Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials

Bernardo L Rapoport, Martin R Chasen, Cesare Gridelli, Laszlo Urban, Manuel R Modiano, Ian D Schnadig, Allen Poma, Sujata Arora, Vikram Kansra, Lee S Schwartzberg, Rudolph M Navari

Summary

Background Highly emetogenic chemotherapy induces emesis in almost all patients in the absence of prophylaxis. Guidelines recommend use of a neurokinin-1 (NK-1) receptor antagonist in conjunction with a 5-HT_3 receptor antagonist and corticosteroid in patients receiving highly emetogenic chemotherapy. We aimed to assess rolapitant, an NK-1 receptor antagonist, for prevention of chemotherapy-induced nausea and vomiting in patients with cancer after administration of cisplatin-based highly emetogenic chemotherapy.

Methods We conducted two global, randomised, double-blind, active-controlled, phase 3 trials (HEC-1 and HEC-2) at 155 cancer centres (76 in HEC-1 and 79 in HEC-2) in 26 countries (17 in HEC-1 and 14 in HEC-2). We enrolled patients with cancer aged 18 years or older, who had not previously been treated with cisplatin, with a Karnofsky performance score of 60 or higher, and a predicted life expectancy of 4 months or longer. We used an interactive web-based randomisation system to randomly assign patients to treatment. Patients were stratified by sex and randomly allocated to either oral rolapitant (180 mg dose; rolapitant group) or a placebo that was identical in appearance (active control group) about 1–2 h before administration of highly emetogenic chemotherapy. All patients received granisetron (10 μg/kg intravenously) and dexamethasone (20 mg orally) on day 1, and dexamethasone (8 mg orally) twice daily on days 2–4. Every cycle was a minimum of 14 days. In up to five subsequent cycles, patients were allowed to receive the same study drug they were assigned in cycle 1, unless removed at the clinician's discretion. Patients could also choose to leave the study at any point. Efficacy analysis was done in the modified intention-to-treat population (comprising all patients who received at least one dose of study drug at a cancer centre compliant with Good Clinical Practice [GCP]). The primary endpoint was the proportion of patients achieving a complete response (no emesis or use of rescue medication) in the delayed phase (>24–120 h after initiation of chemotherapy) in cycle 1. These studies are registered with ClinicalTrials.gov, numbers NCT01499849 and NCT01500213. Both studies have been completed.

Findings Between Feb 21, 2012, and March 12, 2014, 532 patients in HEC-1 and 555 patients in HEC-2 were randomly assigned to treatment. 526 patients in HEC-1 (264 rolapitant and 262 active control) and 544 in HEC-2 (271 rolapitant and 273 active control) received at least one dose of study drug at a GCP-compliant site and were included in the modified intention-to-treat population. A significantly greater proportion of patients in the rolapitant group had complete responses in the delayed phase than did patients in the active control group (HEC-1: 192 [73%] *vs* 153 [58%]; odds ratio 1·9, 95% CI 1·3–2·7; p=0·0006; HEC-2: 190 [70%] *vs* 169 [62%]; 1·4, 1·0–2·1; p=0·0426; pooled studies: 382 [71%] *vs* 322 [60%]; 1·6, 1·3–2·1; p=0·0001). The incidence of adverse events was similar across treatment groups. The most commonly reported treatment-related treatment-emergent adverse events in the rolapitant versus active control groups were headache (three [<1%] *vs* two [<1%]), hiccups (three [<1%] *vs* four [<1%]), constipation (two [<1%] *vs* three [<1%]), and dyspepsia (two [<1%] *vs* three [<1%]). For cycle 1, the most common grade 3–5 adverse events in patients allocated rolapitant versus active control were neutropenia (HEC-1: nine [3%] *vs* 14 [5%]; HEC-2: 16 [6%] *vs* 14 [5%]), anaemia (HEC-1: one [<1%] *vs* one [<1%]; HEC-2: seven [3%] *vs* two [<1%]), and leucopenia (HEC-1: six [2%] *vs* two [<1%]; HEC-2: two [<1%] *vs* two [<1%]). No serious treatment-emergent adverse events were treatment related, and no treatment-related treatment-emergent adverse events resulted in death.

Interpretation Rolapitant in combination with a 5-HT_3 receptor antagonist and dexamethasone is well-tolerated and shows superiority over active control for the prevention of chemotherapy-induced nausea and vomiting during the at-risk period (120 h) after administration of highly emetogenic cisplatin-based chemotherapy.

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The Medical Oncology Centre of Rosebank, Saxonwold, Johannesburg, South Africa (B L Rapoport MD); **The Ottawa Hospital Cancer Center, Ottawa, ON, Canada** (M R Chasen MD); **Division of Medical Oncology, San Giuseppe Moscati Hospital, Avellino, Italy** (C Gridelli MD); **Matrahaza Healthcare Center and University Teaching Hospital, Matrahaza, Hungary** (L Urban MD); **ACRC/Arizona Clinical Research Center and Arizona Oncology, Tucson, AZ, USA** (M R Modiano MD); **Compass Oncology, US Oncology Research, Tualatin, OR, USA** (I D Schnadig MD); **TESARO Inc, Waltham, MA, USA** (A Poma MD, S Arora MSc, V Kansra PhD); **The West Clinic, Memphis, TN, USA** (L S Schwartzberg MD); **and Indiana University School of Medicine, South Bend, IN, USA** (R M Navari MD)

Correspondence to:
Dr Bernardo L Rapoport, The Medical Oncology Centre of Rosebank, Saxonwold 2196, Johannesburg, South Africa
brapoport@rosebankoncology.co.za

Research in context

Evidence before this study

We searched PubMed and Embase between January, 2004, and May, 2015, with the terms "CINV", "NK-1", "netupitant", "aprepitant", and "rolapitant", with no language restrictions. Neurokinin-1 (NK-1) signalling pathways are involved in both the acute and delayed phases of chemotherapy-induced nausea and vomiting. Current treatment guidelines recommend concurrent use of an NK-1 receptor antagonist and a 5-HT_3 receptor antagonist and dexamethasone for prophylaxis of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Currently available NK-1 receptor antagonists (eg, aprepitant, netupitant) are inhibitors or inducers of CYP3A4, which could result in increased adverse events or necessitate dose adjustments of concomitant drugs.

Added value of this study

Rolapitant is a novel NK-1 receptor antagonist that binds with high affinity to the human NK-1 receptor, maintaining more than 90% receptor binding up to 5 days after a 180 mg dose, consistent with its long half-life. Furthermore, the metabolic profile of rolapitant indicates that it does not induce or inhibit CYP3A4. We did two identically designed, randomised, double-blind, phase 3 trials to compare rolapitant with active control and found that rolapitant was safe and effective for prophylaxis of chemotherapy-induced nausea and vomiting when combined with a 5-HT_3 receptor antagonist and dexamethasone in patients with cancer who received cisplatin-based highly emetogenic chemotherapy.

Implications of all the available evidence

These two global studies show that one dose of oral rolapitant taken with a 5-HT_3 receptor antagonist and dexamethasone before administration of chemotherapy provides protection for the entire at-risk period for chemotherapy-induced nausea and vomiting. Rolapitant provides a longacting treatment option for the prevention of chemotherapy-induced nausea and vomiting for cisplatin-based highly emetogenic chemotherapy with little potential for clinically relevant CYP3A4-mediated drug–drug interactions. This simpler regimen could result in better overall cancer treatment adherence in patients receiving highly emetogenic chemotherapy.

Introduction

Chemotherapy-induced nausea and vomiting can impair functional activity and quality of life in patients being treated with cytotoxic chemotherapy and can compromise treatment adherence.[1,2] The primary consideration for determining effective prophylaxis for chemotherapy-induced nausea and vomiting is the emetogenic potential of the chemotherapeutic regimen, which is categorised as high (>90% risk of inducing vomiting), moderate (>30–90% risk), low (10–30% risk), and minimal (<10% risk).[3–5] Cisplatin administered at doses higher than 50 mg/m² has high emetogenic potential,[3–5] with an initial peak in nausea and vomiting in the first 1–2 h, which subsides around 18–24 h,[6] and a second peak at 48–72 h.[7] This pattern led to the definition of two phases of chemotherapy-induced nausea and vomiting: acute (≤24 h after initiation of chemotherapy) and delayed (>24–120 h after chemotherapy).[8] The primary endpoint used in clinical trials assessing agents for control of chemotherapy-induced nausea and vomiting is generally complete response (defined as no emesis or use of rescue medication) during acute, delayed, or overall (0–120 h) phases.[9]

Separate pathophysiological mechanisms seem to underlie the two phases of chemotherapy-induced nausea and vomiting, with serotonin (5-HT) signalling mostly triggering the early vomiting process within 8–12 h after cisplatin chemotherapy. Although NK-1 signalling has some role in acute chemotherapy-induced nausea and vomiting (≤24 h), this pathway primarily mediates the delayed phase (>24–120 h).[10]

Rolapitant (TESARO, Inc, Waltham, MA, USA) is a highly-selective NK-1 receptor antagonist.[11] In a ferret model that predicts antiemetic activity in patients, administration of one oral dose of rolapitant significantly prevented cisplatin-induced retching and vomiting during both acute and delayed phases.[11] Rolapitant binds the human NK-1 receptor with high affinity (K_i 0·66 nmol/L)[11] and maintains greater than 90% receptor binding up to 5 days after a dose of 180 mg.[12] It also is not an inhibitor or inducer of CYP3A4[12] and has a long half-life (roughly 180 h), suggesting that one dose could be sufficient to prevent chemotherapy-induced nausea and vomiting during the entire 5-day (0–120 h) at-risk period. In a phase 2 study assessing the safety and efficacy of four different doses of rolapitant for prevention of chemotherapy-induced nausea and vomiting due to highly emetogenic chemotherapy,[13] a 180 mg oral dose of rolapitant, in combination with a 5-HT_3 receptor antagonist and dexamethasone, was shown to be safe and effective.

In three phase 3 studies, we aimed to assess the safety and efficacy of 180 mg rolapitant for prevention of chemotherapy-induced nausea and vomiting in patients with cancer who received moderately or highly emetogenic chemotherapy. We conducted two identical but separate studies designed for cisplatin-based highly emetogenic chemotherapy to address regulatory requirements and provide adequate evidence of clinical benefit, the results of which are presented here. Results from the randomised trial of moderately emetogenic chemotherapy and regimens containing an anthracycline and cyclophosphamide are presented separately.[14]