Support Care Cancer (2017) 25:607–613
DOI 10.1007/s00520-016-3445-2

ORIGINAL ARTICLE

A randomized trial of olanzapine versus palonosetron versus infused ondansetron for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients undergoing hematopoietic stem cell transplantation

Midori Nakagaki[1] · **Michael Barras**[1,2] · **Cameron Curley**[3] · **Jason P. Butler**[3] · **Glen A. Kennedy**[2,3]

Received: 23 June 2016 / Accepted: 3 October 2016 / Published online: 13 October 2016

Abstract
Purpose The primary aim of this study was to compare the effectiveness of olanzapine, palonosetron and ondansetron infusion (standard of care) for the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) in patients undergoing hematopoietic stem cell transplantation (HSCT).
Method It was a randomized open-label prospective study. Sixty-two patients were randomized to receive either ondansetron 32-mg infusion over 24 h, or olanzapine wafer 10 mg once daily in addition to ondansetron 8 mg IV three times a day or a single dose of palonosetron 0.25 mg IV instead of ondansetron. All groups were allowed rescue antiemetics. The primary endpoint was a composite outcome of no emesis, no use of rescue medication, and nausea score reduction of ≥50 %. The secondary endpoint was nausea score reduction of ≥50 %. Both endpoints were measured at 24 and 48 h after initiation of the study treatment. Statistical analysis was conducted using a double-sided Fisher's exact test.
Result The primary endpoint was achieved in 6, 45, and 18 %, and 6, 64, and 18 % of ondansetron versus olanzapine versus palonosetron patient groups at 24 and 48 h, respectively. The secondary outcome was observed in 17, 60, and 62 %, and 35, 71, and 43 % of ondansetron versus olanzapine versus palonosetron patient groups at 24 and 48 h, respectively. Serious adverse drug reactions were not reported in any arms. Time to engraftment was not significantly different between the arms.
Conclusions Olanzapine was an effective treatment of breakthrough CINV. A single dose of palonosetron significantly reduced nausea up to 24 h.

Keywords Stem cell transplantation · Antiemetics · Ondansetron · Palonosetron · Olanzapine · Nausea and vomiting

Introduction

Hematopoietic stem cell transplantation (HSCT) involves a higher intensity of chemotherapy than the bone marrow can usually tolerate. Despite the traditional drug therapy to prevent chemotherapy-induced nausea and vomiting (CINV), many patients experience prolonged CINV, which can affect patients' wellbeing and treatment outcomes [1].

A number of studies and guidelines have been published to describe the management of CINV [2–10]. However, they mostly focus on general oncology patients who receive standard dose chemotherapy. Almost all studies are prevention studies, due to the general acceptance that prophylaxis is preferred to the treatment of CINV. There is little evidence to

Presented at the American Society of Hematology Annual Meeting (ASH 2015), the Hematology Society of Australia and New Zealand Annual Meeting (HAA 2015), and the Society of Hospital Pharmacists of Australia National Conference (MM2015). The abstract only was published in *Blood* volume 126 (23), pp. 1910, 2015.

✉ Midori Nakagaki
midori.nakagaki@health.qld.gov.au

[1] Pharmacy Department, Level 1 Ned Hanlon Building, Royal Brisbane and Women's Hospital, Butterfield Street, Herston, QLD 4029, Australia

[2] The University of Queensland, Brisbane, Australia

[3] Bone Marrow Transplant Unit, Level 5 Joyce Tweddell Building, Royal Brisbane and Women's Hospital, Butterfield Street, Herston, QLD 4029, Australia

guide the treatment of CINV in HSCT patients who are refractory to the prophylactic antiemetic drugs.

In the past decade, multiple studies demonstrated the usefulness of new antiemetics, in particular aprepitant [8], palonosetron [6, 7], and olanzapine [9] for the prophylaxis of CINV. Aprepitant is recommended with highly emetogenic chemotherapy in American Society of Clinical Oncology (ASCO) [3], National Comprehensive Cancer Network (NCCN) [2] and Multinational Association of Supportive Care in Cancer (MASCC) [4] guidelines. Studies demonstrated its benefit in the prevention of CINV in non HSCT patients [8] and HSCT patients [11, 12]. There seems to be no published randomized studies on aprepitant for the treatment of established CINV.

Palonosetron, a second generation 5-hydroxytryptamine (5HT3) receptor antagonist, has demonstrated its superiority to the older 5HT3 receptor antagonists in prevention of CINV in general oncology patients [6, 7]. A recent study [13] showed palonosetron is at least as effective as the first generation 5HT3 receptor antagonists to prevent CINV in allogeneic HSCT patients. Two other studies showed higher efficacy of palonosetron when comparing with historical control ondansetron [14, 15]. Palonosetron is increasingly used to prevent CINV in HSCT. As far as we are aware, there have been no comparative studies evaluating palonosetron for the treatment of breakthrough CINV in HSCT. One study [16] used a second dose of palonosetron when patients had breakthrough CINV and the response rate was 50 %.

Olanzapine, a drug typically used for the treatment of mental health illness, blocks multiple neurotransmitter receptors including dopamine D1, D2, D3, and D4 receptors, serotonin 5-HT2a, 5-HT2c, 5-HT3, and 5-HT6 receptors, alpha-1 adrenergic receptors, muscarinic receptors, and histamine H1 receptors [10]. It is a novel agent studied in phase III studies for the prophylaxis [9, 17] and the treatment [10] of CINV. These studies showed that olanzapine was at least as effective as aprepitant to prevent CINV and was superior to low dose metoclopramide to treat breakthrough CINV in general oncology patients. Based on these two studies, olanzapine is included in NCCN guidelines as an option to prevent and treat CINV. There are no randomized studies on olanzapine in HSCT patients.

In our hospital, intravenous (IV) ondansetron 8 mg three times daily plus aprepitant single dose 165 mg are used to prevent CINV in HSCT. To treat breakthrough CINV, rescue metoclopramide or lorazepam is used as well as an increasing scheduled ondansetron dose to 32 mg as a continuous infusion. We hypothesized that palonosetron and olanzapine are likely to be effective to treat breakthrough CINV in HSCT patients. Therefore, our aim was to compare the effectiveness of olanzapine, palonosetron, and infused ondansetron for the treatment of CINV in patients undergoing HSCT.

Patients and methods

Study design

This was a randomized open-label prospective study to evaluate the effectiveness of olanzapine versus palonosetron versus infused ondansetron for the treatment of breakthrough CINV associated with high-dose chemotherapy in a HSCT setting. This study received ethical approval from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (RBWH HREC, EC00172).

Patients

Eligible patients were aged 18 to 70 and receiving allogeneic or autologous HSCT following high-dose chemotherapy. The patients who had freely provided informed consent to participate were enrolled to the study. Patients were excluded if they were allergic to any of the study medications, taking olanzapine as a regular medication, at risk for an adverse drug event from the study drugs (e.g., patients with Q-T prolongation), had nausea or vomiting before HSCT or did not have an adequate understanding of written and spoken English.

Study treatment

Patients were admitted as inpatients before they commenced prophylactic therapy prior to high-dose chemotherapy with or without total body irradiation (TBI). All patients were administered the standard prophylaxis of IV ondansetron 8 mg three times a day plus a single dose of oral aprepitant 165 mg. This single dose aprepitant has replaced a 3-day course of 125, 80, and 80 mg aprepitant in Australia and they appear to be pharmacologically equivalent [18, 19]. Aprepitant was given on the same day as high dose cyclophosphamide or melphalan. Metoclopramide 10 mg oral or IV and lorazepam sublingual 1 mg were allowed as rescue medication and patients were instructed to request them only if they have CINV. The treatment phase of the study began when the patient experienced emesis or developed moderate to severe nausea (visual analog scale: VAS ≥30 mm) or required the use of more than one dose of rescue medication per day. Once this occurred, patients were randomized in a 1:1:1 fashion into one of the three treatment arms:

- Arm 1: ondansetron 32 mg daily IV in 250 mL normal saline as a continuous infusion over 24 h (control)
- Arm 2: olanzapine 10 mg oral wafer once daily while continuing ondansetron IV 8 mg three times a day
- Arm 3: palonosetron 0.25 mg IV as a single dose (stop ondansetron for 3 days)

Patients also received other supportive medications according to the standard treatment protocol, including immunosuppressants, anti-infectives, nutritional supplementation, and a proton pump inhibitor. Steroids were not used as antiemetics but allowed to be prescribed to prevent hypersensitivity with drugs and blood products. Once randomized, the allocated treatment was continued for 48 h whenever possible.

Evaluation

The patient's nausea risk was assessed before enrollment into the study by asking about history of CINV, morning sickness, motion sickness, and alcohol intake. The questions were selected from the identified risk factors for CINV in numerous studies [20–22]. Once chemotherapy was started, the number of emesis events, severity of nausea, and rescue antiemetic dose were recorded every morning as part of routine nursing observation. Assessment of emesis events and severity of nausea were documented by patients, while rescue antiemetic usage was obtained from the medication administration record. After patients were randomized, data was collected at 24 h to assess the first 24 h and at 48 h to assess the 24–48 h period after starting treatment. The use of additional corticosteroids and antihistamines for any other reasons were recorded.

To quantify the severity of nausea, patients were asked to use the 100 mm VAS on a data collection sheet, a method validated [23] and used in the similar studies [9, 10]. VAS = 0 mm is defined as no nausea and VAS = 100 mm being the worst possible nausea. As nausea changes over time, the patients were instructed to score the overall intensity and frequency of nausea during the past 24 h.

The primary endpoint was a composite outcome of no emesis, no use of rescue medication, and nausea score reduction of ≥50 % compared to the VAS at randomization. The secondary endpoint was nausea score reduction of ≥50 %. Both endpoints were measured per 24-h period at 24 and 48 h after initiation of the study treatment. Statistical analysis of study arms was conducted using a double-sided Fisher's exact test. The p value less than 0.05 was considered to be statistically significant.

Results

Patients

In total, 94 patients were enrolled between May 2014 and July 2015. In 21 patients, CINV was well prevented and they were not randomized. Seventy-three patients met the randomization criteria; however, eight patients were not randomized due to the absence of the staff familiar to the study on weekends. In addition, one patient did not tolerate ondansetron. Of the 64 patients who were randomized, one patient did not provide data due to difficulty in using VAS and monitoring emesis and one patient was taking the rescue medication prophylactically and did not provide appropriate data. Therefore, 62 patients were included in the final data analysis (Fig. 1).

Patients' age, gender, HSCT type, disease, conditioning regimen, alcohol intake, and past CINV are shown in Table 1. Overall 55 % of patients had undergone autologous and 45 % had allogeneic HSCT. Conditioning regimens included high-dose melphalan (200 mg/m^2) and BEAM for autologous HSCT and Cy/TBI and fludarabine/melphalan (melphalan 120 mg/m^2) for allogeneic protocols. There were no significant differences between autologous and allogeneic, or between conditioning regimens in any of the arms. Patients' age, gender, and other risk factors such as history of CINV were not significantly different between arms.

CINV and nausea score at randomization

When randomized, more than 50 % of patients had nausea without emesis (Table 2). Two patients were randomized due to emesis only with no nausea. The initial VAS nausea scores were approximately the same for each arm.

Treatment efficacy

Figure 2 presents the percentage of patients who achieved the primary endpoint. The primary endpoint was achieved in 6 % (1/18) of patients on ondansetron, 45 % (10/22) of patients on olanzapine, and 18 % (4/22) of patients on palonosetron at 24 h. At 48 h, it was achieved in 6 % (1/17), 64 % (14/22), and 18 % (4/22), respectively. Overall, olanzapine was significantly more effective at controlling breakthrough CINV compared to ondansetron at both 24 and 48 h ($p = 0.01$ and 0.0002,

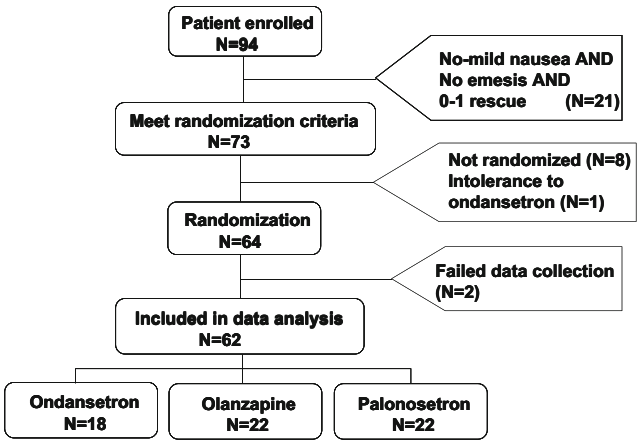

Fig. 1 Consort diagram (N = number of patients)

Table 1 Patient characteristics

		Ondansetron	Olanzapine	Palonosetron
Age (years)	Median	53	58	51
	Range	26–65	20–68	21–65
Gender	Male	14 (78 %)	14 (64 %)	11 (50 %)
	Female	4	8	11
HSCT type	Allogeneic	7	8	13
	Autologous	11	14	9
Conditioning	BEAM	2	5	2
	FluMel	4	6	6
	HDM	6	5	5
	CyTBI	1	1	5
	FluCy	2	1	1
	Other	3	4	3
Alcohol intake	Chronic	1	4	3
Past CINV	Nil	5	6	3
	Mild-moderate	5	13	7
	Severe	6	2	4

respectively). Olanzapine was also more effective than palonosetron at 48 h ($p = 0.005$). Palonosetron failed to show statistically significant benefits above ondansetron at 24 h ($p = 0.36$) and at 48 h ($p = 0.36$).

The secondary outcome, nausea score reduction of ≥50 %, was observed in 17 % (3/18) of patients on ondansetron, 60 % (12/20) of patients on olanzapine, and 62 % (13/21) of patients on palonosetron, and 35 % (6/17), 71 % (15/21), and 43 % (9/21) at 24 and 48 h, respectively (Fig. 3). Olanzapine was more effective than ondansetron at controlling nausea at both 24 and 48 h ($p = 0.0009$ and $p = 0.048$, respectively). However, there was no significant difference between olanzapine and palonosetron in reduction of nausea score ≥50 % at either time point. Palonosetron was superior to ondansetron at nausea control at 24 ($p = 0.008$) but not at 48 h.

Table 2 Emesis and nausea experience (patient number) and VAS score at randomization

	Ondansetron ($N = 18$)	Olanzapine ($N = 22$)	Palonosetron ($N = 22$)
Emesis only	0	1	1
Nausea only	14	17	11
Emesis and Nausea	4	4	10
Mean VAS	50	51	54
Range	19–80	0–100	0–82

N number of patients, *VAS* visual analog scale (0–100 mm)

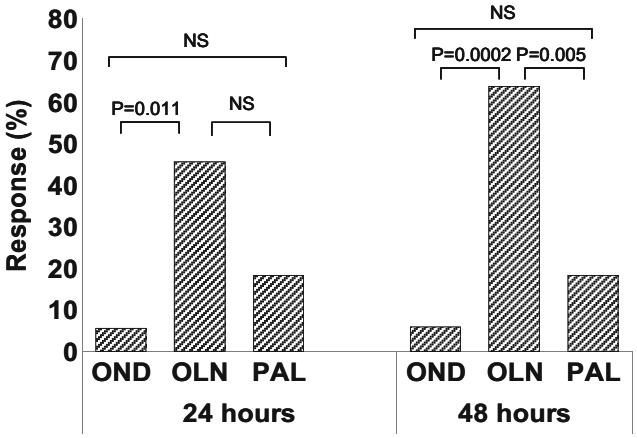

Fig. 2 Overall response rate (primary endpoint). Olanzapine (OLN) was significantly more effective than ondansetron (OND) at 24 and 48 h. It was also more effective than palonosetron (PAL) at 24 h

Safety

Serious adverse drug reactions were not reported in any arms. Some patients reported mild constipation with ondansetron and mild sedation with olanzapine. The median duration from stem cell infusion to the engraftment was 13, 13, and 14 days, respectively (p-NS) for ondansetron, olanzapine, and palonosetron arms. In the patients who were not randomized, the median duration was 13 days.

Discussion

The high-dose chemotherapy in association with a HSCT presents a special challenge to achieving good antiemetic control. In this study, only 22 % of the 94 patients had complete protection (no emesis, up to one dose of rescue and had no or mild nausea); however, an additional 37 % were emesis free until

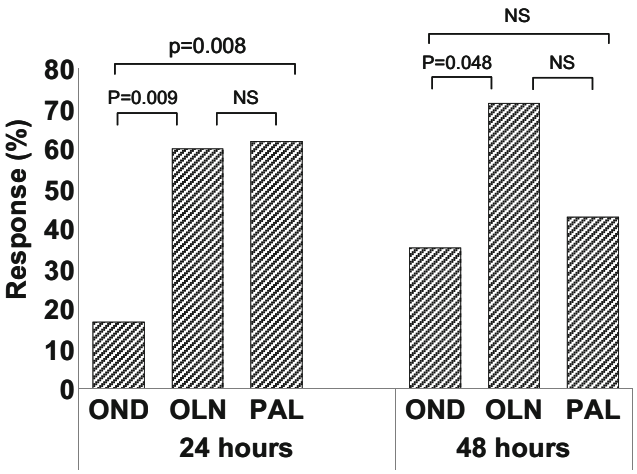

Fig. 3 Nausea response rate (secondary endpoint). Olanzapine (OLN) was more effective than ondansetron (OND) at 24 and 48 h. Palonosetron (PAL) was more effective than ondansetron (OND) at 24 h but not at 48 h

the end of the observation period. The response rate to the prophylaxis (22 % complete protection) is comparative to two recently published data using palonosetron and dexamethasone in HSCT patients [16, 24], but lower than the response rate in two other studies [11, 12] that used aprepitant for 3 days, ondansetron/granisetron, and dexamethasone. Our result could be explained due to the fact that we did not use a corticosteroid or due to the once only aprepitant dosing regimen. Further studies are needed to clinically evaluate the appropriate regimen of aprepitant. Considering that 80 % of patients had emesis or more than one dose of rescue or moderate to severe (VAS ≥30 mm) nausea in our data, better antiemetic prophylaxis regimens are required in HSCT patients. Timing of breakthrough nausea was most commonly day 2 to 4 after highly emetogenic chemotherapy was given although it is difficult to determine as most regimens are multi-day. From the results of this study, 32 mg daily ondansetron given as a 24-h continuous infusion provides a minimum response rate for the patients who developed breakthrough CINV despite ondansetron and aprepitant prophylaxis. Increasing the dose of the same agent or changing administration method does not provide any greater benefits. Instead, changing to or adding different agents would provide more promising results. Considering this result with recent FDA warnings against ondansetron 32 mg (due to the risk of Q-T prolongation), this practice needs to be reviewed at a local level. Of note, palonosetron has not been shown to prolong Q-T interval [25].

For the primary endpoint, palonosetron did not show a statistically significant benefit over ondansetron. However, when only nausea score was considered, palonosetron showed a significantly higher response rate at 24 h (62 vs 17 %, $p = 0.008$). Although palonosetron and ondansetron are both 5HT3 receptor antagonists, this high response rate after failing ondansetron suggests that switching 5HT3 receptor antagonists is a useful option to treat CINV. This is a similar result to the double blind trial conducted in solid tumor patients, in which patients who experienced breakthrough CINV while using ondansetron were successfully treated with granisetron [26]. In this study, the response rate was 47 % compared to 5 % with continuation of ondansetron. In our study, it is not clear whether the effectiveness is due to switching 5HT3 antagonist or due to the superiority of palonosetron over ondansetron.

For many patients, nausea is more troublesome compared to the occasional emesis without nausea. Therefore, the drugs that reduce nausea score without significant effects on emesis can still be beneficial to the patients. The benefits of palonosetron were reduced past 24 h and not superior to ondansetron at 48 h. This indicates that a single dose or 48 hourly dose are not sufficient, and most likely a once daily dose of 0.25 mg is required to effectively control CINV.

The safety and efficacy of multiple dose of palonosetron has not been fully established. However, according to the studies [16, 21, 23], daily palonosetron for 3 to 5 days appears to be safe as it was not associated with increased adverse drug reactions compared to once only dose. The use of daily palonosetron should be further explored in HSCT patients to establish the most effective dose strategy.

Olanzapine appears highly effective to treat emesis, and when assessing the nausea score only, 71 % of the patients responded within 48 h. The high response rate to olanzapine is most likely due to multiple extra receptor brockage while maintaining 5HT3 blockage. This result is similar to the study published by Navari et al. who assessed olanzapine for the treatment of CINV in solid tumor patients [10]. In this study, they treated breakthrough CINV associated with highly emetogenic chemotherapy with olanzapine or metoclo pramide. Olanzapine had a higher response rate than metoclopramide (no emesis 70 vs 31 %, no nausea 68 vs 23 %, $p < 0.01$). Although HSCT patients have mostly multi-day high-risk chemotherapy, our result was comparative with general oncology patients. Olanzapine was initially approved in Australia in 1996 and is currently inexpensive. Although this indication is yet to be approved by the local regulatory bodies therefore considered "off label," olanzapine is an effective and cost-efficient treatment for CINV compared to palonosetron or aprepitant.

The safety of ondansetron and single-dose palonosetron is well established. We assessed the effects of olanzapine on the time to engraftment based on the uncommon adverse reaction of bone marrow suppression and cytopenias. Only patients who used peripheral blood stem cells were included in the analysis. The duration from stem cell infusion to engraftment was not different between arms and the cohort that were not randomized. A short course of olanzapine 10 mg seems to be a safe antiemetic in HSCT patients.

There are some limitations to this study. Possibly due to the small sample size, the palonosetron arm failed to show a statistically significant benefit over ondansetron for the primary outcome at 24 h ($p = 0.104$), despite the significant nausea improvement at 24 h. In addition, the study patients were heterogeneous and received different conditioning chemotherapy regimens, although majority of patients had CINV after either cyclophosphamide or melphalan administration. As this is a treatment study and previously conducted study [10] also used patients with a variety of cancers, we believe it should not affect our result extensively.

Despite these limitations, there were novel findings. First, the number of studies evaluating antiemetics for the established CINV is surprisingly low in the cancer care setting. In HSCT patients, a literature review identified only one study, showing that the response rate for the second dose of palonosetron was 50 % [16]. In general cancer patients, there was only one study [26] until the study was published by Navari et al. [10], which showed the benefits of olanzapine. Our study showed significant benefit of olanzapine over

increasing the ondansetron dose from 24 to 32 mg. This result matched their study. Our study only showed the significant nausea control by palonosetron at 24 h. The effect at 48 h could be further investigated with more frequent use of palonosetron.

Secondly, as far as we are aware, this is the first study evaluating olanzapine in HSCT patients. Our results showed that olanzapine is beneficial in this population. Nausea and vomiting in HSCT patients tend to be more prolonged, and in later stage, it can be multifactorial. Given that olanzapine is a multi-receptor antagonist and originally showed the benefit in patients with advanced cancer and refractory nausea, it can be particularly useful in HSCT patients.

Finally, what would be interesting in the future is a comparison of antiemetics such as olanzapine and aprepitant without the influence of corticosteroid throughout conditioning chemotherapy, as they always have been evaluated in combination with dexamethasone.

Conclusions

Olanzapine is an effective treatment of breakthrough CINV in HSCT patients. In addition, palonosetron is an effective treatment of nausea up to 24 h. Further studies are required to determine the ideal dosing frequency of palonosetron in HSCT patients.

Acknowledgment We thank Prof. Peter O'Rourke for his help with the statistical analysis, Prof. Jason Roberts for his support with the ethics application, and the nursing staff in BMT unit, Royal Brisbane and Women's Hospital for their assistance with data collection.

Compliance with ethical standards

Conflict of interest This study was financially supported in part by the Royal Brisbane and Women's Hospital Foundation. It was also conducted as dissertation in Master of Oncology, Newcastle University, UK.

Financial disclosure This study was supported partly by RBWH foundation.

References

1. Trigg ME, Inverso DM (2008) Nausea and vomiting with high dose chemotherapy and stem cell rescue therapy: a review of antiemetic regimens. Bone Marrow Transplant 42:501–506
2. NCCN guidelines, Antiemetics Version 1, 2016, National Comprehensive Cancer Network, 2016. [Online]. Available: www.nccn.org. Accessed 15 Jan 2016
3. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Somerfield MR, Lyman GH (2012) Antiemetic use in oncology: updated guideline recommendations from ASCO. Am Soc Clin Oncol Educ Book 532–40
4. MASCC/ESMO ANTIEMETIC GUIDELINE 2016, Multinational Association of Supportive Care in Cancer, 2016. [Online]. Available: http://www.mascc.org/antiemetic-guidelines
5. Navari R, Aapro M (2016) Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. N Engl J Med 374: 1356–1367
6. Likun Z, Xiang J, Yi B, Xin D, Tao ZL (2011) A systematic review and meta-analysis of intravenous palonosetron in the prevention of chemotherapy-induced nausea and vomiting in adults. Oncologist 16(2):207–216
7. Jin Y, Sun W, Gu D, Yang J, Xu Z, Chen J (2013) Comparative efficacy and safety of palonosetron with the first 5-HT3 receptor antagonists for the chemotherapy-induced nausea and vomiting: a meta-analysis. Eur J Cancer Care (Engl) 22(1):41–50
8. Dos Santos LV, Souza FH, Brunetto AT, Sasse AD, Da Silveira Nogueira Lima JP (2012) Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review. J Natl Cancer Inst 104(17):1280–1292
9. Navari RM, Gray SE, Kerr AC (2011) Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 9(5):188–195
10. Navari RM, Nagy CK, Gray SE (2013) The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 21(6): 1655–1663
11. Schmitt T, Goldschmidt H, Neben K, Freiberger A, Hüsing J, Gronkowski M, Thalheimer M, Pelzl LH, Mikus G, Burhenne J, Ho AD, Egerer G (2014) Aprepitant, granisetron, and dexamethasone for prevention of chemotherapy-induced nausea and vomiting after high-dose melphalan in autologous transplantation for multiple myeloma: results of a randomized, placebo-controlled phase III trial. J Clin Oncol 32(30):3413–3420
12. Stiff PJ, Fox-Geiman MP, Kiley K, Rychlik K, Parthasarathy M, Fletcher-Gonzalez D, Porter N, Go A, Smith SE, Rodriguez TE (2013) Prevention of nausea and vomiting associated with stem cell transplant: results of a prospective, randomized trial of aprepitant used with highly emetogenic preparative regimens. Biol Blood Marrow Transplant 19(1):49–55
13. Chou C-W, Chen Y-K, Yu Y-B, Chang K-H, Hwang W-L, Teng C-LJ (2014) Palonosetron versus first-generation 5-hydroxytryptamine type 3 receptor antagonists for emesis prophylaxis in patients undergoing allogeneic hematopoietic stem cell transplantation. Ann Hematol 93(7):1225–1232
14. Pielichowski W, Barzal J, Gawronski K, Mlot B, Oborska S, Wasko-Grabowska A, Rzepecki P (2011) A triple-drug combination to prevent nausea and vomiting following beam chemotherapy before autologous hematopoietic stem cell transplantation. Transplant Proc 43(8):3107–3110
15. Pielichowski W, Gawronski K, Mlot B, Oborska S, Wasko-Grabowska A, Rzepecki P (2011) Triple drug combination in the prevention of nausea and vomiting following busulfan plus cyclophosphamide chemotherapy before allogeneic hematopoietic stem cell transplantation. J BUON 16(3):541–546
16. Musso M, Scalone R, Crescimanno A, Bonanno V, Polizzi V, Porretto F, Bianchini C, Perrone T (2010) Palonosetron and dexamethasone for prevention of nausea and vomiting in patients receiving high-dose chemotherapy with auto-SCT. Bone Marrow Transplant 45:123–127
17. Navari RM, Qin R, Ruddy KJ, Liu H, Powell SF, Bajaj M, Dietrich L, Biggs D, Lafky JM, Loprinzi CL(2016) Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med 375(2):134–142
18. Grunberg S, Chua D, Maru A, Dinis J, DeVandry S, Boice JA, Hardwick JS, Beckford E, Taylor A, Carides A, Roila F, Herrstedt J (2011) Single-dose fosaprepitant for the prevention of

chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol-EASE. J Clin Oncol 29(11):1495–1501
19. Shadle C, Murphy M, Liu Y, Ho M, Tatosian D, Li S, R.A B (2012) A single-dose bioequivalence and food effect study with aprepitant and fosaprepitant dimeglumine in healthy young adult subjects. Clin Pharmacol Drug Dev 1(3):93–101
20. Molassiotis A, Stamataki Z, Kontopantelis E (2013) Development and preliminary validation of a risk prediction model for chemotherapy-related nausea and vomiting. Support Care Cancer 21(10):2759–2767
21. Molassiotis A, Aapro M, Dicato M, Gascon P, Novoa SA, Isambert N, Burke TA, Gu A, Roila F (2014) Evaluation of risk factors predicting chemotherapy-related nausea and vomiting: results from a European prospective observational study. J Pain Symptom Manag 47(5):839–848.e4
22. Bouganim N, Dranitsaris G, Hopkins S, Vandermeer L, Godbout L, Dent S, Wheatley-Price P, Milano C, Clemons M (2012) Prospective validation of risk prediction indexes for acute and delayed chemotherapy-induced nausea and vomiting. Curr Oncol 19(6):e414–e421
23. Meek R, Kelly AM, Xue FH (2009) Use of the visual analog scale to rate and monitor severity of nausea in the emergency department. Acad Emerg Med 16(12):1304–1310
24. Giralt SA, Mangan KF, Maziarz RT, Bubalo JS, Beveridge R, Hurd DD, Mendoza FL, Rubenstein EB, DeGroot TJ, Schuster MW (2011) Three palonosetron regimens to prevent CINV in myeloma patients receiving multiple-day high-dose melphalan and hematopoietic stem cell transplantation. Ann Oncol 22(4):939–946
25. Navari R (2013) The current status of the use of palonosetron. Expert Opin Pharmacother 14(10):1281–1284
26. De Wit R, De Boer AC, Vd Linden GHM, Stoter G, Sparreboom A, Verweij J (2001) Effective cross-over to granisetron after failure to ondansetron, a randomized double blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy. Br J Cancer 85(8):1099–1101