

Differential clinical pharmacology of rolapitant in delayed chemotherapy-induced nausea and vomiting (CINV)

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Abstract: Rolapitant is a highly selective neurokinin-1 receptor antagonist, orally administered for a single dose of 180 mg before chemotherapy with granisetron D1, dexamethasone 8 mg BID on day 2–4. It has a unique pharmacological characteristic of a long plasma half-life (between 163 and 183 hours); this long half-life makes a single use sufficient to cover the delayed emesis risk period. No major drug–drug interactions between rolapitant and dexamethasone or other cytochrome P450 inducers or inhibitors were observed. The clinical efficacy of rolapitant was studied in two phase III trials in highly emetogenic chemotherapy and in one clinical trial in moderately emetogenic chemotherapy. The primary endpoint was the proportion of patients achieving a complete response (defined as no emesis or use of rescue medication) in the delayed phase (>24–120 hours after chemotherapy). In comparison to granisetron (10 µg/kg intravenously) and dexamethasone (20 mg orally) on day 1, and dexamethasone (8 mg orally) twice daily on days 2–4 and placebo, rolapitant showed superior efficacy in the control of delayed and overall emesis. This review aims at revising the pharmacological characteristics of rolapitant, offering an updated review of the available clinical efficacy and safety data of rolapitant in different clinical settings, highlighting the place of rolapitant in the management of chemotherapy-induced nausea and vomiting (CINV) among currently available guidelines, and exploring the future directions of CINV management.

Keywords: nausea, vomiting, chemotherapy, rolapitant, CINV

Introduction

Cancer treatment has evolved over time, with new treatment strategies improving the treatment outcomes. However, chemotherapy-induced nausea and vomiting (CINV) is still considered a distressing and annoying adverse event for chemotherapy. The perception of patients for nausea and vomiting has changed overtime, CINV ranked first as the most apprehended adverse events of chemotherapy in a study reported in 1983.¹ In a similar study reported in 2014, nonphysical adverse effects ranked first as the most important adverse events affecting patients daily life (social life disturbance fatigue and loss of hair), and nausea is still considered one of the most distressing physical adverse effects, while vomiting came at the 39th position.² Patients may accept temporary alterations in their health status for a gain in survival.³

There have been major advances in CINV control with the advent of new drug classes during the past 2 decades, but many barriers prevent the optimal control of CINV. These barriers include the awareness of physicians and oncology nurses with the existing guidelines and adherence to these guidelines in everyday practice.^{4–8} Guideline-inconsistent CINV prophylaxis leads to suboptimal control of CINV, and this reflects on

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the patients' quality of life, compliance to chemotherapy, and increased rates of hospitalization and emergencies.⁴ Underestimation of other contributing factors affecting CINV, such as coadministration of opioids, female gender, disease-related factors, drug availability, and cost, represents an obstacle in the way to proper management of CINV.

Our understanding of the pathophysiology of CINV and neurotransmitters through which chemotherapy induces CINV supported the rationale of combinational therapy for control of CINV.⁹ Emesis is classically classified according to the time of onset¹⁰ as: 1) acute-phase emesis (during the first 24 hours of chemotherapy administration), which is mediated by serotonin release from enterochromaffin cells and through binding to 5-hydroxytryptamine₃ (5-HT₃) receptors, 2) delayed-phase emesis (after 24–120 hours after chemotherapy) and is mediated by substance P and neurokinin receptors.^{9,11} Dopamine (D₂) receptors also contribute to CINV.¹²

Acute and delayed emesis pathways are not completely separate and may overlap, with some NK-1-mediated activity noted during the acute phase.¹³ Targeting different receptors and neurotransmitters with different classes of drugs maximize the overall control rates of CINV (defined as no emesis and no use of rescue drugs during the 120 hours after chemotherapy). Inadequate control of emesis in acute and delayed phases further complicates the CINV, with the development of anticipatory vomiting in patients who had poor control of acute and delayed phases, and anticipatory vomiting is refractory and very difficult to control.⁹

The tachykinin family of neurotransmitters and their receptors had been recognized since the 1970s, neurokinin-1 (NK-1) receptor is one of substance P receptors and the main mediator of delayed nausea and vomiting.¹⁴ The identification of NK-1 receptor role in delayed emesis was followed by the development of NK-1 receptor antagonizing agents (NK-1RA).¹⁵ Aprepitant and fosaprepitant are the first NK-1-targeting drugs used in clinical practice since their approval in 2004, with improved complete response (CR) rates and control of delayed emesis. Newer drugs targeting NK-1 were developed including casopitant, rolapitant, and netupitant.¹⁶

Rolapitant is a highly selective NK-1 receptor antagonist with a long half-life up to 180 hours. Rolapitant was previously tested for prevention of postoperative emesis, but with dose levels different than those studied for CINV (5, 20, 70, and 200 mg).¹⁷ It was superior to placebo in the control of postoperative emesis in a dose-dependent manner. In September 2015, rolapitant has been approved by the US Food and Drug Administration for use in three drug regimens

in combination with 5HT₃ antagonists and corticosteroids for prophylaxis against CINV.¹⁸

This paper aims to revise the pharmacological characteristics of rolapitant, to offer an updated review of the available clinical efficacy and safety data of rolapitant in different clinical settings, to highlight the place of rolapitant in the management of CINV in currently available guidelines, and to explore the future directions of CINV management.

Rolapitant: NK-1 RA with unique characteristics

Rolapitant is a highly selective NK-1 receptor antagonist with minimal affinity to NK-2 or NK-3 receptors.¹⁹ Studies of pharmacokinetics in animal models confirmed the unique pharmacological characters of rolapitant as a potent competitive inhibitor of NK-1.²⁰

Rolapitant is well absorbed after oral intake and could be measured in plasma after 30 minutes of oral intake; maximum plasma concentration (C_{max}) level is reached after 4 hours of administration. The systemic exposure to rolapitant increases by increasing the dose (for an increase in dose by 4 times from the recommended clinical dose of 180 mg, the C_{max} and area under the curve of rolapitant increased by 3.1-fold and 3.7-fold, respectively), with no effect of fatty meal intake on its absorption.¹⁹

The drug crosses the blood–brain barrier and remains bound to the NK-1 for a median of 120 hours. The NK-1 receptor occupancy by the rolapitant increases in a dose-dependent manner with 73% occupancy with the dose of 180 mg.²¹ The correlation between receptor occupancy and efficacy has not been established, although the higher efficacy of higher doses of rolapitant (180 mg) in comparison to other lower dose levels has been established.²²

One of the main characteristics of rolapitant is the long plasma half-life (between 163 and 183 hours), which is longer than the half-life of aprepitant (9–13 hours) and netupitant (90 hours). This long half-life supports the use of a single dose of the drug sufficient to cover the delayed phase emesis risk period of 120 hours.²³

Pharmacokinetics in different cancer patient populations was studied, including in patients with hepatic and renal impairment. No change in drug exposure was noted based on patient characteristics, with a pattern of distribution in patients with renal and hepatic impairment similar to that in healthy population.²⁴ The elimination of rolapitant is mainly through hepatic/biliary route, and there are no safety data available for use in severe hepatic impairment nor in severe renal impairment.¹⁸

The main difference in pharmacokinetics between rolapitant and other NK-1 RA is the lack of major drug–drug interactions. While the main drug–drug interactions reported with other NK-1RA is through the activation of cytochrome P450 (CYP) enzyme, causing variable degrees of interactions and requiring dose modifications of concomitant medications as dexamethasone.¹⁶ Rolapitant is metabolized by CYP3A4, but it is neither an inhibitor nor an activator of it. The influence of other drugs on rolapitant metabolism comes from the drugs competing with the CYC3A4 enzyme, mainly as inducers. No dose adjustments are required for midazolam, ondansetron, or dexamethasone with rolapitant. Rifampicin is a CYP3A4 inducer, and it is better to avoid concurrent use with rolapitant.¹⁸

However, it is a moderate CYP2D6, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) inhibitor. This requires close monitoring on concurrent administration with other CYP2D6 substrates as digoxin. It is better to avoid concurrent use with thioridazine, as a significant prolongation of Q-T interval may occur as a result of the increase in thioridazine in plasma.¹⁸

Dosage regimens and modifications

The most effective dose of rolapitant is 180 mg once before chemotherapy, with concurrent use of dexamethasone on D2-3 (8 mg twice daily). This dose was validated through a randomized, double-blind, active-controlled, global study that evaluated four different dose levels of rolapitant (9, 22.5, 90, and 180 mg) in patients receiving HEC mainly with cisplatin-based chemotherapy. 180 mg was superior to other dose levels in acute and delayed phases. The improvement was seen in terms of efficacy and quality of life.²²

Safety of rolapitant in severe hepatic and renal impairment was not tested, and no dose modifications are required for mild to moderate hepatic or renal impairment.¹⁹

Aprepitant and fosaprepitant dosage schedules are different; aprepitant multiday dosage of 125 mg on D1 then 80 mg on D2,3 is the standard treatment. Fosaprepitant is the active prodrug of aprepitant that could be administered intravenously, and the dose of fosaprepitant is 150 mg on day 1 only and it has similar kinetics and efficacy to oral aprepitant.²⁵ NEPA (netupitant and palonosetron combination) has the privilege of being an exclusively oral regimen that can be administered once before chemotherapy.²⁶ With all of the previously mentioned NK-1 inhibitors, dose modifications for dexamethasone and precautions in concurrent use with warfarin are required; many drug interactions develop as a result of the activation of CYP3A4.¹⁶ This is not reported with rolapitant.¹⁹

Clinical efficacy studies

Three phase III trials studied the clinical efficacy of rolapitant for the control of delayed CINV: two studies in patients receiving HEC²⁷ (highly emetogenic chemotherapeutic agents) and one study in patients receiving MEC²⁸ (moderately emetogenic chemotherapy agents). The proper interpretation of the results of these trials requires a revision of the history of chemotherapeutics classification according to emetogenicity and its modifications over time.

Hesketh et al²⁹ proposed a classification for the acute emetogenicity of antineoplastic agents administered by short course intravenous infusion (less than 3 hours). They classified antineoplastic agents into five classes based on the proportion of patients developing acute emesis after chemotherapy administration without prophylactic antiemetic treatment. The five levels into which antineoplastic agents were classified were as follows: level I (<10% of patients experience acute emesis); level II (10%–30%); level III (30%–60%); level IV (60%–90%); and level V (>90%).²⁹

Refinements and modifications took place later on with the combination of level III and level IV in one group (MEC) including drugs with emetogenic potentiality between 90% and 30%.³⁰ MEC class of antineoplastic agents is a heterogeneous group, including agents like carboplatin with associated rate of emesis around 82% and the development of delayed emesis.³¹ Adriamycin/cyclophosphamide (AC) was commonly classified as moderately emetogenic combination till 2011; then, according to the cumulative data showing a higher emetogenicity of AC than other MEC agents, it was reclassified in the ASCO recommendations and it was included in the HEC group.³²

Efficacy in HEC

HEC1 and HEC2 study population were mainly males (63%); lung cancer was the most frequent represented malignancy (43%). Patients with other malignancies were enrolled as well (head and neck malignancies 19%, breast cancer 5%, ovarian cancer 5%, and gastric cancer 5%). The mean dose of cisplatin received was 77 mg/m² in HEC1 and 76 mg/m² in HEC2.¹⁹ The age range of patients in HEC1 was 20–90 years, and the age range for patients in HEC2 was 19–83 years. Other chemotherapeutic agents in combination with cisplatin were allowed including paclitaxel, gemcitabine, 5FU, vinorelbine, docetaxel, pemetrexed, and etoposide.²⁷

The dose of rolapitant was 180 mg on day 1 two hours before chemotherapy concurrently with dexamethasone 20 mg orally and granisetron on day 1, dexamethasone 8 mg BID on day 2–4. The control arm was granisetron (10 µg/kg

intravenously) and dexamethasone (20 mg orally) on day 1, and dexamethasone (8 mg orally) twice daily on days 2–4 and placebo.²⁷

The primary endpoint was the proportion of patients achieving a CR (defined as no emesis or use of rescue medication) in the delayed phase (>24–120 hours after chemotherapy). Acute and overall responses were also studied as secondary endpoints, together with no clinically significant nausea (maximum nausea on a visual analog scale [VAS] <25 mm) in the overall phase.²⁷

The combined analysis of both studies showed significant increase in the proportion of patients having a CR in the delayed phase in comparison to the active control arm (pooled studies: 382 [71%] versus 322 [60%], odds ratio 1.6, confidence interval [CI]: 1.3–2.1; $P=0.0001$). The secondary endpoint of acute phase control and overall control proportion was different between the two studies; HEC1 showed significant increase in the rate of control of both acute and overall emesis, while in HEC2 results there was no difference between the rolapitant arm and the active control arm in these points. The pooled analysis of both trials showed superiority of rolapitant in the control of both acute and overall emesis.²⁷

Efficacy in MEC

The trial evaluating rolapitant in MEC²⁸ included patients receiving cyclophosphamide and anthracycline-based combinations (52% of the study population), 30% receiving carboplatin, 6% receiving irinotecan, and 3% receiving oxaliplatin. The mean age was 57 years, and male patients represented 20% of study population, which is expected in a study including breast cancer patients (64%). The study started enrollment in 2010 before the reclassification of AC as highly emetogenic combination.³²

The active control arm was granisetron and dexamethasone, and the intervention arm was rolapitant 180 mg once before chemotherapy with 1 hour and no steroids at subsequent days in combination with granisetron and dexamethasone. The primary endpoint was complete control in the delayed phase as defined in HEC studies, and secondary endpoints were proportions of patients with CR in the acute (0–24 hours after initiation of chemotherapy) and overall (0–120 hours) phases.²⁸

The trial met the primary endpoint with a significant increase in proportion of patients achieving a CR in the delayed phase (475 [71%] versus 410 [62%]; odds ratio 1.6, 95% CI: 1.2–2.0; $P=0.0002$). This benefit was not seen at the acute emesis control, as there was no difference between the rolapitant and active control arms.²⁸

Multiple analyses were done based on the data proposed by these three studies in different population and specific disease areas. For patients above 65 years old, rolapitant showed efficacy and safety comparable to that in patients younger than 65 years old.

Efficacy and safety in patients receiving carboplatin was also evaluated in a post hoc analysis examining a subgroup of MEC study on carboplatin (401 patients).³³ The proportion of patients who achieved complete control of delayed emesis was 82% in the rolapitant group versus 63% in the control group ($P<0.001$).³³

During the three previously mentioned trials, patients were allowed to continue on the same antiemetic treatment regardless of the response for up to six cycles. A post hoc analysis for the pooled data from these three phase III trials and a phase II trial²² was performed assessing the outcomes of treatment beyond the first cycle (cycle 2–6).³⁴ The rate of treatment discontinuation was similar between the intervention and the control group and was attributed to completion of chemotherapy course. The rolapitant control of emesis remains significantly higher with no increased toxicity in patients receiving it beyond the first cycle.

Efficacy in specific types of malignancies

A post hoc analysis was done based on the subgroup of breast cancer patients in the MEC trial. Breast cancer group represented around two-thirds of patients; of this subgroup, 333 received rolapitant and 347 received placebo. Rolapitant showed higher efficacy in controlling CINV in patients receiving AC and non-AC regimens with no increase in toxicity.³⁵

Another post hoc analysis based on the three phase III trials of rolapitant evaluated efficacy and safety in patients with lung cancer treated with either cisplatin or carboplatin. In this analysis, rolapitant increased the rate of CR of delayed emesis by 12% (77% versus 65% among controls) as well as other endpoints, with improved control of nausea (unlike breast cancer population with no improvement in nausea).³⁶

In patients with colorectal and other gastrointestinal (CRC/GI) tumors, receiving MEC or HEC, 188 patients were included (101 received rolapitant, 87 were in the control group). The endpoint studied in this post hoc analysis was CR in overall phase, with 73.3% CR in rolapitant group versus 48.3% in the control, denoting significantly higher rates of CR in the interventional arm ($P<0.001$).³⁷ And finally in patients with gynecological cancers, a post hoc including 200 patients with 55% of them receiving cisplatin-based HEC and 45% received MEC (98% of them received carboplatin), in the overall and

delayed phases, showed improved rates of CR, no emesis, no nausea, and CP with rolapitant compared with control.³⁸

Efficacy in controlling nausea

The concept of describing the nausea and vomiting collectively has been challenged, as the control of emesis does not necessarily imply the control of nausea, rates of uncontrolled nausea around 60% while emesis control around 90%.³⁹

Nausea is very subjective yet a depressive symptom that may interfere with daily life and also a long-term impact on nutritional status of patients along with delayed emesis.⁴⁰ The term nausea is used by patients to describe a variety of symptoms; dizziness, bloating, reflux, inability to concentrate, fatigue, and restlessness are all interpreted by patients as nausea.³⁹

Clinically significant nausea was assessed in the three trials by a VAS as a secondary endpoint. The rates of controlling nausea were superior with rolapitant in HEC1, but no difference was noted in HEC2.²⁷ No difference was noted with rolapitant in rates of nausea in the MEC trial.²⁸ In a post hoc based on the three phase III trials, rolapitant was superior in controlling nausea in all phases (delayed, acute, and overall) in patients receiving cisplatin-based chemotherapy, but in the MEC trial it showed superiority in delayed and overall phases in patients receiving carboplatin-based chemotherapy.⁴¹

Functional Living Index-Emesis (FLIE) was used during the rolapitant studies for quality of life assessment, completed on day 6 of the first cycle.^{27,28} A prespecified analysis on the MEC data and a post hoc on the pooled analysis of HEC trials was done to explore the impact of rolapitant on QOL.⁴² The endpoints explored were FLIE total score, emesis domain scores, and the proportion of patients with no impact on daily life. A significant improvement was observed in QOL in both HEC pooled analysis and MEC study.

Adverse events reported in clinical trials were neutropenia, febrile neutropenia, constipation, dizziness, and fatigue. On comparing the adverse events to the control arm, no significant increase in adverse events were noted and no treatment-related deaths reported.^{27,28} Rolapitant is generally well tolerated with acceptable safety profile.

Place in therapy

The updated Multinational Association for Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO) consensus guidelines 2016 included rolapitant as one of the NK-1 inhibitors used in management of delayed and acute CINV with highly emetogenic chemotherapy (AC HEC and non-AC HEC).^{43,44} The NCCN latest version, 2016, also included rolapitant for the same indication.

For the moderately emetogenic chemotherapy, NK-1RA is not recommended by MASCC/ESMO guidelines in patients receiving MEC with high potential of delayed emesis (including irinotecan, oxaliplatin, and cyclophosphamide). Carboplatin-based MEC is an indication for adding NK-1 RA for prevention of acute emesis, and there is no consensus on prophylaxis against delayed emesis.⁴⁵ Prophylaxis of delayed emesis in patients receiving MEC at first cycle remains dependent mainly on the emetogenic potential of the chemotherapy rather than other factors such as age, gender, and alcohol consumption.^{44,45} NCCN included rolapitant as an acceptable option for moderately emetogenic chemotherapy (category 1 recommendation). The updated ASCO recommendations did not include rolapitant as a treatment option.²⁶

For patients receiving low or minimally emetogenicity antineoplastic, there is no role for NK-1 RA in the acute or delayed phases of emesis. CINV prophylaxis in the low emetogenicity group requires one drug, either dexamethasone, metochlopramide, or 5HT3 antagonist, and no need for combinations to control acute emesis and no need for prophylaxis against delayed emesis.⁴⁶ In patients not attaining a complete CINV control for LEC, palonosetron or olanzapine could be considered, and there are no data to support using NK-1 in this group either.⁴⁶

Till now, no head-to-head trials have been performed to compare NK-1 RA agents' efficacy. The main factors that may give rolapitant an advantage is the lack of drug–drug interactions because of absence of effect on CYP3A4, with major interactions noted with thioridazine, and hence it should be avoided. There is no need for dose modifications for dexamethasone with rolapitant. A network meta-analysis was conducted to evaluate the efficacy of different NK-1RA agents in patients receiving highly emetogenic chemotherapy (HEC), including trials evaluating aprepitant, fosaprepitant, netupitant (NEPA), casopitant, and rolapitant.⁴⁷ The main clinical outcome evaluated in this analysis was the rate of CR, and an indirect comparison between NK-1RA suggested rolapitant/ondan or grani/dexa was inferior to that casopitant/grani, ondansetron/dexa, aprepitant/grani or ondansetron/dexa in terms of CR achievement.⁴⁷ No differences in efficacy were described on indirect comparison between NK-1RAs in controlling nausea.⁴⁷

Aprepitant was included in the algorithm of CINV prophylaxis after high-dose chemotherapy prior to stem cell transplantation. The efficacy of rolapitant in this setting is not clearly defined and is not included in the MASCC/ESMO recommendations for this indication.⁴⁵ Also, there are no efficacy data for NK-1 RA for breakthrough vomiting.

With the established role of the three-agent combination in prevention of CINV (5HT antagonists, NK-1 antagonists, and steroids), the combination of different drugs from each class needs further studies. And also the possibility of replacing two drugs from two different classes with one drug from one class needs to be tested. Only dexamethasone seems to have an irreplaceable role till now, with various schedules in combination with different drug regimens, while other drugs from other classes are used interchangeably with optimal combination not known, as well as the newly introduced drugs as olanzapine.

Other treatment options

NEPA (a combination of neputant and palonosetron) was added to the ASCO recommendations as an option in treating delayed emesis.⁴⁸ This was based on the results of two phase III trials^{49,50} and one phase II trial⁵¹ in comparison to two drug regimens not containing NK-1 inhibitor and dexamethasone on day 1 only. Being a fully oral treatment makes it an appealing option, but the ASCO recommendations raised the concern of cost effectiveness.

Aprepitant dose 165 mg single is registered by EMA,⁵² but this practice is still not adapted by MASCC or other guidelines.

Dopamine antagonist metoclopramide is an old drug, with 5HT3 antagonistic effect in high doses. However, extrapyramidal manifestations may develop in patients receiving high-dose metoclopramide, especially the elderly.¹² Metoclopramide in combination with dexamethasone is a valuable option for delayed emesis prophylaxis in patients receiving cisplatin-based chemotherapy. It was at least noninferior to aprepitant and dexamethasone in preventing delayed emesis.⁵³

Olanzapine, an atypical antipsychotic has been previously evaluated in treatment of breakthrough emesis and showed superior efficacy in comparison to metoclopramide in patients receiving HEC.⁵⁴ Olanzapine targets multiple receptors including dopamine and serotonin receptors. Efficacy and safety of olanzapine as an antiemetic has been studied in multiple phase I and II studies, the rates of no nausea were remarkable across all phases (acute and delayed phase).⁵⁵ The efficacy in these trials led to the conduction of other trials comparing olanzapine versus aprepitant for delayed emesis control in patients receiving HEC. Olanzapine was at least as effective as aprepitant in this study, replacing NK-1RA.⁵⁶ It was also studied in combination with NK-1RA and showed improvement in nausea prevention.⁵⁷ Currently, olanzapine is included in guidelines as an option in management of delayed emesis and nausea.⁴⁴ Adverse events like sedation

and worsening of diabetes are the main concerns while treating patients with olanzapine.⁵⁸

Future directions and emerging data

Treatment options for CINV are expanding, with evolution of new drugs or changes in the dose, route of administration, and schedules for already existing drugs. Improving CINV control with the least adverse events and drug–drug interactions along with proper route of administration is the goal of the ongoing trials.

TESARO (Waltham, MA, USA) submitted a new drug approval request for IV form of rolapitant, supported by data from an open label, single-center, parallel-group, randomized study of bioequivalence in 138 patients (67 received IV rolapitant, 71 received the oral form).⁵⁹ These data were presented in an abstract form in the last MASCC/International Society of Oral Oncology (ISOO) annual meeting (2016) abstract MASCC-0485. The study by Wang et al²⁴ showed comparable efficacy and plasma concentration of IV dose of 166.3 mg of rolapitant to the conventional dose of 180 mg single dose. No approvals for IV rolapitant by any drug agency have been declared till the time of writing this paper.³⁶

APF 530 is a subcutaneous sustained release form of granisetron, with a long half-life of about 180 hours. A comparative noninferiority study was conducted to evaluate the efficacy of subcutaneous APF530 versus palonosetron in acute and delayed emesis in HEC and delayed emesis in MEC. Two dose levels (250 and 500 mg) were not inferior to palonosetron in controlling acute and delayed emesis after HEC and delayed emesis after MEC.⁶⁰ Another phase III trial evaluated APF530 in a three-drug regimen containing NK-1RA (fosaprepitant 150 mg) and steroids, the comparison arm included ondansetron with fosaprepitant and steroids.⁶¹ APF 530 was superior to the ondansetron-containing three-drug regimen in controlling delayed emesis. Exploratory subpopulation analysis for breast cancer patient receiving HEC or MEC for a total of four cycles and APF530 was also noninferior to palonosetron in preventing delayed emesis in this population although no NK-1 RA was included in the regimens.⁶² The place of APF 530 or further utilization in management of delayed emesis is yet to be defined.

Conclusion

Rolapitant represents a valuable addition to CINV prophylaxis armamentarium owing to its high efficacy and acceptable adverse event profile. Being orally administered once before chemotherapy makes it a good option and

improves the patients' compliance with treatment. There is no available data to suggest the use of specific NK-1RA more than another including rolapitant. Comparative studies between the NK-1 RA are required to answer this question. Till then, the drug cost, availability, patient preference, route of administration, and concurrent medications are the main factors that will guide the choice of NK-1RA in consistence with the available guidelines.

Disclosure

This paper does not contain any studies with human participants or animals performed by any of the authors. The authors report no conflicts of interest in this work.

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