab is recommended for patients who achieve a complete or partial response to first-line therapy (2). Among PARP inhibitors, niraparib is an approved first-line maintenance therapy for patients with newly diagnosed advanced-stage OC, regardless of homologous recombination deficiency status.

Niraparib was approved in Japan in September 2020 for the indications of “maintenance therapy after first-line chemotherapy in epithelial ovarian cancer”, “maintenance therapy in platinum-sensitive recurrent epithelial ovarian cancer”, and “homologous recombination-deficient platinum-sensitive recurrent epithelial ovarian cancer” (3). These approvals were based on the results of the PRIMA trial (4), in which patients with advanced epithelial OC achieved complete/partial responses to first-line platinum-based chemotherapy, as well as on those of the NOVA SCIENCE PUBLISHERS (5) and QUADRA (6) trials in patients with recurrent epithelial OC. In addition, Japanese clinical trials conducted by Takehara *et al.* (7) and Okamoto *et al.* (8) contributed evidence leading to the approval of niraparib. These trials demonstrated significantly improved progression-free survival with niraparib compared to placebo (4-9).

The safety findings of niraparib were consistent with the known drug safety profile, with hematologic toxicity being the most common $\geq$ grade 3 treatment-emergent adverse event (AE) (4). However, in clinical practice, cases of sudden hematologic toxicity requiring hospitalization have been encountered; thus, hematologic toxicity is an AE that must be considered in niraparib treatment.

A population pharmacokinetic analysis reported slightly reduced niraparib clearance in patients with mild and moderate renal impairment compared with individuals with normal renal function (10). Renal failure and hypoalbuminemia may also be associated with niraparib-induced thrombocytopenia (11). Hashimoto *et al.* (12) suggested the serum creatinine ratio (the rate of increase in serum creatinine between baseline and after the start of niraparib therapy) as a potential marker for predicting severe hematologic toxicity after niraparib

therapy. However, the authors did not propose a specific value (borderline).

The incidence of OC increases rapidly after 40 years of age, with the highest incidence in patients in their 50s, followed by those in their 60s; therefore, many patients are elderly. Elderly individuals generally exhibit reduced renal function. Since niraparib is administered after chemotherapy with platinum agents, its metabolism and excretion may be affected. Therefore, specific indicators to predict severe hematologic toxicity after niraparib therapy may be useful for future treatment and for instructing patients on precautions to take in their daily lives.

This study aimed to develop an indicator for predicting severe hematologic toxicity after niraparib therapy.

Patients and Methods

Patients and methods. We retrospectively identified 32 patients who were administered niraparib for OC at the Ogaki Municipal Hospital (Ogaki, Japan) between January 2020 and December 2024. Patient characteristics were extracted from anonymized patient records. Patient characteristics, estimated Ccr (according to the Cockcroft–Gault formula), and hematologic toxicity (thrombocytopenia, leukopenia, neutropenia, and anemia) were analyzed retrospectively using data collected from electronic charts and pharmacy service records. The most severe AE grades were determined according to the Common Terminology Criteria for Adverse Events, version 5.0 (13). The retrospective protocol of the study was approved by the Institutional Review Board of Ogaki Municipal Hospital (Ogaki, Japan; 20250227-21), which waived the requirement for informed consent because of the retrospective study design.

Assessment of risk factors for severe hematologic toxicity after niraparib administration. The patients were divided into two groups based on whether they had (16 patients) or had not (16 patients) developed severe hematologic toxicity. Severe hematologic toxicity was defined as $\geq$ grade 3 hematologic toxicity after niraparib administration. We compared patient age, height, body weight, and laboratory

test results before chemotherapy (serum albumin concentration or Ccr), performance status, and the presence or absence of hematologic toxicity from chemotherapy before niraparib administration between the two groups. We also explored the incidence of $\geq$ grade 3 hematologic toxicity (thrombocytopenia, leukopenia, neutropenia, and anemia) according to Ccr.

Niraparib administration. Niraparib is usually administered orally at a dose of 200 mg, once daily. However, adults weighing ≥ 77 kg with a platelet count of $\geq 150,000/\mu\text{l}$ before the first dose, were administered 300 mg niraparib once daily.

Statistical analysis. We evaluated the differences between the two groups using Fisher's exact probability test, as appropriate. We performed univariate analyses to evaluate the relationships between the patients' baseline characteristics and the development of severe hematologic toxicity. Factors showing significant differences in the univariate analysis, as well as age, were entered into the multivariate logistic regression model. We determined the optimal cutoff values for significant variables based on receiver-operating characteristic (ROC) curve analyses. Significance was defined as $p < 0.05$, and all statistical analyses were performed using EZR software (v1.30; Saitama Medical Center, Jichi Medical University, Saitama, Japan) (14).

Results

Patient characteristics. The patients' characteristics are shown in Table I. The median age was 65 years (range=46-85 years), and the median body weight was 49.4 kg (range=39-76.5 kg). Additionally, 21 of the 32 patients (65.6%) experienced $\geq$ grade 3 hematologic toxicity during chemotherapy before niraparib therapy.

Risk factors for severe hematologic toxicity after niraparib treatment. Table II and Table III show the results of the univariate and multivariate logistic regression analyses of the risk factors for the development of severe hematologic

Table I. Patient characteristics.

n	32
Patient demographics	
Age, years	
Median (range)	65 (46-85)
Height, cm	
Median (range)	154 (140-168)
Weight, kg	
Median (range)	49.4 (39-76.5)
Performance status	0 (0-1)
Indication 1/2/3	21/11/0
Laboratory test values before chemotherapy	
Albumin, g/dl	4.2 (3.2-4.8)
Aspartate aminotransferase, IU/l	22 (15-54)
Alanine aminotransferase, IU/l	17.5 (7-34)
Total bilirubin, mg/dl	0.5 (0.2-1)
Creatinine, mg/dl	0.66 (0.45-1.02)
Leukocyte count, /mm ³	4,075 (2,980-6,530)
Hemoglobin, g/dl	10.7 (8.6-13.5)
Platelet count, $\times 10^4/\text{mm}^3$	19 (11-29.4)
Neutrophil count, /mm ³	2,328 (1,079-3,713)
Grade 3 or higher hematologic toxicity during previous chemotherapy, n	21
Time from prior chemotherapy to niraparib, days	36 (21-62)

Indication 1: maintenance therapy after initial chemotherapy for ovarian cancer; Indication 2: maintenance therapy for recurrent ovarian cancer sensitive to platinum-based anticancer drugs; Indication 3: recurrent ovarian cancer with homologous recombination repair deficiency and sensitivity to platinum-based anticancer drugs.

toxicity after niraparib treatment. Patients with hematologic toxicity were grouped according to whether they did (16 patients) or did not (16 patients) develop $\geq$ grade 3 hematologic toxicity. Severe hematologic toxicity was independently associated with pre-treatment Ccr [odds ratio (OR)=15.7; 95% confidence interval (CI)=1.180-209.000; $p=0.037$].

The results of the ROC curve analysis showed an area under the curve for Ccr before niraparib administration of 0.809, indicating its high accuracy for detecting severe hematologic toxicity (95%CI=0.659-0.958). The cutoff value calculated using the Ccr curve was 59.8 ml/min. Using this cutoff value, the sensitivity and specificity of Ccr to detect $\geq$ grade 3 hematologic toxicity before niraparib administration were 75.0% and 75.0%, respectively (Figure 1).

Table II. Univariate logistic regression analysis of risk factors for niraparib treatment-related severe hematologic toxicity (Grades 3-4).

Factors	Odds ratio	95% Confidence interval	p-Value
Age	1.050	0.987-1.120	0.117
Height	0.933	0.836-1.040	0.214
Body weight	0.868	0.771-0.976	0.018*
Albumin	1.580	0.217-11.500	0.653
Aspartate aminotransferase	0.984	0.900-1.080	0.722
Alanine aminotransferase	0.892	0.795-1.010	0.072
Total bilirubin	44.6	0.497-4000.0	0.098
Creatinine clearance	0.937	0.891-0.985	0.011*
Leukocyte count	1.000	0.999-1	0.358
Neutrophil count	1.000	0.999-1.0	0.564
Platelet count	1.110	0.975-1.26	0.116
Hemoglobin	1.040	0.935-1.15	0.502
Indications	0.634	0.167-2.410	0.504
Time from last chemotherapy to niraparib administration	1.000	1.000-1.000	0.478
Presence or absence of hematologic toxicity from previous chemotherapy	1.200	0.274-5.250	0.809
Performance status	1.850	0.366-9.340	0.458

* $p < 0.05$.

Ccr cutoff during niraparib administration to predict severe hematologic toxicity. The area under the ROC curve of Ccr at the time of $\geq$ grade 3 hematologic toxicity was 0.859, demonstrating high accuracy for detecting severe hematologic toxicity (95%CI=0.731-0.987). The cutoff value calculated using the Ccr curve was 47.0 ml/min. Using this cutoff value, the sensitivity and specificity of Ccr to detect $\geq$ grade 3 hematologic toxicity during niraparib administration were 87.5% and 75.0%, respectively (Figure 2).

Incidence of hematologic toxicity due to differences in Ccr. Table IV shows the incidence of hematologic toxicity due to the differences in Ccr (47.0 ml/min). Grade 3 or higher thrombocytopenia was more frequently observed in patients with Ccr < 47.0 ml/min (six patients) than in those with Ccr > 47.0 ml/min (one patient) ($p=0.027$). The incidences of $\geq$ grade 3 leukopenia, neutropenia, and anemia did not differ significantly according to Ccr.

Ccr before treatment and at the time of the onset of worst-grade hematologic toxicity. The Ccr values before and during niraparib therapy in patients with $\geq$ grade 3 hematologic toxicity were 54.3 (33.7-101.7) ml/min and 37 (21-79) ml/min ($p=0.052$), respectively. In contrast, the values in

Table III. Multivariate logistic regression analysis of risk factors for niraparib treatment-related severe hematologic toxicity (Grades 3-4).

Factors	Odds ratio	95% Confidence interval	p-Value
Age	0.946	0.853-1.050	0.298
Ccr**, < 59.8 ml/min	15.700	1.180-209.000	0.037*
Body weight	0.902	0.783-1.040	0.153

* $p < 0.05$. **Pre-treatment-related Ccr. Ccr: Creatinine clearance.

those with $\leq$ grade 2 hematologic toxicity were 84.7 (46-132.6) ml/min and 75.5 (38-133) ml/min, respectively ($p=0.724$).

Discussion

In this study, we identified Ccr as a risk factor for severe hematologic toxicity following niraparib therapy. Although the study sample size was small, we suggest that Ccr < 47.0 ml/min may indicate a slightly increased risk of developing this toxicity in patients with OC receiving niraparib. Our findings also provide useful information for monitoring hematologic toxicity in patients with cancer receiving niraparib.

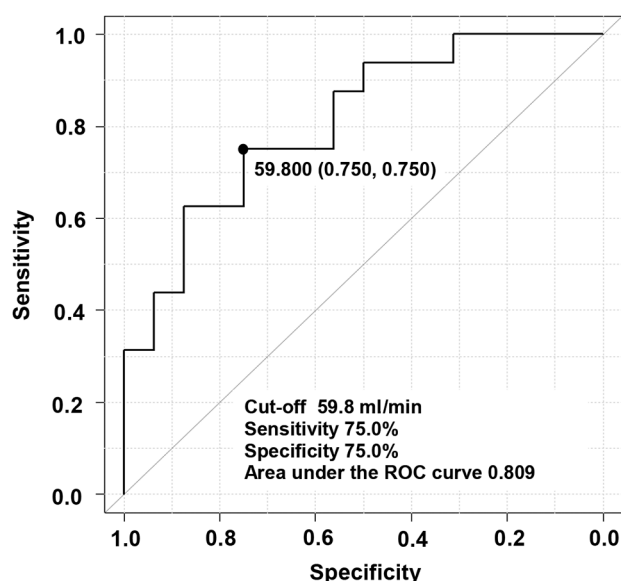


Figure 1. Area under receiver operating characteristic (ROC) curves for creatinine clearance. ROC curves from univariate logistic regression analysis to estimate the ability of creatinine clearance before niraparib administration to predict severe hematologic toxicity.

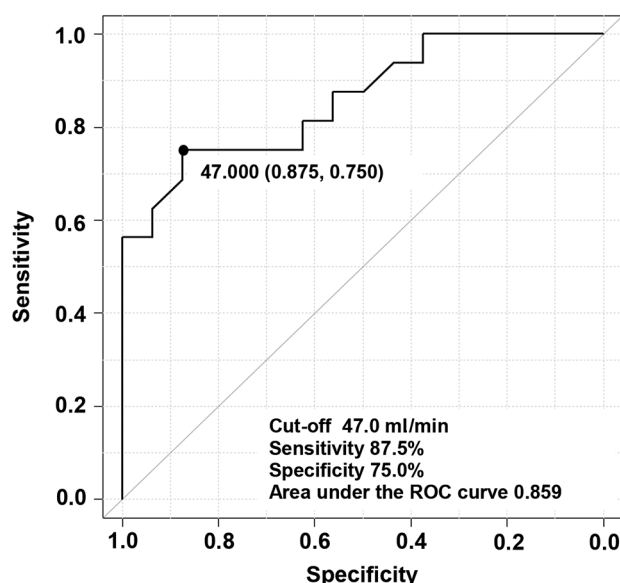


Figure 2. Area under receiver operating characteristic (ROC) curves for creatinine clearance. ROC curves for creatinine clearance at the time to estimate the ability of worst-grade hematologic toxicity during niraparib administration to predict severe hematologic toxicity.

Table IV. Incidence of hematologic toxicity due to differences in creatinine clearance (Ccr).

	≥Ccr** 47.0 (n=18)		<Ccr** (n=14)		p-Value (all grades)	p-Value (≥grade 3)
	All grades	≥Grade 3	All grades	≥Grade 3		
Thrombocytopenia	5	1	7	6	0.277	0.027*
Leukopenia	10	3	9	4	0.725	0.669
Neutropenia	12	3	10	4	1	0.669
Anemia	14	1	14	4	0.113	0.142

* $p < 0.05$. **Ccr at worst grade during niraparib treatment.

Moreover, our findings suggesting that the Ccr can be used as an indicator to predict severe hematologic toxicity after niraparib therapy are consistent with observations of Hashimoto *et al.* (12), who proposed the blood concentration of niraparib and serum creatinine ratio as potential markers for predicting severe hematologic toxicity after niraparib therapy.

In this study, patients who experienced ≥grade 3 hematologic toxicity tended to show a decrease in Ccr compared to that before treatment. Niraparib is a

substrate for renal multidrug excretion protein (MATE) 1 and MATE 2-K transporters, which excrete creatinine and other substances from the renal tubules into the urine (15). Niraparib increases serum creatinine levels, which may be related to the inhibition of MATE 1/2-K transporters (16). Therefore, the increase in serum creatinine levels caused by PARP inhibitors may represent an apparent increase in creatinine levels due to transporter inhibition and may not be related to a true decrease in the glomerular filtration rate (16, 17). Zibetti

Dal Molin *et al.* reported that despite the increase in serum creatinine levels during treatment and the subsequent significant decrease in calculated Ccr, the glomerular filtration rate estimated from renal scans was similar to the patients' baseline values (17). In other words, the results of this study based on Ccr estimated using the Cockcroft–Gault formula suggest that the decrease in Ccr after treatment initiation may be due to a spurious increase in creatinine levels.

However, in the population pharmacokinetic analysis, patients with mild (Ccr 60-90 ml/min) and moderate (30-60 ml/min) renal impairment showed slightly reduced niraparib clearance compared with individuals with normal renal function, which did not warrant dose adjustment (10).

Nevertheless, this does not indicate that these changes are unrelated to hematologic toxicity. Smith *et al.* suggested that renal failure and hypoalbuminemia may be related to the development of niraparib-induced thrombocytopenia (18). Additionally, a preliminary in vitro study demonstrated a concentration-dependent relationship between niraparib and direct toxicity in platelets. In the present study, we identified pre-treatment Ccr level as a risk factor for severe hematologic toxicity. In other words, moderate renal impairment is associated with severe hematologic toxicity.

Platinum-based chemotherapy affects renal function. Nakamura *et al.* reported that maintenance therapy in patients with platinum-sensitive advanced OC is likely to cause deterioration of renal function and underscored the need for careful administration (19). However, Donadio *et al.* reported that carboplatin, used as a prior treatment, had no toxic effects on glomerular and tubular function, either acutely or chronically, except for a transient increase in the urinary excretion of proteins and tubular enzymes (20). In the present study, the presence or absence of severe hematologic toxicity before treatment was not significantly associated with the incidence of the development of $\geq$ grade 3 hematologic toxicity. Therefore, prior treatment had no effect.

Body weight is a risk factor for thrombocytopenia (21). In the present study, body weight was a risk factor in the

univariate but not the multivariate analysis. This may be due to the low body weight of most of the patients in this study (median body weight, 49.4 kg). The median body weight in the QUADRA study was 70 kg, whereas the median body weight in Japanese patients in clinical practice is 48.7 kg, which is comparable to the patient population in the present study (6).

In this study, the cutoff value showed that the frequency of severe hematologic toxicity differed only for thrombocytopenia. Therefore, niraparib-induced bone marrow suppression affected platelets. Thrombocytopenia is caused by a reversible inhibition of megakaryocyte maturation and proliferation. The high frequency of thrombocytopenia during maintenance therapy may be due to its extensive tissue distribution. A basic study comparing the tissue concentrations of niraparib and the PARP inhibitor olaparib showed high bone marrow distribution of niraparib, which may affect bone marrow suppression (22).

Study limitations. First, we included a relatively small number of patients. However, our results showed good accuracy (area under the ROC curve 0.80-0.90), supporting the robustness of the findings. Second, we did not verify the relationships between the blood concentration of niraparib, renal function, and hematologic toxicity. Blood concentration of niraparib is also related to AEs (23), in which blood concentration is positively correlated with MATE1/2-K transporter inhibition (24, 25). Future studies should verify the effects of changes in the blood concentration of niraparib or the inhibition of MATE1/2-K transporters.

Conclusion

Common AEs associated with niraparib include bone marrow suppression, anemia, and thrombocytopenia. The results of this study indicate that Ccr during niraparib treatment can predict severe hematologic toxicity and identify patients requiring special attention when monitoring for AEs. Niraparib is a convenient drug that can be administered orally once daily; however, careful

observation is required for elderly patients and other patients with impaired renal function.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

MK contributed to the study design, collected and provided the data, is the principal author of the report, and is the guarantor of this article. SY, RM, MG, and EU contributed to the study design, reviewed the manuscript, and supervised the drafting of the report and submission process. All the Authors approved the final version of the manuscript.

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