Objective: Palonosetron is effective for the management of acute and delayed chemotherapy-induced nausea and vomiting (CINV). While emetogenic carboplatin-based chemotherapy is widely used to treat gynecologic cancers, few studies have evaluated the antiemetic effectiveness of palonosetron in this setting.

Methods: A multicenter, single-arm, open-label phase II trial was conducted to evaluate the safety and effectiveness of palonosetron in controlling CINV in patients with gynecologic cancer. Chemotherapy-naïve patients received intravenous palonosetron (0.75 mg/body) and dexamethasone before the infusion of carboplatin-based chemotherapy on day 1. Dexamethasone was administered (orally or intravenously) on days 2–3. The incidence and severity of CINV were evaluated using the patient-completed Multinational Association of Supportive Care in Cancer Antiemesis Tool and treatment diaries. The primary endpoint was the proportion of patients experiencing complete control (CC) of vomiting, with “no rescue antiemetic medication” and “no clinically significant nausea” or “only mild nausea” in the...
delayed phase (24–120 hours post-chemotherapy). Secondary endpoints were the proportion of patients with a complete response (CR: “no vomiting” and “no rescue antiemetic medication”) in the acute (0–24 hours), delayed (24–120 hours), and overall (0–120 hours) phases, and CC in the acute and overall phases.

Results: Efficacy was assessable in 77 of 80 patients recruited. In the acute and delayed phases, the CR rates the primary endpoint, were 71.4% and 59.7% and the CC rates, the secondary endpoint, were 97.4% and 96.1%, respectively.

Conclusion: While palonosetron effectively controls acute CINV, additional antiemetic management is warranted in the delayed phase after carboplatin-based chemotherapy in gynecologic cancer patients (Trial registry at UMIN Clinical Trials Registry, UMIN000012806).

Keywords: Palonosetron; Carboplatin; Nausea; Vomiting; Gynecologic Neoplasm

INTRODUCTION

Chemotherapy is often associated with multiple adverse reactions including nausea and emesis (vomiting), which may compromise the effectiveness of treatment, dissuade patients from complying with the treatment regimen, weaken a patient’s overall physical condition, cause emotional distress, and impair the quality of life [1-4]. Therefore, to achieve optimal therapeutic effectiveness as well as improve patient compliance and quality of life, it is necessary to administer antiemetic therapies to alleviate and prevent chemotherapy-induced nausea and vomiting (CINV). During the past 30 years, significant strides in our understanding of the pathophysiology underlying CINV have guided the development of more effective and better tolerated antiemetic drugs. Thus, multiple neurotransmitters and their cognate receptors involved in the emetic response have been identified as targets for therapeutic intervention. Further, antagonists of some of these signaling pathways have shown promise in alleviating CINV in a clinical setting. Indeed, an array of antiemetic prophylaxis strategies, employing distinct combinations of drugs, timing, and routes of administration, has been integrated into routine clinical practice [5]. Nonetheless, as cancer therapies evolve into increasingly complex combination regimens, vomiting, and especially nausea, remain among the most distressing adverse reactions of chemotherapy.

In the early 2000s, the U.S. Food and Drug Administration and European Medicines Agency approved palonosetron. Palonosetron is a second-generation, potent, and selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonist for the prevention of acute and delayed CINV in patients receiving moderately or highly emetogenic chemotherapy [6-8]. In addition to its activity as a direct 5-HT3 receptor antagonist, palonosetron uniquely inhibits the crosstalk between the 5-HT3 and neurokinin 1 (NK-1) receptor pathways, a property not shared by first-generation 5-HT3 receptor antagonists [9,10]. Palonosetron also has a higher binding affinity for the 5-HT3 receptor than first-generation 5-HT3 receptor antagonists [11], as well as a long plasma elimination half-life (approximately 40 hours) [8]. Taken together, these properties are thought to underpin the superior clinical efficacy of palonosetron in alleviating the delayed and acute phases of CINV. Multiple phase II and III trials have demonstrated the prolonged effectiveness of palonosetron throughout the period of emetic risk [9,12-18]. These studies helped establish a single intravenous dose of palonosetron, administered in combination with dexamethasone before chemotherapy, as a mainstay of antiemetic strategies for both the acute and delayed phases of CINV.
Carboplatin-based chemotherapy is widely administered as a standard-of-care neoadjuvant and adjuvant therapy for gynecologic cancers, including ovarian, endometrial, and cervical cancers [19-21]. While many studies have evaluated palonosetron in low to moderately emetogenic settings in various malignancies [12,15,17,18,22-25], few studies have been conducted in patients with gynecologic cancers who receive moderately to highly emetogenic chemotherapy [26]. The aim of the present study was to evaluate the effectiveness and safety of antiemetic therapy with palonosetron and dexamethasone in alleviating and/or preventing CINV in patients receiving carboplatin-based combination chemotherapy for gynecologic cancers. While recently revised guidelines no longer specify palonosetron as the 5-HT₃ receptor antagonist of choice, our study nevertheless demonstrates the safety and effectiveness of palonosetron plus dexamethasone against acute CINV in this setting. While this regimen is highly effective for the prevention of CINV in the acute phase, additional antiemetic management is warranted in the delayed phase.

MATERIALS AND METHODS

1. Study design
The study described herein was conducted by the West Japan Gynecologic Oncology Group (WJGOG) between September 2013 and January 2015. The study — designated WJGOG 131 — was a multicenter, single-arm, open-label phase II clinical trial designed to ascertain the safety and efficacy of palonosetron for the management of nausea and vomiting in patients with gynecologic cancers who received carboplatin-based combination chemotherapy. The study protocol and the informed consent form were approved by the institutional review board of each participating institution, and the study was conducted in accordance with the principles of the Declaration of Helsinki. The trial is registered in the UMIN Clinical Trials Registry System (UMIN trial ID: UMIN000012806).

2. Patient enrollment and eligibility criteria
The subjects enrolled in this study were chemotherapy-naïve Japanese patients aged ≥20 years (median age, 57; age range, 26 to 78 years) with newly diagnosed gynecologic cancer who had been assigned to receive a carboplatin-based combination chemotherapy regimen. Written informed consent was obtained from all participants before enrollment via a central registration system. On enrollment, patients were requested to complete a questionnaire concerning CINV risk factors such as age, history of alcohol consumption (women drinking alcohol on ≥5 days/week were categorized as habitual drinkers), and previous history of nausea and vomiting (morning sickness, motion sickness, or both).

3. Carboplatin-based combination chemotherapy regimens
Patients were assigned to receive one of the following three emetogenic carboplatin-based combination chemotherapy regimens: carboplatin at an area-under-the-curve (AUC) exposure of 5–6 mg/mL per minute in combination with paclitaxel (175–180 mg/m²) once every 3 weeks (q3w PTX), or 3-weekly carboplatin (AUC: 5–6 mg/mL per minute) in combination with weekly paclitaxel (80 mg/m²; q1w PTX), dose-dense taxotere and cyclophosphamide (TC), or 3-weekly carboplatin (AUC: 5–6 mg/mL per minute) in combination with docetaxel (70–75 mg/m²; DTX).

4. Antiemetic medications and dosing schedules
Palonosetron (0.75 mg/patient) and dexamethasone (19.8 mg/body for regimen 1, and 9.9 mg/body for regimens 2 and 3) were administered as a single intravenous bolus immediately
before the initiation of chemotherapy on day 1. In addition, dexamethasone (8.0 mg/body orally, or 6.6 mg/body intravenously) was administered on days 2 and 3. Concurrent use of other preventive antiemetics was prohibited during the 120 hours after the initiation of chemotherapy, with the exception of cases where rescue antiemetic medication was required to counteract CINV. The chemotherapy and antiemetic regimens are schematically represented in Fig. 1.

5. Assessment of emetic episodes, nausea, or both
Nausea and vomiting were evaluated in chemotherapy-naïve patients over the course of 5 days (0–120 hours) during the first cycle of carboplatin-based chemotherapy. The number, frequency, and intensity/severity of emetic episodes, nausea, or both were evaluated through patient self-reporting by means of the patient-completed Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool (MAT) \[27\] and treatment diaries during the 120 hours after the initiation of chemotherapy infusion. Accordingly, patients completed a daily treatment diary to report the incidence of vomiting episodes (number of episodes per 24 hours), their use of rescue antiemetic medication against CINV, changes in appetite and eating habits (ability to tolerate oral intake of solids and liquids), and their assessment of nausea during the period from the initiation of chemotherapy infusion (0 hours) until 120 hours after treatment (days 1–5). Patient-completed MAT and treatment diaries were comprehensively reviewed and evaluated by clinical staff according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, and adverse events were graded accordingly. The observation periods were defined as the acute phase (0–24 hours) the delayed phase (24–120 hours), with the entire period of emetic risk spanning 0–120 hours, referred to as the overall phase.

6. Assessment of efficacy endpoints
The primary endpoint was the proportion of patients who experienced complete control (CC) of vomiting with “no rescue antiemetic medication” and “no clinically significant nausea” or “only mild nausea” in the delayed phase (24–120 hours following the initiation of chemotherapy infusion). The following secondary endpoints were also analyzed: 1) the complete vomiting suppression rate (complete response [CR]), defined as the proportion of patients who reported “no vomiting” and “no use of rescue antiemetic medication” in the...
acute (0–24 hours) and delayed (24–120 hours) phases, as well as the overall phase (0–120 hours); and 2) the proportion of patients who experienced CC of vomiting, with “no rescue antiemetic medication” and “no clinically significant nausea” or “only mild nausea”, in the acute phase (0–24 hours) or the overall phase (0–120 hours). “No clinically significant nausea” or “only mild nausea” was assigned a MAT score of ≤1.

7. Adverse events
Adverse drug reactions (ADRs) were defined as adverse events known to have a causal relationship with palonosetron antiemetic treatment (such as constipation, headache, dizziness, neuralgia, and arthralgia) and were evaluated according to the NCI CTCAE, version 4.0.

8. Statistical analysis
For all eligible patients, the delayed phase CC rate was considered the primary endpoint. Given the results of previously conducted phase II and phase III trials of single-dose palonosetron combined with dexamethasone for preventing nausea and vomiting in patients receiving moderately emetogenic chemotherapy, the CR rate was measured at 70%–75% [25,28]. In our study, since all participants were of female gender (a known risk factor for CINV) [29,30], the CC rate was anticipated to be 10% to 20% lower than the CR rate [25,28-30]. Assuming a threshold CC rate of 45%, and an expected CC rate of 60%, we estimated that 76 patients were required to achieve a one-sided type I error rate of 5%, and a statistical power of 80%. Taking into account an estimated dropout rate of 5%, we set the target sample size at 80 patients.

The primary endpoint was analyzed with a one-sample binomial test. The confidence intervals (CIs) for the CC and CR rates were estimated by the Clopper–Pearson exact method. Exploratory analysis of the CR and CC rates in the delayed phase in patients categorized according to CINV risk factors was performed by logistic regression analysis. A one-sided p-value of <0.05 was considered to indicate statistical significance in the analysis of the primary endpoint. Efficacy analyses were carried out on the full analysis set (FAS), which consisted of patients who were confirmed to be eligible. All statistical analyses were conducted using SPSS software, version 9.4 (SAS Inc., Chicago, IL, USA).

RESULTS

1. Patient characteristics
Eighty consecutive chemotherapy-naïve patients with newly diagnosed gynecologic cancers who were scheduled to receive carboplatin-based combination chemotherapy were enrolled in this study. Seventy-seven of these patients had evaluable data on the primary outcome and were included in the FAS. Three patients were excluded from the efficacy analysis because of deviations or data inadequacies or flaws. Table 1 shows the patient baseline characteristics and demographics, including factors associated with an increased risk of CINV in women (age, alcohol consumption, and a previous history of morning sickness, motion sickness, or both) [29,30]. All patients recruited in the trial were aged >20 years, and 61.0% of the patients were aged ≥55 years, while 39.0% were <55 years. The most common types of malignancies among the study participants were ovarian cancer (54.5%) and endometrial cancer (35.1%). All patients received carboplatin-based chemotherapy, with the majority of women (68.8%) receiving a TC regimen. The remaining patients were given either dose dense TC (ddTC; 18.2%) or a doxetaxel and cisplatin (DC) regimen (13.0%).
2. Assessment of efficacy endpoints

The percentages of patients in the eligible study cohort who had CR and CC are graphed against the acute and delayed phases (0–24 hours and 24–120 hours after chemotherapy initiation, respectively), and the entire study period (0–120 hours) in Fig. 2, and are presented in Table 2.

Table 1. Patient baseline characteristics and demographics

<table>
<thead>
<tr>
<th>Patient background (n=77)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>57 (26–78)</td>
</tr>
<tr>
<td>&lt;55</td>
<td>30 (39.0)</td>
</tr>
<tr>
<td>≥55</td>
<td>47 (61.0)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>27 (35.1)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>42 (54.5)</td>
</tr>
<tr>
<td>Double cancer (endometrial cancer + ovarian cancer)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Regimen</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel + carboplatin</td>
<td>53 (68.8)</td>
</tr>
<tr>
<td>Dose dense paclitaxel + carboplatin</td>
<td>14 (18.2)</td>
</tr>
<tr>
<td>Docetaxel + carboplatin</td>
<td>10 (13.0)</td>
</tr>
<tr>
<td>Drinking habit</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>69 (90)</td>
</tr>
<tr>
<td>Present (drink alcohol on ≥5 days/week)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>History of hyperemesis (n=48)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>Absent</td>
<td>34 (69.4)</td>
</tr>
<tr>
<td>History of motion sickness (n=74)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Absent</td>
<td>69 (93.2)</td>
</tr>
</tbody>
</table>

Values indicate the number of patients in each group, with the corresponding percentage (%) of the eligible patient cohort given in brackets.

Fig. 2. CR and CC rates in the indicated phases.
CC, complete control; CR, complete response.

Table 2. CR and CC following carboplatin-based chemotherapy

<table>
<thead>
<tr>
<th>Time interval after chemotherapy</th>
<th>CR, % (95% CI)</th>
<th>CC, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute phase (0–24 hr)</td>
<td>97.4 (91.0–99.3)</td>
<td>96.1 (89.1–98.7)</td>
</tr>
<tr>
<td>Delayed phase (24–120 hr)</td>
<td>71.4 (60.5–80.3)</td>
<td>59.7 (48.6–70.0)</td>
</tr>
<tr>
<td>Entire period (0–120 hr)</td>
<td>71.4 (60.5–80.3)</td>
<td>59.7 (48.6–70.0)</td>
</tr>
</tbody>
</table>

CC, complete control; CR, complete response.
We defined the primary endpoint as the proportion of patients who had CC with “no vomiting,” “no use of rescue antiemetic,” and “no clinically significant nausea” or “only mild nausea” during the delayed phase. The CC rate during the delayed phase was 59.7% (95% CI=49.7%–70.0%), indicating that the combination of palonosetron plus dexamethasone is only moderately effective and ultimately insufficient as a first-line antiemetic therapy for the control of symptoms during the delayed phase following carboplatin-based chemotherapy in patients with gynecologic cancers.

We defined the key secondary endpoints as the proportion of patients with CR (“no vomiting” and “no rescue antiemetic medication”) during the acute, delayed, and overall phases of the observation period. Other secondary endpoints were the proportion of patients who had CC of vomiting with “no rescue antiemetic medication” and “no clinically significant nausea” or “only mild nausea” during the acute phase (0–24 hours) or the entire study period (0–120 hours).

In the delayed phase, the CR rate was 71.4% (95% CI=60.5%–80.3%), indicating that palonosetron is effective for the control of vomiting even during the delayed phase. As expected, the palonosetron plus dexamethasone regimen was highly effective during the acute phase, with very few patients experiencing CINV, as indicated by the very high proportions of patients achieving a CR (97.4%; 95% CI=91.0%–99.3%) and CC (96.1%; 95% CI=89.1%–98.7%). In the overall phase, the CR rate was 71.4% (95% CI=60.5%–80.3%) and the CC rate was 59.7% (95% CI, 48.6%–70.0%), reflecting the reduced efficacy for the control of CINV in the delayed phase.

The incidence of nausea associated with the DC regimen was 10% (1/10; grade 1 in one patient) from 0 to 24 hours and 60% (6/10; grade 1 in four patients and grade 2 in two patients) from 24 to 120 hours. The incidence of nausea associated with the TC/ddTC regimen was 6% (4/67; grade 1 in three patients and grade 2 in one patient) from 0 to 24 hours and 56.7% (34/67; grade 1 in 20 patients, grade 2 in 11 patients, and grade 3 in three patients) from 24 to 120 hours. There was no difference in the incidence of nausea between the regimens.

### 3. CINV risk factors

As for other risk factors, 39% of patients were younger than 55 years, 30.6% had a prior history of hyperemesis, and 6.8% had a prior history of motion sickness ([Table 1](https://ejgo.org)). In the univariate analysis, none of the CINV risk factors examined were significantly associated with the delayed CR and CC rates ([Fig. 3](https://doi.org/10.3802/jgo.2018.29.e77)). Only a history of morning sickness tended to be associated with poor delayed CR and CC rates. As for the multiplicity of risk factors, 64% of the patients had at least 1 risk factor, and 47% had at least 2 risk factors for CINV. In the multivariate analysis, the number of risk factors tended to be associated with poorer CR and CC rates during the delayed phase, but the relationship was not statistically significant. Although the differences observed herein were non-significant, these risk factors may be worthy of further investigation in subsequent more highly powered studies.

### 4. Tolerability and adverse events

Safety was evaluated in all 77 eligible patients. The most commonly reported adverse effect associated with palonosetron plus dexamethasone was constipation ([Table 3](https://ejgo.org)). Grade 1 constipation occurred in 23 patients (29.9%), whereas grade 2 constipation occurred in eight patients (10.4%). Low incidences of grade 1 headache, dizziness, and neuralgia/arthralgia...
were also reported (one patient per ADR; 1.3%). No grade ≥3 adverse events occurred, consistent with the established safety profile of palonosetron and dexamethasone.

**DISCUSSION**

Few evidence-based studies of antiemetic regimens have been conducted specifically in patients with gynecologic cancers who receive moderately to highly emetogenic chemotherapy [26]. The objective of this phase II clinical trial was to ascertain the safety and effectiveness of 0.75 mg/body of palonosetron (plus dexamethasone) for alleviating or preventing CINV (or both) in patients with gynecologic cancers who received carboplatin-based combination chemotherapy.

The palonosetron plus dexamethasone regimen was well tolerated, with constipation being the most commonly reported adverse effect. No grade ≥3 adverse events were observed, consistent with the established tolerability and safety profile of palonosetron. In the acute, delayed, and overall phases, CINV CR rates were 97.4%, 71.4%, and 71.4%, respectively, whereas the CINV CC rates were 96.1%, 59.7%, and 59.7%, respectively. The high CR and CC rates in the acute phase underscore the efficacy of palonosetron plus dexamethasone against acute CINV. However, based on our findings, the palonosetron plus dexamethasone regimen is not sufficient for the control of CINV during the delayed phase after carboplatin-based combination chemotherapy. Nevertheless, the results of the present study are at par with past reports regarding the efficacy and tolerability of
Palonosetron and dexamethasone in patients who receive moderately to highly emetogenic chemotherapy for different types of cancers [12,15,25,26]. In addition, the delayed phase CR rates obtained in our study demonstrate that palonosetron is comparably effective as granisetron, a first-generation 5-HT$_3$-receptor antagonist, administered in combination with either rolapitant or aprepitant [31,32], two recently approved NK-1 receptor antagonists. Together, these findings suggest that combinations of palonosetron, dexamethasone, and NK-1 receptor antagonists should be evaluated in future studies for the control of delayed phase symptoms in the gynecologic malignancy setting.

Several reports indicate that female gender, an age younger than 55 years, a history of non-habitual alcohol intake, as well as a history of motion sickness, morning sickness, or both, increase the risk of CINV [29,30]. In the present study, we also examined CINV risk factors in the eligible patient cohort. Although the delayed phase CC and CR rates did not differ significantly in patients categorized according to the CINV risk factors examined herein, the subgroup with a prior history of morning sickness, and the subgroup with multiple risk factors seemed more prone to experiencing relative treatment failure in the delayed phase. Although the observed differences were non-significant, these risk factors may merit further investigation in subsequent more highly powered studies.

The strengths of the present study are the size of the patient cohort, the focus on patients with gynecologic cancers who receive carboplatin-based chemotherapy, and the assessment of CINV risk factors. The present study has several limitations: namely, this study was conducted as a phase II trial with a nonrandomized design and no control group.

With the ongoing and fast-paced development of novel antiemetic treatments and regimens, the publication of practice guidelines and updates has enabled physicians to integrate the latest advances into routine clinical practice. However, during the past few years, the antiemetic practice guidelines have been revised several times, which may be confusing to providers resulting in reduced adherence with the recommendations [33-35]. When the present trial was initiated, the combination of palonosetron plus dexamethasone was the recommended antiemetic regimen for the management of acute CINV caused by moderately emetogenic chemotherapy [36], which at the time included carboplatin regimens. Currently, the American Society of Clinical Oncology (ASCO)-convened Expert Panel no longer specifies palonosetron as the 5-HT$_3$ receptor antagonist of choice and has extended its recommendation to include the use of any of the available 5-HT$_3$ receptor antagonists [37]. Moreover, the emetic risk of carboplatin was also revised recently: at an AUC of ≥4 mg/mL per minute, carboplatin is now considered highly emetogenic, whereas an AUC of <4 mg/mL per minute is still categorized as moderately emetogenic [35,37]. Under the current, newly revised guidelines (2017), adult patients who receive carboplatin at an AUC of ≥4 mg/mL per minute (highly emetogenic) should be offered a three-drug combination of an NK-1 receptor antagonist, a 5-HT$_3$ receptor antagonist, and dexamethasone [37,38]. Indeed, our study suggests that palonosetron is only moderately effective against delayed CINV in patients with gynecologic cancers who receive carboplatin-based combination chemotherapy. Encouragingly, recent phase II studies, conducted in patients with gynecologic cancer who received moderately emetogenic carboplatin and paclitaxel chemotherapy, reported notably superior efficacy and no serious adverse events with antiemetic triplet therapy comprising aprepitant, palonosetron, and dexamethasone [39,40]. Moreover, in this study, patients with fewer CINV risk factors tended to have more favorable symptom control in the delayed phase. Therefore, for patients with one or more CINV risk factors in whom NK-1 receptor
antagonists are contraindicated, treatment with palonosetron plus dexamethasone could represent a viable alternative. In summary, the antiemetic efficacy of the palonosetron and dexamethasone regimen could potentially be enhanced through the administration of an NK1 receptor antagonist, or palonosetron and dexamethasone could be administered as a simpler regimen for the control of delayed symptoms in patients with one or more CINV risk factors. Future larger studies should evaluate supportive-care data for such a regimen, specifically in the setting of patients with gynecologic malignancies.

In conclusion, the CR and CC rates observed in this phase II trial are consistent with current evidence-based guidelines on the use of palonosetron plus dexamethasone as an antiemetic regimen in different types of cancers, even though palonosetron is no longer specified as the 5-HT3 receptor antagonist of choice. Specifically, our findings advocate palonosetron plus dexamethasone as an effective, well-tolerated antiemetic regimen for patients with gynecologic cancers who receive carboplatin-based combination chemotherapy. While this regimen is highly efficacious for the prevention of CINV in the acute phase, additional antiemetic management is warranted in the delayed phase. Future studies should evaluate the administration of an NK1 receptor antagonist alongside palonosetron and dexamethasone for the management of delayed CINV in this setting.

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