PARP INHIBITORS-INDUCED NAUSEA AND VOMITING IN PATIENTS WITH GYNECOLOGIC CANCER (JASCC-CINV 2002) A PROSPECTIVE, OBSERVATIONAL, MULTICENTER STUDY

JASCC-CINV 2002

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ABSTRACT

Introduction: The incidence of nausea and vomiting caused by PARP inhibitors in the clinical trials were quite high. However, there are no recommendations for the antiemetic treatment for these oral anticancer agents. There remains an unmet clinical need for the control of nausea and vomiting with oral chemotherapy, especially molecular targeted agents.

Methods: Patients with gynecologic cancer who were scheduled to receive a PARP inhibitor were included. The primary outcome was the incidence of vomiting during the 21 days after starting PARP inhibitors. Data on PARP inhibitor-induced nausea and vomiting were collected from patient diaries over 21 days. The percentages of patients receiving antiemetic prophylaxis and PARP inhibitor-induced nausea and vomiting with and without prophylaxis were assessed.

Results: The patients were enrolled between January 2020 and March 2023. A total of 129 patients were evaluated. Of these patients, 28 (21.7%) received prophylactic antiemetics, taken internally for 21 days and 101 (78.3%) did not receive prophylaxis. The overall incidence of PARP inhibitors-induced vomiting, the primary outcome, was 16.3%. The incidence of vomiting in the group that did not receive antiemetic prophylaxis was 13.9% for the overall population, and 18.6% and 10.3% for olaparib and niraparib, respectively.

Conclusions: Olaparib and niraparib should be classified in the low emetogenic risk category because the incidence of emesis without antiemetic prophylaxis ranges from 10% to 30%. Therefore, prophylactic antiemetic therapy at the initiation of treatment may be unnecessary.

INTRODUCTION

Olaparib and niraparib, poly (ADP-ribose) polymerase (PARP) inhibitors, exhibit potent antitumor activity in ovarian cancer patients.

However, clinical trials have reported a considerable incidence of nausea and vomiting (CINV) associated with these agents.

Despite the lack of antiemetic guidelines for oral anticancer agents, managing nausea and vomiting induced by PARP inhibitors is crucial.

<u>This study aimed to investigate the incidence of nausea and vomiting caused by PARP inhibitors and the actual situation of antiemetic therapy in patients with gynecologic cancer.</u>

METHODS AND MATERIALS

Study design and patient selection

- This study was a prospective observational study conducted at 13 centers in Japan.
- We analyzed patients with ovarian cancer who were receiving olaparib or niraparib-containing anticancer chemotherapy for the first time between January 2020 and March 2023.
- Data were collected from the patient diaries. Patients filled out a diary daily from the start of therapy with PARP inhibitors for 21 days.

【Key eligibility criteria】
1) Age ≥ 20 years
2) Ability to keep an accurate patient diary
3) Provided written informed consent

【Key exclusion criteria】
1) Starting on a reduced dose of olaparib or niraparib
2) Nausea and vomiting requiring antiemetic treatment at enrollment

Primary endpoint

- The overall incidence of vomiting, including retching, during the entire evaluation period (0-21 days).

Secondary endpoints

- The incidence of nausea, significant nausea, anorexia, taste disturbance, fatigue, constipation, diarrhea, insomnia, and patient satisfaction (Significant nausea was defined as the "moderate" and "severe" categories).
- Adverse events were evaluated according to PRO-CTCAE and the CTCAE ver 5.0.

Statistical analysis

- Descriptive statistics: Patient characteristics, rate of CINV control, and treatment-related adverse events
- The impact of prophylactic antiemetics on vomiting, nausea, and significant nausea was assessed using a Cox proportional hazards regression model which incorporated age and age and previous experience of CINV as covariates.

Sample size

- **Baseline assumption:** Without anti-emetic prophylaxis, around 30% of patients would experience vomiting.
- **Expected clinically meaningful risk reduction:** Greater than 20% with anti-emetic therapy.
- **Ratio of patients with and without anti-emetic treatment:** 1:9 (Estimated as low as 10% of the total sample).
- **Calculated number of cases required to detect a 20% difference in vomiting rate:** 210.
- **Significance level:** One-sided at 2.5%.
- **Power:** 80% based on log-rank test, assuming proportional hazards.
- **Hazard ratio:** Estimated as the log of vomiting rate with anti-emetics divided by the log of vomiting rate without anti-emetics.
- **Planned total sample size:** 234 patients, considering a 10% dropout rate after follow-up.

Actual enrollment affected by COVID-19 pandemic outbreak, unable to achieve planned sample size, but enrolled as many patients as possible.

RESULTS

Figure 1. Trial profile

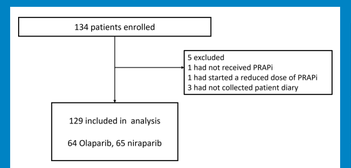


Table 1. Patients' characteristics

Characteristic	N = 129 n (%)
Age	
Median	62
IQR	54–71
Chemotherapy regimen	
Olaparib	42 (32.6%)
Olaparib+bevacizumab	22 (17.1%)
Niraparib	64 (49.6%)
Niraparib+pertuzumab+trastuzumab	1 (0.8%)
ECOG Performance Status	
0	120 (93.0%)
1	9 (7.0%)
Prophylactic antiemetic administration	
Yes	28 (21.7%)
No	108 (78.3%)
Motion sickness	
Yes	35 (27.1%)
No	93 (72.1%)
Unknown	1 (0.8%)
Morning sickness	
Yes	60 (46.5%)
No	49 (38.0%)
No experience of pregnancy	19 (14.7%)
Unknown	1 (0.8%)
Habitual alcohol consumption	
Yes	35 (27.1%)
No	93 (72.1%)
Unknown	1 (0.8%)
Previous experience of nausea and vomiting with chemotherapy	
Yes	63 (48.8%)
No	65 (50.4%)
Unknown	1 (0.8%)

Abbreviations
ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range

Table 2. Incidence of CINV for 21 days after the start of PARP inhibitors

PARPi	Groups	n (%) Vomiting	Nausea	Significant nausea
Overall	All (N=129)	21 (16.3%)	92 (71.3%)	42 (32.6%)
	With antiemetic prophylaxis (N=28)	7 (25.0%)	21 (75.0%)	10 (35.7%)
	Without antiemetic prophylaxis (N=101)	14 (13.9%)	71 (70.3%)	32 (31.7%)
Olaparib	All (N=64)	14 (21.9%)	52 (81.3%)	26 (40.6%)
	With antiemetic prophylaxis (N=21)	6 (28.6%)	16 (76.2%)	10 (47.6%)
	Without antiemetic prophylaxis (N=43)	8 (18.6%)	36 (83.7%)	16 (37.2%)
Niraparib	All (N=65)	7 (10.8%)	40 (61.5%)	16 (24.6%)
	With antiemetic prophylaxis (N=7)	1 (14.3%)	5 (71.4%)	0 (0%)
	Without antiemetic prophylaxis (N=58)	6 (10.3%)	35 (60.3%)	16 (27.6%)

Abbreviations, PARPi: poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitor

Figure 2. Event-free time

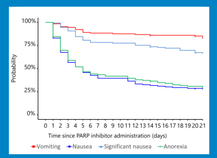


Figure 3. Prevalence rates of CINV

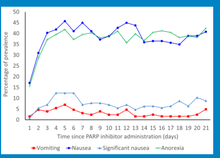
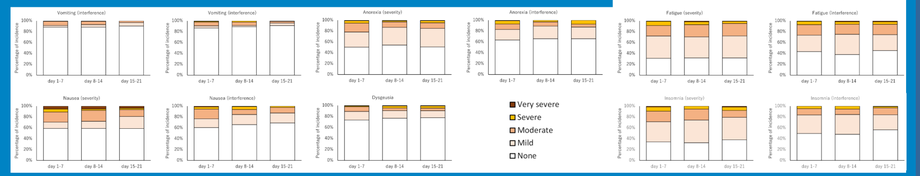


Table 3. The effect of prophylactic antiemetics on CINV

Outcomes		Univariable analysis HR	95% CI	*p*-Value	Multivariable analysis* HR	95% CI	*p*-Value
Overall	Vomiting	1.894	0.764–4.692	0.168	1.899	0.766–4.708	0.166
	Nausea	1.058	0.650–1.722	0.819	1.088	0.666–1.778	0.737
	Significant nausea	1.163	0.572–2.367	0.676	1.206	0.592–2.457	0.606
Olaparib	Vomiting	1.548	0.537–4.463	0.418	1.519	0.526–4.391	0.440
	Nausea	0.850	0.472–1.533	0.590	0.806	0.446–1.457	0.475
	Significant nausea	1.318	0.598–2.907	0.494	1.367	0.616–3.036	0.442
Niraparib	Vomiting	1.313	0.158–10.909	0.801	1.624	0.192–13.732	0.656
	Nausea	0.953	0.373–2.434	0.920	1.055	0.404–2.758	0.912
	Significant nausea**	0.001	0.000–6.274×10^{17}	0.773	0.001	0.000–5.067×10^{17}	0.768

Abbreviations, HR: Hazard ratio; 95% CI: 95% confidence intervalrange
*Covariates: age and previous experience of nausea and vomiting with chemotherapy
**The observed wide confidence intervals for the hazard ratios are attributable to the no incidence of significant nausea among patients using prophylactic antiemetics.

Figure 4. Changes over time in PRO-CTCAE



Percentage satisfied with their ability to live without the feeling nausea and vomiting

Overall study group: 85.9% (110/128)

Antiemetic prophylaxis: 88.9% (24/27)

Without Antiemetic prophylaxis: 86.9% (86/99)

DISCUSSION and CONCLUSIONS

Olaparib and niraparib, with the incidence of emesis without antiemetic prophylaxis ranging from 10% to 30% among patients, can be classified in the low emetogenic risk category, and prophylactic antiemetic therapy may be considered unnecessary at the time of treatment initiation.

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