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ORIGINAL ARTICLE

Integrated safety analysis of rolapitant with coadministered drugs from phase II/III trials: an assessment of CYP2D6 or BCRP inhibition by rolapitant

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Background: Rolapitant, a long-acting neurokinin $(NK)_1$ receptor antagonist (RA), has demonstrated efficacy in prevention of chemotherapy-induced nausea and vomiting in patients administered moderately or highly emetogenic chemotherapy. Unlike other NK_1 RAs, rolapitant does not inhibit or induce cytochrome P450 (CYP) 3A4, but it does inhibit CYP2D6 and breast cancer resistance protein (BCRP). To analyze potential drug–drug interactions between rolapitant and concomitant medications, this integrated safety analysis of four double-blind, randomized phase II or III studies of rolapitant examined adverse events (AEs) by use versus non-use of drug substrates of CYP2D6 or BCRP.

Patients and methods: Patients were randomized to receive either 180 mg oral rolapitant or placebo ~1–2 h before chemotherapy in combination with a 5-hydroxytryptamine type 3 RA and dexamethasone. Data for treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs (TESAEs) during cycle 1 were pooled across the four studies and summarized in the overall population and by concomitant use/non-use of CYP2D6 or BCRP substrate drugs.

Results: In the integrated safety population, 828 of 1294 patients (64%) in the rolapitant group and 840 of 1301 patients (65%) in the control group experienced at least one TEAE. Frequencies of common TEAEs were similar in the rolapitant and control populations. Overall, 53% of patients received CYP2D6 substrate drugs, none of which had a narrow therapeutic index (like thioridazine or pimozide), and 63% received BCRP substrate drugs. When grouped by concomitant use versus non-use of CYP2D6 or BCRP substrate drugs, TEAEs and TESAEs occurred with similar frequency in the rolapitant and control populations.

Conclusions: The results of this study support the safety of rolapitant as part of an antiemetic triple-drug regimen in patients receiving emetogenic chemotherapy, including those administered concomitant medications that are substrates of CYP2D6 or BCRP, such as ondansetron, docetaxel, or irinotecan.

Key words: breast cancer resistance protein, chemotherapy-induced nausea and vomiting, cytochrome P450, rolapitant, safety

Introduction

Patients receiving chemotherapy as treatment of cancer often experience nausea and vomiting. The acute phase (≤24 h) of chemotherapy-induced nausea and vomiting (CINV) is primarily mediated by 5-hydroxytryptamine $(5\text{-HT})_3$-receptor signaling, whereas the delayed phase (>24–120 h) is primarily mediated by neurokinin $(NK)_1$-receptor signaling [1]. A combination of a 5-HT_3 receptor antagonist (RA) and dexamethasone has demonstrated protection against acute-phase CINV but limited efficacy against delayed-phase CINV [1, 2]; the addition of an NK_1 RA to this regimen increases overall CINV control [3]. Accordingly, the most commonly used clinical practice guidelines recommend this triple-drug therapy for antiemetic prophylaxis in patients

receiving cisplatin, anthracycline/cyclophosphamide (AC), and other highly emetogenic chemotherapy (HEC) regimens and in patients receiving carboplatin [4–6].

On average, a patient with cancer receives five drugs concomitantly as part of his or her anticancer regimen or for comorbidities [7, 8]. Even before cancer diagnosis, patients who are 70 years and older generally receive five prescription medications for underlying diseases [9]. Therefore, the use of CINV prophylactics may be complicated by drug–drug interactions (DDIs) with these medications. In particular, interactions with inhibitors of metabolic enzymes or xenobiotic transporters could result in increased substrate drug bioavailability, leading to adverse events (AEs). The cytochrome P450 (CYP) class of enzymes, expressed primarily in the liver but also in the gastrointestinal (GI) tract, is responsible for the metabolism and disposition of many drugs, with the isoforms CYP3A4 and CYP2D6 having the highest activity [10]. CYP3A4 is much more abundant than CYP2D6 in both the GI tract (82% versus <1%) and the liver (40% versus 2%) [11]. A large number of known drugs, including the NK_1 RAs aprepitant and netupitant, are inhibitors, inducers, and/or substrates of CYP3A4, increasing the likelihood of DDIs with CYP3A4 substrates [12]. Breast cancer resistance protein (BCRP), which transports potentially harmful substances out of cells, is expressed in the liver, kidneys, GI tract, and blood-brain barrier; multiple tumor cells overexpress this xenobiotic transporter, affecting drug distribution and absorption [13, 14].

Rolapitant, a highly selective, long-acting NK_1 RA, was approved in oral formulation in 2015 by the US Food and Drug Administration in combination with other antiemetic agents in adults for the prevention of delayed CINV [15]. In randomized phase II and III trials, a single 180-mg oral dose of rolapitant with a 5-HT_3 RA and dexamethasone regimen on the same day as chemotherapy provided superior protection against nausea and/or vomiting on days 2–5 after chemotherapy [16–18]. The safety profile of rolapitant was consistent across studies, with a low incidence of treatment-related AEs generally comparable to that observed in control arms [16–18]. Unlike other approved oral NK_1 RAs [19], rolapitant does not induce or inhibit CYP3A4 [20, 21]. Oral rolapitant is a moderate inhibitor of CYP2D6 and an inhibitor of BCRP [22, 23]. While concomitant use of rolapitant with a CYP2D6 or BCRP substrate drug with a narrow therapeutic index is not contraindicated, if such concomitant use cannot be avoided, patients should be monitored for AEs [15]. There is no such recommendation for CYP2D6 or BCRP substrate drugs without a narrow therapeutic index.

Here, we report an integrated analysis of safety using pooled data from the phase II and III rolapitant studies [16–18] to assess possible safety signals in patients administered concomitant drugs that are substrates of CYP2D6 or BCRP.

Methods

Study designs and treatment

The phase II cisplatin-based HEC (NCT00394966) [16], phase III cisplatin-based HEC-1 (NCT01499849) and cisplatin-based HEC-2 (NCT01500213) [17], and phase III moderately emetogenic chemotherapy or AC-based chemotherapy (NCT01500226) [18] randomized, double-blind, parallel-group trials enrolled patients scheduled to receive their first chemotherapy treatment. Eligibility criteria for these studies have been described [16–18] and are included in the supplementary material, available at *Annals of Oncology* online.

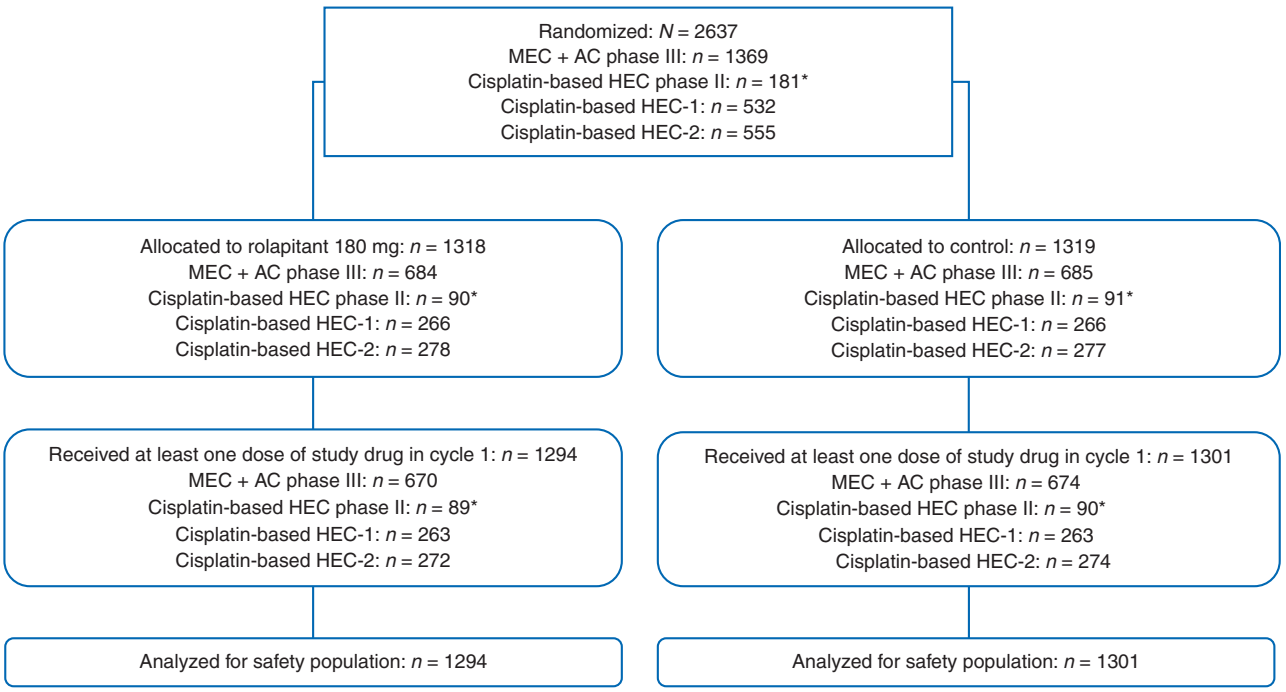

Figure 1. CONSORT diagram of integrated safety analysis. Asterisk indicates only patients randomized to placebo or the 180 mg dose group were included in this analysis. AC, anthracycline and cyclophosphamide; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy.

Patients received oral rolapitant or placebo ~1–2 h before chemotherapy in combination with a 5-HT_3 RA and dexamethasone (active control) (supplementary Figure S1, available at *Annals of Oncology* online). The phase II trial was a dose-ranging study of rolapitant (9, 22.5, 90, or 180 mg) [16]; patients from the 180 mg rolapitant and active-control groups were included in the current analysis. The phase III trials evaluated 180 mg rolapitant versus active control [17, 18]. The studies were approved by the institutional review board at each study site and conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines.

Integrated safety analysis

Safety was analyzed in all patients who received at least one dose of study drug, and AEs were classified according to MedDRA v15.0 [24]. The relationship of AEs to study treatment was determined by the investigator. Data for treatment-emergent AEs (TEAEs) during cycle 1 were pooled. Safety was descriptively summarized in the overall population and by concomitant use or non-use of substrates of CYP2D6 or BCRP (with medications coded using the World Health Organization Drug Dictionary, March 2012 [25]). Safety data were further evaluated in the rolapitant and control arms for patients administered specific BCRP substrate chemotherapeutic agents, e.g. docetaxel, doxorubicin, epirubicin, fluorouracil, etoposide, irinotecan, methotrexate, or topotecan.

Table 1. Baseline demographics

	Rolapitant 180 mg ($N = 1294$)	Control ($N = 1301$)
Age, median (range)	58 (20–86)	57 (18–90)
Gender, *n* (%)		
Female	774 (60)	782 (60)
Male	520 (40)	519 (40)
Race, *n* (%)		
White	968 (75)	966 (74)
Black or African American	29 (2)	35 (3)
American Indian or Alaska Native	14 (1)	15 (1)
Asian	188 (15)	183 (14)
Other	95 (7)	102 (8)
Alcohol consumption, *n/N* (%)[a,b]		
0 drinks/week	975/1199 (81)	950/1209 (79)
>0 to ≤ 5 drinks/week	158/1199 (13)	168/1209 (14)
>5 drinks/week	66/1199 (6)	91/1209 (8)
Primary tumor site, *n/N* (%)[c]		
Breast	431/1205 (36)	459/1211 (38)
Lung	338/1205 (28)	351/1211 (29)
Head and neck	101/1205 (8)	107/1211 (9)
Ovary	68/1205 (6)	55/1211 (5)
Colon/rectum	40/1205 (3)	28/1211 (2)
Stomach	42/1205 (3)	44/1211 (4)
Uterine	25/1205 (2)	33/1211 (3)
Other	160/1205 (13)	134/1211 (11)

[a]Patients in the phase II HEC study ($n = 90$ and $n = 91$ in the rolapitant and control arms, respectively) were excluded from the alcohol consumption counts because the information was not collected.
[b]The denominator is based on the number of subjects with valid answers.
[c]Patients in the phase II HEC study were excluded from the primary tumor site counts because the information was not collected.

Results

Patients

Of 2637 patients, 2595 received at least one dose of study drug during cycle 1 and were included in the integrated safety analysis (Figure 1); 1294 patients received 180 mg oral rolapitant and 1301 received placebo. Baseline demographics were balanced between these groups (Table 1). The majority of patients were female (60%) and white (75%) and reported no alcohol consumption (80%). The most commonly diagnosed malignancies were breast cancer (37%) and lung cancer (29%).

Overall integrated safety analysis

In the integrated safety population, 828 of 1294 rolapitant-treated patients (64%) and 840 of 1301 control patients (65%) experienced at least one TEAE during cycle 1 (Table 2); 90 rolapitant-treated patients (7%) and 82 control patients (6%) experienced at least one TEAE considered drug related. All patients received dexamethasone, a CYP3A4 substrate. TEAEs were generally considered to be the result of chemotherapy or underlying disease. The most common TEAEs occurred with similar frequency in the rolapitant and control populations. TEAEs led to treatment discontinuation in 40 patients (3%) in the rolapitant group and 48 patients (4%) in the control group and to death in 21 patients (2%) in the rolapitant group and 15 patients (1%) in the control group. The only treatment-emergent serious AE (TESAE) reported in >1% of patients in either group was febrile

Table 2. Summary of TEAEs in cycle 1: overall integrated safety analysis

	Rolapitant 180 mg ($N = 1294$)	Control ($N = 1301$)
Patients with ≥1 TEAE, *n* (%)	828 (64)	840 (65)
TEAE in ≥ 5% of patients in either group, *n* (%)		
Fatigue	153 (12)	146 (11)
Constipation	117 (9)	151 (12)
Neutropenia	106 (8)	88 (7)
Decreased appetite	101 (8)	100 (8)
Alopecia	98 (8)	112 (9)
Diarrhea	87 (7)	89 (7)
Headache	81 (6)	101 (8)
Asthenia	76 (6)	100 (8)
Nausea	72 (6)	104 (8)
Patients with ≥1 TESAE, *n* (%)	102 (8)	126 (10)
TESAE in ≥ 1% of patients in either group, *n* (%)		
Febrile neutropenia	14 (1)	22 (2)

TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Table 3. Summary of TEAEs according to use of concomitant CYP2D6 substrate drugs

	Concomitant CYP2D6 substrate use		No CYP2D6 substrate use	
	Rolapitant 180 mg (*N* = 648)	Control (*N* = 720)	Rolapitant 180 mg (*N* = 646)	Control (*N* = 581)
Patients with ≥1 TEAE, *n* (%)	493 (76)	548 (76)	335 (52)	292 (50)
TEAE in ≥ 10% of patients in any group, *n* (%)				
Fatigue	103 (16)	101 (14)	50 (8)	45 (8)
Constipation	81 (13)	101 (14)	36 (6)	50 (9)
Decreased appetite	65 (10)	84 (12)	36 (6)	16 (3)
Nausea	52 (8)	92 (13)	20 (3)	12 (2)
Alopecia	50 (8)	48 (7)	48 (7)	64 (11)
Asthenia	43 (7)	72 (10)	33 (5)	28 (5)
Patients with ≥1TESAE, *n* (%)	74 (11)	96 (13)	28 (4)	30 (5)
TESAE in ≥ 1% of patients in any group, *n* (%)				
Febrile neutropenia	10 (2)	14 (2)	4 (1)	8 (1)
Neutropenia	3 (<1)	7 (1)	2 (<1)	5 (1)
Neutrophil count decreased	1 (<1)	8 (1)	1 (<1)	0

CYP, cytochrome P450; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Table 4. Summary of TEAEs according to use of concomitant BCRP substrate drugs

	Concomitant BCRP substrate use		No BCRP substrate use	
	Rolapitant 180 mg (*N* = 803)	Control (*N* = 834)	Rolapitant 180 mg (*N* = 491)	Control (*N* = 467)
Patients with ≥1 TEAE, *n* (%)	529 (66)	568 (68)	299 (61)	272 (58)
TEAE in ≥ 10% of patients in any group, *n* (%)				
Fatigue	123 (15)	114 (14)	30 (6)	32 (7)
Alopecia	80 (10)	98 (12)	18 (4)	14 (3)
Constipation	77 (10)	103 (12)	40 (8)	48 (10)
Headache	57 (7)	85 (10)	24 (5)	16 (3)
Patients with ≥1 TESAE, *n* (%)	72 (9)	88 (11)	30 (6)	38 (8)
TESAE in ≥ 1% of patients in any group, *n* (%)				
Febrile neutropenia	12 (1)	20 (2)	2 (<1)	2 (<1)
Neutropenia	4 (<1)	11 (1)	1 (<1)	1 (<1)
Neutrophil count decreased	2 (<1)	3 (<1)	0	5 (1)

BCRP, breast cancer resistance protein; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

neutropenia, occurring in 1% and 2% of patients receiving rolapitant and placebo, respectively (Table 2). No TESAEs or deaths were considered drug related.

Concomitant CYP2D6 substrate drugs

In all, 1368 patients (53%) received concomitant CYP2D6 substrate drugs, none of which had a narrow therapeutic index (like thioridazine and pimozide). The CYP2D6 substrate drugs most commonly administered in the rolapitant and control groups were antiemetic agents, such as ondansetron (administered to 8% and 12% of patients, respectively) and metoclopramide (administered to 7% and 9% of patients, respectively), as well as ranitidine (administered to 8% and 10% of patients, respectively). When grouped by concomitant CYP2D6 substrate use versus non-use, common TEAEs and TESAEs occurred with similar frequency in the rolapitant and control populations (Table 3).

Concomitant BCRP substrate drugs

In all, 1637 patients (63%) received concomitant BCRP substrate drugs. The most frequently administered BCRP substrate drugs in the rolapitant and control populations were doxorubicin (administered to 23% of patients in each group), fluorouracil (administered to 17% and 18% of patients, respectively), docetaxel (administered to 11% of patients in each group), and epirubicin (administered to 9% and 10% of patients, respectively). Common TEAEs and TESAEs occurred with comparable frequencies in the rolapitant and control populations when patients were grouped by BCRP substrate drug use versus non-use (Table 4) or by use of specific BCRP substrate chemotherapeutic

agents, e.g. docetaxel, doxorubicin, epirubicin, fluorouracil, etoposide, irinotecan, methotrexate, or topotecan (supplementary Tables S1 and S2, available at *Annals of Oncology* online).

Discussion

Patients with cancer frequently receive multidrug regimens, including treatment of the underlying disease and comorbidities as well as supportive care therapies for analgesia, anemia, depression, neutropenia, and CINV. Thus, identification of DDIs that may affect the safety or efficacy of these treatments is crucial. This integrated safety analysis of 2595 patients receiving emetogenic chemotherapies, some of which were CYP2D6 or BCRP substrates [16–18], demonstrated that oral 180 mg rolapitant was well tolerated, with an incidence and profile of TEAEs and TESAEs similar to those in the control population. In general, observed TEAEs (e.g. fatigue and alopecia) could be attributed to chemotherapy or underlying disease. When analyzed by CYP2D6 or BCRP substrate drug use versus non-use, the incidence and profile of TEAEs were similar in the rolapitant and control groups, revealing no new safety signals for rolapitant, with the safety profile observed consistent with that reported in individual rolapitant studies [16–18]. In a separate post hoc analysis of these trials, rolapitant was well tolerated over multiple cycles of emetogenic chemotherapy agents, with no increase in the frequency of TEAEs and no cumulative toxicity [26].

As rolapitant is a moderate inhibitor of CYP2D6, there is a potential for DDIs with CYP2D6 substrate drugs. For example, antidepressants are commonly prescribed to patients with cancer, and some are metabolized by CYP2D6 [27, 28]. In this large cohort, specific antidepressants were not identified among the commonly used CYP2D6 substrate drugs, and as a class, overall use of these medications was 6% and 7% in the rolapitant and control groups, respectively. Instead, ondansetron, metoclopramide, and ranitidine were the most commonly administered CYP2D6 substrates. Importantly, no use of CYP2D6 substrate drugs with a narrow therapeutic index such as thioridazine or pimozide occurred across the nearly 2600 patients in these studies, suggesting that such agents are rarely used [29]. In this analysis, inhibition of CYP2D6 by rolapitant did not increase the frequency of TEAE or TESAEs in patients using concomitant substrate drugs of CYP2D6, consistent with the low expression of CYP2D6 versus CYP3A4 in the GI tract (<1% versus 40%) and the liver (2% versus 80%), both of which are important for drug metabolism and disposition [11, 30].

Oral rolapitant is an inhibitor of BCRP, and caution should be exercised with concomitant use of BCRP substrates with a narrow therapeutic index (e.g. irinotecan, methotrexate, rosuvastatin, or topotecan); patients requiring these substrates should be carefully monitored for adverse reactions related to the concomitant drug [15]. In this large cohort, overall use of irinotecan, methotrexate, and topotecan was 2.7% and 2.6% in the rolapitant and control groups, respectively. In these patients, inhibition of BCRP did not increase the frequency of TEAEs or TESAEs associated with concomitant use of a BCRP substrate chemotherapy agent with a narrow therapeutic index. Overall, our data indicate that concomitant administration of rolapitant with frequently used BCRP substrate drugs did not adversely affect its safety profile.

Of note, some substrate drugs may have overlapping substrate specificity with other CYP isozymes. For example, ondansetron is a substrate of CYP1A2/CYP2D6/CYP3A4 [31]. Moreover, some BCRP substrates are also *P*-glycoprotein substrates [32]. Our *in vitro* and *in vivo* studies demonstrated that rolapitant did not inhibit CYP1A2, CYP3A4, CYP2E1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 [15, 21, 23]; it inhibited BCRP and, only modestly inhibited *P*-glycoprotein [22]. Therefore, the specificity of rolapitant in inhibiting CYP isozymes and drug transporters suggested that CYP2D6 and BCRP inhibition was likely the main mechanism of DDIs. Furthermore, for drugs with overlapping substrate specificity, inhibiting CYP2D6 or BCRP alone may not lead to a clinically relevant increase in AEs of substrate drugs since they likely undergo other elimination pathways. Our analysis supported this hypothesis and demonstrated that inhibition of CYP2D6 or BCRP by rolapitant did not increase AEs of co-administered drugs in CINV patients. However, this post hoc analysis did not investigate the dose or number of concomitant CYP2D6 or BCRP substrate drugs used, factors which may alter the risk of DDIs. The overall results of this post hoc analysis support the tolerability of rolapitant in a large number of patients as part of an antiemetic triple-drug regimen in patients receiving emetogenic chemotherapy, including those administered concomitant medications that are substrates of CYP2D6 or BCRP.

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Disclosure

SB has received travel fees from TESARO, Inc. XW, DP, SA, and VK are employees and stockholders at TESARO, Inc. MA is a consultant or has received other honoraria from Helsinn, Merck, Roche, and TESARO, Inc. JH is a member of the rolapitant advisory board at TESARO, Inc. and has taught courses on antiemetics at Sobi. TS has declared no conflicts of interest.

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