Efficacy and safety of rolapitant for prevention of chemotherapy-induced nausea and vomiting over multiple cycles of moderately or highly emetogenic chemotherapy

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Abstract  Objective: Rolapitant, a novel neurokinin-1 receptor antagonist (RA), was shown to protect against delayed chemotherapy-induced nausea and vomiting (CINV) during the first cycle of moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) in randomized, double-blind trials. This analysis explored the efficacy and safety of rolapitant in preventing CINV over multiple cycles of MEC or HEC.

Patients and methods: Patients in one phase III MEC, one phase II HEC, and two phase III HEC clinical trials were randomized to receive oral rolapitant (180 mg) or placebo in combination with a 5-hydroxytryptamine type 3 RA and dexamethasone. Regardless of response in cycle 1, patients could continue the same antiemetic treatment for up to six cycles. On days 6–8 of each subsequent chemotherapy cycle, patients reported the incidence of emesis and/or nausea interfering with normal daily life. Post hoc analyses of pooled safety and efficacy data from the four trials were performed for cycles 2–6.

Results: Significantly more patients receiving rolapitant than control reported no emesis or interfering nausea (combined measure) in cycles 2 (p = 0.006), 3 (p < 0.001), 4 (p = 0.001), and 5 (p = 0.021). Over cycles 1–6, time-to-first emesis was significantly longer
1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a debilitating side-effect of anticancer treatment that significantly impairs quality of life for patients [1,2]. Use of a 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist (RA), particularly when combined with dexamethasone, has proven highly efficacious for controlling nausea and vomiting that occur in the acute phase (<24 h) following administration of emetogenic chemotherapy; however, its efficacy in controlling CINV during the delayed phase (>24–120 h) is limited [3]. Because patients with acute CINV became uncommon in the clinic following the introduction of 5-HT3 RAs, health care professionals may not be aware of delayed CINV. Current antiemetic guidelines recommend the addition of a neurokinin-1 (NK-1) RA to a 5-HT3 RA and dexamethasone in patients receiving highly emetogenic chemotherapy (HEC) [3–5]. For patients receiving moderately emetogenic chemotherapy (MEC), the addition of an NK-1 RA is supported for select patients with additional CINV risk factors [3,4].

In clinical practice, patients typically receive four to six cycles of chemotherapy. The severity of CINV can increase over repeated chemotherapy cycles when CINV protection is not achieved [6–8], and failure to protect against delayed CINV can impair protection against acute CINV in subsequent cycles [8]. Anticipatory CINV may also develop, which may compromise adherence to anticancer treatment [9].

The goal of developing new antiemetics should be to improve CINV protection throughout the entire at-risk period, with preservation of the benefit over multiple chemotherapy cycles while maintaining safety and tolerability. Improved CINV protection over multiple cycles has been shown with the addition of an NK-1 RA to standard therapy in studies of aprepitant [10–13] and netupitant [14]. However, the use of these agents may be complicated by their interaction with the cytochrome P450 3A4 (CYP3A4) enzyme, often necessitating dose adjustment of certain concomitantly administered medications [15,16].

Rolapitant (VARUBI®) is an orally active, long-acting NK-1 RA that was recently approved by the US Food and Drug Administration in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy [17]. At the 180-mg dose of rolapitant, the mean NK-1 receptor occupancy was >90% in the cortex and 73% in the striatum at 120 h after a single oral dose [18], consistent with its long half-life (approximately 180 h) [19]. In addition, rolapitant does not inhibit or induce CYP3A4; therefore, it may reduce the potential for CYP3A4-mediated drug-drug interactions and decrease the need for dose modification of certain drugs metabolized by CYP3A4 [20]. An intravenous version of rolapitant is under investigation.

The efficacy of oral rolapitant (180 mg) in protecting against CINV was established in four randomized, placebo-controlled double-blind studies [21–23]. A greater percentage of patients administered MEC or HEC demonstrated a complete response (CR: defined as no emesis and no use of rescue medication) in the delayed phase (>24–120 h) in cycle 1 with rolapitant combined with a 5-HT3 RA and dexamethasone compared with a 5-HT3 RA and dexamethasone alone [21–23]. The proportion of patients in rolapitant and control groups who achieved a CR in the delayed phase (the primary end-point) was 71.3% and 61.6%, respectively, in a phase III MEC study (p < 0.001) and 71.4% and 60.2%, respectively, in two pooled phase III cisplatin-based HEC studies (p < 0.001) [21,22]. It should be noted that 53% of patients in the MEC study received anthracyline/cyclophosphamide (AC)–based chemotherapy, which is now classified as HEC [3–5]; other patients received a variety of MEC agents, the most common of which was carboplatin (30% of patients), and a higher CR rate in the delayed phase with rolapitant was maintained in this group [21]. In addition, in a phase II cisplatin-based HEC study, CR in the delayed phase (a secondary end-point) was achieved by 63.6% and 48.9% of patients in rolapitant and control groups, respectively (p = 0.045) [23]. Collectively, these data support the recently updated National Comprehensive Cancer Network guidelines that recommend rolapitant (category 1) for CINV prevention in patients receiving HEC and in select patients receiving MEC [3].

Patients who completed cycle 1 in the rolapitant studies had the option to continue the same randomized study.
treatment for up to five additional cycles regardless of their response in cycle 1. Here, we report the efficacy and safety of rolapitant over multiple cycles of MEC or HEC in a pooled analysis of the four similarly designed studies: one phase III MEC study (randomized N = 1369) [21], one phase II HEC study (randomized N = 181) [23], and two phase III HEC studies (randomized N = 1087) [22].

2. Patients and methods

Four global, randomized, double-blind, placebo-controlled studies (NCT01500226, NCT00394966, NCT01499849 and NCT01500213) were conducted in North America, Central and South America, Europe, Asia, and Africa in accordance with the Declaration of Helsinki and the International Conference on Harmonisation and Good Clinical Practice (GCP) guidelines. The institutional review boards at each study site approved the protocols. All patients provided written informed consent.

2.1. Patients

Eligibility requirements for each study included patient age ≥18 years, Karnofsky performance score ≥60, predicted life expectancy ≥4 months (≥3 months in the phase II study), and adequate bone marrow, kidney, and liver function. Patients in the MEC study were required to be naive to MEC or HEC and scheduled to receive a first course of one or more of the following agents: intravenous cyclophosphamide (<1500 mg/m²), doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, and/or intravenous cytarabine (>1 g/m²). The MEC study was designed before AC-based chemotherapy was reclassified as HEC; the study protocol prespecified that at least 50% of patients enrolled were to receive an AC-based regimen. In the HEC studies, patients were required to be naive to cisplatin and scheduled to receive their first course of cisplatin-based chemotherapy (≥70 mg/m² in the phase II study and ≥60 mg/m² in the phase III studies).

Prior to initiating study drug, patients were not permitted to use any of the following medications: 5-HT₃ RAs, phenothiazines, benzamides, domperidone, cannabinoids, NK-1 RAs, or benzodiazepines within 48 h; palonosetron within 7 d; or systemic corticosteroids or sedative antihistamines (e.g. dimenhydrinate or diphenhydramine) within 72 h of day 1, with the exception of premedication for chemotherapy (e.g. taxanes).

2.2. Treatment

Patients were stratified by sex (and concomitant emetogenic chemotherapy in the phase II study) and randomized using an interactive, web-based randomization system to receive either oral rolapitant 180 mg or placebo approximately 1–2 h before receiving either MEC or HEC. All patients received a 5-HT₃ RA and dexamethasone regimen. Patients in the MEC study were administered oral granisetron 2 mg on days 1–3 and dexamethasone 20 mg on day 1. Patients in the cisplatin-based HEC studies were administered intravenous granisetron 10 μg/kg (intravenous ondansetron 32 mg in the phase II trial) on day 1 and oral dexamethasone 20 mg on day 1 and 8 mg twice daily on days 2–4. Patients administered taxanes received dexamethasone according to the package insert.

2.3. Efficacy and safety assessments

During the first 5 days after administration of chemotherapy in cycle 1, patients used a daily diary to record all events of vomiting and use of rescue medication and to self-assess nausea. The primary end-point was CR in the delayed phase in the phase III studies and CR in the overall phase (0–120 h) in the phase II study. At the end of cycle 1, eligible patients were permitted to continue the same randomized treatment regimen for up to five additional cycles whether or not they achieved a CR in cycle 1. Response in cycles 2–6 was assessed for the exploratory end-points of no emesis or nausea that interfered with normal daily life (a combined measure), no emesis, no interfering nausea, and time-to-first emesis. Patients were asked the following two CINV assessment questions on days 6–8 of each subsequent cycle: 1) have you had any episode of vomiting or retching since your chemotherapy started in this cycle? and 2) have you had any nausea since your chemotherapy started in this cycle that interfered with normal daily life?

Safety variables, including treatment-emergent adverse events (TEAEs), physical and neurological examinations, vital signs, electrocardiograms, and clinical laboratory values, were assessed in all cycles.

2.4. Statistical analysis

Post hoc analyses of pooled safety and efficacy data from the four studies were performed for cycles 2–6 (only data from patients receiving the 180-mg rolapitant dose or control were included from the dose-finding phase II HEC study). The subsequent cycle efficacy population consisted of all patients who received at least one dose of study drug in a given cycle and were enrolled at a GCP-compliant site. Between-group comparisons were conducted using the Cochran–Mantel–Haenszel χ² test adjusted for sex and study. Time-to-first emesis was summarized using Kaplan–Meier methodology, and the between-group treatment comparison was conducted using a log-rank test in the population of patients who received study drug at a GCP-compliant site. p-values <0.05 were considered statistically significant and were not adjusted for multiplicity.
The safety population included all patients who received at least one dose of study drug in a given cycle.

3. Results

3.1. Patients

Baseline characteristics were balanced between patients in the rolapitant and control groups in the overall pooled analysis (Table 1). The majority of patients in the MEC study were female (80%), and breast cancer was the most commonly diagnosed malignancy (67%) [21]. AC-based chemotherapy (now classified as HEC [3–5]) was received by 53% of patients, and carboplatin-based chemotherapy was received by 30% of patients; other patients received a variety of MEC regimens (Supplemental Table 1) [21]. In the pooled phase III cisplatin-based HEC studies, the majority of patients were male (63%) and lung cancer was the most commonly diagnosed malignancy (44%) [22].

Patient discontinuations occurred with similar frequencies in both treatment arms for cycle 1 and the combined cycles 2–6 (Fig. 1). The most common reason for patient discontinuation was completion of the required number of chemotherapy cycles (observed in 36.0% of patients overall). This most often occurred after four cycles, a typical treatment course for many chemotherapy regimens, with 34.0% and 37.2% of patients discontinuing after cycle 4 in the rolapitant and control arms, respectively (Supplemental Table 2).

3.2. Efficacy

Over multiple cycles, a greater proportion of patients in the rolapitant group than the control group reported no emesis or interfering nausea (combined measure); the improvement reached statistical significance in cycles 2 ($p = 0.006$), 3 ($p < 0.001$), 4 ($p = 0.001$), and 5 ($p = 0.021$, Fig. 2A). A significantly higher proportion of patients reported no emesis events in the rolapitant group than the control group in cycles 2–6 ($p < 0.001$ for each subsequent cycle, Fig. 2B). A significantly greater percentage of patients reported no interfering nausea with rolapitant versus control in cycles 2 ($p = 0.010$), 3 ($p < 0.001$), 4 ($p = 0.012$), and 5 ($p = 0.029$, Fig. 2C), but not in cycle 6 ($p = 0.682$). There was a general trend of decreased CINV over repeated cycles in the control group. However, the improvement in no emesis and no interfering nausea (combined and individual measures) with rolapitant relative to control remained generally consistent over multiple cycles.

Kaplan–Meier curves showing time-to-first emesis separated in cycle 1 and favored rolapitant over control with sustained separation that remained consistent over cycles 2–6 ($p < 0.001$, Fig. 3).

3.3. Safety

The safety dataset comprised 1012 patients who received rolapitant and 999 patients who received control in cycles 2–6. Rolapitant was well tolerated over multiple cycles of MEC or HEC, with an incidence of treatment-

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Table 1
Baseline demographics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rolapitant, 180 mg (n = 1007)</th>
<th>Control (n = 991)</th>
<th>Total (n = 1998)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>58 (20–86)</td>
<td>57 (18–90)</td>
<td>57 (18–90)</td>
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<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>620 (61.6)</td>
<td>625 (63.1)</td>
<td>1245 (62.3)</td>
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<tr>
<td>Male</td>
<td>387 (38.4)</td>
<td>366 (36.9)</td>
<td>753 (37.7)</td>
</tr>
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<td>Race, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>806 (80.0)</td>
<td>777 (78.4)</td>
<td>1583 (79.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>95 (9.4)</td>
<td>97 (9.8)</td>
<td>192 (9.6)</td>
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<td>Black or African American</td>
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<td>29 (2.9)</td>
<td>52 (2.6)</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>13 (1.3)</td>
<td>13 (1.3)</td>
<td>26 (1.3)</td>
</tr>
<tr>
<td>Native Hawaiian/other Pacific islander</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Multiracial/other/unknown</td>
<td>69 (6.9)</td>
<td>73 (7.4)</td>
<td>142 (7.1)</td>
</tr>
<tr>
<td>Alcohol consumptionb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 Drinks/week, n/N (%)</td>
<td>890/943 (94.4)</td>
<td>849/922 (92.1)</td>
<td>1739/1865 (93.2)</td>
</tr>
<tr>
<td>&gt;5 Drinks/week, n/N (%)</td>
<td>53/943 (5.6)</td>
<td>73/922 (7.9)</td>
<td>126/1865 (6.8)</td>
</tr>
<tr>
<td>Region, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>224 (22.2)</td>
<td>226 (22.8)</td>
<td>450 (22.5)</td>
</tr>
<tr>
<td>Central/South America</td>
<td>109 (10.8)</td>
<td>113 (11.4)</td>
<td>222 (11.1)</td>
</tr>
<tr>
<td>Europe</td>
<td>554 (55.0)</td>
<td>530 (53.5)</td>
<td>1084 (54.3)</td>
</tr>
<tr>
<td>Asia/South Africa</td>
<td>120 (11.9)</td>
<td>122 (12.3)</td>
<td>242 (12.1)</td>
</tr>
</tbody>
</table>

* Demographics shown are for patients who received the 180-mg rolapitant dose or control during cycles 2–6 at a Good Clinical Practice compliant site.

* Data for alcohol consumption were not collected in the phase II study and are based on patients who self-reported alcohol consumption.
related TEAEs similar to that of control. The incidence of the most common treatment-related TEAEs, which included fatigue, constipation, and headache, was low (<2%, Table 2). In addition, the incidence of treatment-related TEAEs over multiple cycles remained similar to that observed in cycle 1. The incidence of treatment-related TEAEs did not increase with each subsequent cycle, and no cumulative toxicity was observed (Supplemental Table 3). For cycles 2–6, the total number of patients discontinuing due to an adverse event, disease progression, or death was low (6.5%, 4.9%, and 1.0% of patients, respectively, Fig. 1).

4. Discussion

Rolapitant combined with a 5-HT3 RA and dexamethasone provided superior protection against CINV in patients receiving multiple cycles of MEC or HEC compared with a 5-HT3 RA and dexamethasone alone. In a pooled analysis of four similarly designed phase II and III studies, the proportion of patients reporting no emesis and no interfering nausea was significantly higher with rolapitant group than with control over multiple cycles.

The rolapitant trials included a diverse population of patients with cancer [21–23], a majority of whom were at high risk for CINV [1], as 60% of the population in the pooled analysis was female and over 90% reported little or no alcohol consumption. In this pooled analysis, the treatment arms were well balanced for these risk factors.

In multiple-cycle studies, the incidence of CINV has generally been found to increase over cycles of chemotherapy [7,8]. In contrast, we observed a trend of decreased CINV over multiple cycles in the control group; healthier patients may have been more likely to remain in the study for reasons such as a greater ability to comply with clinic visit follow-ups as well as a lower rate of disease progression or death, whereas those with poor CINV control may have been more likely to discontinue after cycle 1. Despite this trend, the improvement in patient-reported outcomes of no emesis and no interfering
Nausea with rolapitant relative to control remained generally consistent over multiple cycles. Furthermore, Kaplan–Meier curves showing time-to-first emesis demonstrated a consistent improvement favoring rolapitant over control that was sustained over six cycles.

There are challenges inherent in collecting data over multiple cycles of chemotherapy [6]. In an effort to facilitate data collection, the rolapitant trials used a simple measure of response in cycles 2–6. Patients answered two yes/no questions about whether nausea or emesis events and nausea interfering with normal daily life.

Fig. 2. Rates of no emesis and/or no interfering nausea in cycles 2–6. Rates of (A) no emesis or interfering nausea (combined measure), (B) no emesis, and (C) no interfering nausea based on patient response to two yes/no questions about emesis events and nausea interfering with normal daily life.
vomiting had occurred since the start of chemotherapy instead of using the 5-d daily diary employed in cycle 1 [21,22]. As is typical with multiple-cycle trials [6], the number of enrolled patients decreased over the course of six cycles. The frequency of discontinuations in each cycle was similar in rolapitant and control arms. Completion of the required number of chemotherapy cycles was the most common reason for discontinuation in both arms and occurred most often after four cycles, which is a typical course for many chemotherapy regimens. The MEC trial included approximately 50% patients receiving AC-based chemotherapy for breast cancer [21], which is administered over four cycles [24]; completion of chemotherapy in these patients was a major reason for the discontinuations in the pooled analysis. The number of patients who discontinued due to an adverse event, disease progression, or death was low in both arms.

In summary, oral rolapitant effectively protected against CINV, with sustained benefit over multiple cycles of MEC or HEC. Rolapitant was also well-tolerated, with no increase in the frequency of treatment-related TEAEs and no cumulative toxicity with treatment over multiple cycles. These results support the benefit of adding rolapitant to the supportive care of a diverse population of patients with cancer receiving multiple cycles of MEC or HEC.

**Role of the funding source**

The phase III studies were designed through a collaboration of academic researchers and the study sponsor, TESARO, Inc. Study data were collected by clinical investigators, and trials conducted were monitored by TESARO, Inc. Statistical analyses were managed by TESARO, Inc., according to a predefined statistical plan; data presented here include post hoc analyses. This manuscript was developed with full author participation and assistance from a medical writer in accordance with Good Publication Practice.
Conflict of interest statement

BR has received honoraria for speaking engagements from MSD and Roche Malaysia; he has been a consultant and has had travel/accommodations paid for by MSD and TESARO, Inc. LS has served as a consultant for TESARO, Inc., Helsinki, and Eisai. DP is an employee of TESARO, Inc. SA has received contracting fees from TESARO, Inc., to direct statistical analyses during this study and outside the submitted work. IS has served on an advisory board for TESARO, Inc. MC and RN have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.12.023.

References