Omission of dexamethasone from antiemetic treatment for highly emetogenic chemotherapy in breast cancer patients with hepatitis B infection or diabetes mellitus

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Background Chemotherapy with anthracycline- and cyclophosphamide-containing regimens are classified as highly emetogenic. Combinatory treatments of aprepitant (Apr), palonosetron (Pal), or granisetron (Gra) with dexamethasone are recommended as antiemetic treatments for such emetogenic chemotherapy. We retrospectively examined whether omission of dexamethasone is tolerable for patients with hepatitis B virus (HBV) and diabetes mellitus (DM), for whom it is recommended not receive dexamethasone.

Patients and methods During August 2009 and September 2007, we reviewed the medical records of patients with breast cancer who were HBV carriers or had been diagnosed with DM. 97 patients were treated with anthracycline- and cyclophosphamide-containing regimens with omission of dexamethasone in antiemetic treatment because of their HBV or DM status.

Results The number of patients treated with Gra only, Apr and Gra, Apr and Pal, were 29, 29, and 39, respectively. Complete response (CR) in the acute phase (0-<24 hours after chemotherapy) or delayed phase (24-120 hours after chemotherapy) for Gra only, Apr-Gra, and Apr-Pal was 44.8% and 44.8%, 72.4% and 72.4%, and 76.9% and 74.4%, respectively. Complete control (CC) in the acute or delayed phase in each regimen for Gra only, Apr-Gra, and Apr-Pal was 31.0% and 27.6%, 48.2% and 51.7%, and 46.2% and 46.2%, respectively. Apr-Gra or Apr-Pal tended to be superior to Gra only in CR and CC in both the acute and delayed phases. HBV reactivation or aggravation of DM control was not observed in any of the 3 therapy options. CR and CC were about 20% higher for the dexamethasone-containing regimen than for the non-dexamethasone regimen in both the acute and delayed phases.

Conclusion Omission of dexamethasone in antiemetic treatment is tolerable when anthracycline- and cyclophosphamide-containing chemotherapy is administered to patients with breast cancer who have comorbidities of being HBV carriers or of DM.

Anthracycline- and cyclophosphamide-containing regimens are generally used for breast cancer patients in the neoadjuvant or adjuvant settings as well as for the treatment of advanced breast cancer.[1] Chemotherapies that contain anthracycline and cyclophosphamide are classified as highly emetogenic. Combinations of aprepitant (Apr), palonosetron (Pal), granisetron (Gra), and dexamethasone are recommended as antiemetic therapies for highly emetogenic chemotherapy (HEC).[2]

Dexamethasone was one of the first agents found to be effective in protecting against nausea and vomiting both in the acute and delayed phases. It is currently used extensively, especially in combination with other antiemetic treatments such as 5-HT3 receptor antagonists. Dexamethasone can lower the incidence of nausea and vomiting by about 25%-30% in the acute and delayed phases.[3,4,5] In the combination regimen with dexamethasone and 5-HT3 receptor antagonists, complete response (CR) was almost 90%.[3,4,5]

Aprepitant has been shown to significantly improve both acute-onset nausea and vomiting (AONV) and delayed-onset nausea and vomiting (DONV) when combined with dexamethasone and 5-HT3 receptor antagonists. An aprepitant-containing regimen was beneficial in improving the CR

Accepted for publication March 10, 2016. Correspondence: Yoshie Nakayama, MD; nakayama01077@gmail.com. Disclosures: The authors report no disclosures or financial conflicts of interests. JCSO 2016;14:210-214. doi: 10.12788/jcso.0256.

rates for patients who were treated with doxorubicin and cyclophosphamide, in 2 phase 3 trials.[6,7] Palonosetron (a second-generation 5-HT3 antagonist) was not inferior to other 5-HT3 antagonists such as granisetron, ramosetoron, and ondansetron for CR in the acute and delayed phases, and it was superior to granisetron in the overall phase (the acute and delayed phases) for complete control (CC; $P < .01$).[8] Combination treatments of aprepitant, palonosetron, and dexamethasone is recognized as the best regimen so far for prevention of vomiting and nausea in breast cancer patients who have been treated with anthracycline- and cyclophosphamide-containing regimens.[5]

However, dexamethasone often deteriorates the control of hepatitis B virus (HBV) and diabetes mellitus (DM), and it has been recommended that it is not administered to patients with breast cancer who have those comorbidities. Reactivation of hepatitis B during chemotherapy or molecular target therapy sometimes occurs in patients who are positive for the hepatitis B surface (s) antigen (HBsAg) as well as in patients with an antibody against HBcAb (anti-HBc) or HBsAb (anti-HBs). The spontaneous reactivation is often asymptomatic or mild, but can be severe or even fatal. Some study findings have shown that HBV reactivation during chemotherapy developed in 20%-50% of HBV-seropositive breast cancer patients, usually before overt clinical hepatitis.[9,10,11,12]

Glucocorticoids augment hepatic gluconeogenesis and lower glucose uptake by peripheral tissues such as muscle cells and adipocytes, thereby causing hyperglycemia with insulin resistance. Hemoglobin A1c (HbA1c) testing is recommended for identifying diabetes and prediabetes. American Diabetes Association guidelines recommend an HbA1c level of 6.5% or more to diagnose diabetes and an HbA1c level of 5.7%-6.4% to identify prediabetes. Steroid therapy often deteriorates the control of blood sugar level, so it is recommended that patients with DM should avoid dexamethasone during chemotherapy.[13] There was no definition of safety for the use of steroids for breast cancer patients with DM, with any level of HbA1c. National Comprehensive Cancer Network (NCCN) guidelines (version 1.2012) for antiemesis do not address the use of steroids for patients who are HBV carriers or have diabetes mellitus.[2] As there have been no reports on this question, we retrospectively examined CR, CC, and safety in relation to antiemetic treatment without dexamethasone in breast cancer patients who were treated with anthracycline- and cyclophosphamide-containing chemotherapy.

Patients and methods

Breast cancer patients were treated with the anthracycline- and cyclophosphamide-containing regimens, AC, CAF, and CEF:

- AC consisted of intravenous doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 on day 1;
- CAF consisted of intravenous doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2, and fluorouracil 500 mg/m^2 on day 1, followed by intravenous fluorouracil 500 mg/m^2 on day 8; and
- CEF consisted of intravenous epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2, and fluorouracil 500 mg/m^2 on day 1.

There were 63 HBV-carrier patients and 34 patients with DM (the diagnosis of DM in this study was based on and HbA1c of ≥6.5%). A regimen with granisetron (Gra) only was administered to 29 patients during August 2009-November 2009, of whom 14 were HBV carriers and 15 had DM. A regimen combining aprepitant and granisetron (Apr-Gra) was administered to 29 patients during December 2009-March 2010, of whom 20 were HBV carriers and 9 had DM. A regimen combining aprepitant and palonosetron (Apr-Pal) was administered to 39 patients during July 2010-September 2010, of whom 29 were HBV carriers and 10 patients had DM (Table 1).

Written informed consent about chemotherapeutic agents and antiemetic agents was obtained from each patient before chemotherapy was started. Gra only consisted of intravenous granisetron 3 mg on day 1, followed by oral granisetron 2 mg on days 2-6. Apr-Gra consisted of oral aprepitant 125 mg, and intravenous granisetron 3 mg, on day 1, followed by oral aprepitant 80 mg on days 2-3 and oral granisetron 2 mg on days 2-6. Apr-Pal consisted of oral aprepitant 125 mg and intravenous palonosetron 0.75 mg on day 1, followed by oral aprepitant 80 mg on days 2 and 3 (Figure 1). There was no evidence that longer use of granisetron was better for prevention of emesis. Anthracycline- and cyclophosphamide-containing regimens were highly emetogenic. Thus, until approval of aprepitant, in accordance with our institutional consensus, we used granisetron 2 mg on days 2-6 for as long as possible within acceptable use for insurance.

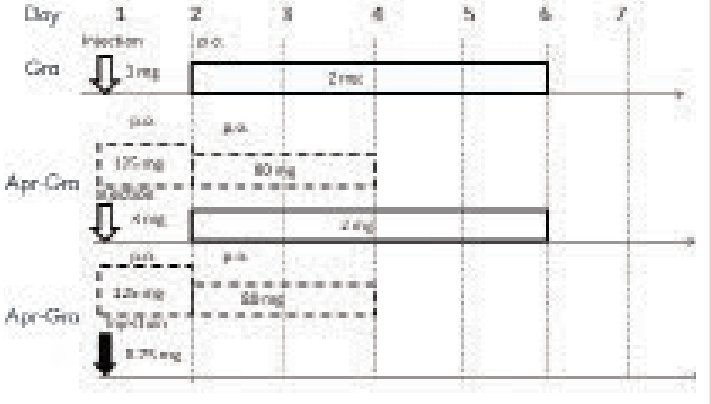

FIGURE 1 The administration schedule

Apr-Gra, aprepitant and granisetron; Apr-Pal, aprepitant and palonpsetron; Gra, granisetron; p.o., orally

TABLE 1 Patient characteristics

Characteristic	Gra only (n = 29)	Apr-Gra (n = 29)	Apr-Pal (n = 39)
Age, y			
Mean (range)	59 (27-74)	58 (36-72)	56 (31-72)
<55, n (%)	10 (34.5)	12 (41.4)	18 (46.2)
≥55, n (%)	19 (65.5)	17 (58.6)	21 (53.8)
Status, n (%)			
HBV carrier	14 (48.3)	20 (69.0)	10 (25.6)
Diabetes mellitus	15 (51.7)	9 (31.0)	29 (74.4)
Performance status, n (%)			
0	29 (100)	27 (93.1)	32 (82.1)
1	0 (0)	2 (6.9)	7 (17.9)
Treatment setting, n (%)			
Neoadjuvant	9 (31.0)	9 (31.0)	11 (28.2)
Adjuvant	20 (69.0)	18 (62.0)	21 (53.8)
Advanced	0 (0)	2 (7.0)	9 (17.9)
Regimen, n (%)			
AC	12 (41.4)	13 (44.8)	12 (30.8)
CAF/CEF	17 (58.6)	16 (55.2)	27 (69.2)
Previous chemotherapy, n (%)			
Naïve	29 (100)	28 (96.6)	37 (94.9)
Non-naïve	0 (0)	1 (3.5)	2 (5.1)
Psychiatric disease, n (%)			
No	23 (79.3)	27 (93.1)	36 (92.3)
Yes	6 (20.7)	2 (6.9)	3 (7.7)
History of GI disease, n (%)			
Yes	2 (6.9)	5 (17.2)	6 (15.4)
No	27 (91.3)	24 (82.8)	33 (84.6)

AC, doxorubicin and cyclophosphamide; Apr-Gra, aprepitant and granisetron; Apr-Pal, aprepitant and palonpsetron; CAF, cyclophosphamide, doxorubicin, and fluorouracil; CEF cyclophosphamide, epirubicin, and fluorouracil; Gra, granisetron; HBV, hepatitis B virus

We used the standard dosage of aprepitant and palonosetron, according to the Japanese Society of Clinical Oncology 2010 guidelines for antiemetics in oncology.[14] We assessed AONV and DONV on day 15 in the first cycle of chemotherapy. Emesis was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The dates of symptoms of nausea and vomiting were collected from questionnaires completed by patients when they visited our department. The questionnaires thus revealed the time the events occurred. Moreover, medical oncologists, nurses, and pharmacists also interviewed the patients about their compliance with the prescribed therapies and confirmed the symptoms they had recorded in the questionnaire responses. We evaluated the proportion of patients with complete response (CR) and complete control (CC) in the acute phase (0-<24 h after chemotherapy) and delayed phase (24-120 h after chemotherapy), as well as the level of nausea and vomiting 1 or 2 weeks after chemotherapy for the Gra only, Apr-Gra, and Apr-Pal groups. Based on the NCCN guidelines, CR was defined as the percentage of no vomiting episodes when no rescue medication was needed, and CC was defined as the percentage of no vomiting episodes when no rescue medication was needed. We calculated no-more-than-mild nausea using the formula, CR+G0+G1/ the number of patients (G0, no nausea; G1, little nausea, but can eat). Differences between CR and CC for Gra only, Apr-Gra, and Apr-Pal were analyzed using the Fisher exact test.

We explained to patients how to use rescue medications

TABLE 2 Complete response and complete control in acute and delayed phases

Phase	Complete response			Complete control		
	Gra (n = 29)	Apr-Gra (n = 29)	Apr-Pal (n = 39)	Gra (n = 29)	Apr-Gra (n = 29)	Apr-Pal (n = 39)
Acute,[a] %	44.8	72.4	76.9	31	48.2	46.2
Delayed,[b] %	44.8	72.4	74.4	27.6	51.7	46.2

Apr-Gra, aprepitant and granisetron; Apr-Pal, aprepitant and palonpsetron; Gra, granisetron

[a]0-<24 hours after chemotherapy. 0-≥24 hours after chemotherapy.

when they were aware of emesis. The rescue medications prescribed were domperidone (suppository only), metoclopramide, bromazepam, lorazepam, aprepitant 5 days in all groups, to standardize CR and CC results. We determined whether the rescue medications were successful or unsuccessful after interviewing the patients when they visited our department. If the rescue medications were not effective, we prescribed additional or other rescue medications. HBV reactivation was defined as 1 of the following: a 10-fold or greater increase in HBV DNA levels compared with the baseline level (using the Quantiplex d DNA assay, Chiron assay); or an absolute increase of HBV DNA level that exceeded 1,000 cells x 10^6 log-genome equivalent/ml.[15,16] Therefore, we monitored HBV DNA once a month. In patients with DM, we monitored blood sugar level using serological tests, and HbA1c concentrations were measured once a month to monitor the patient's DM status.

Results

The numbers of patients treated with Gra only, Apr-Gra, and Apr-Pal were 29, 29, and 39, respectively (Table 1). Age, disease status, treatment setting, regimens, and the presence of psychiatric diseases or gastrointestinal diseases in each group were slightly different. The numbers of HBV carriers with Gra only, Apr-Gra, and Apr-Pal were 14, 20, and 29, respectively. The numbers of DM patients with Gra only, Apr-Gra, and Apr-Pal were 15, 9, and 10, respectively. There was a slight difference in the patient number in each group.

CR in the acute phase for Gra only, Apr-Gra, and Apr-Pal was 44.8%, 72.4%, and 76.9%, respectively (Table 2). CR in the acute phase was not significantly different for the 3 groups, but Apr-Gra and Apr-Pal were superior to Gra only (Figure 2). CR in the delayed phase for Gra only, Apr-Gra, and Apr-Pal was 44.8%, 72.4%, and 74.4%, respectively. CR in the delayed phase was not significantly different for the 3 groups, but Apr-Gra and Apr-Pal were superior to Gra only (Figure 2).

CC in the acute phase for Gra only, Apr-Gra, and Apr-Pal was 31.0%, 48.2%, and 46.2%, respectively. CC in the acute phase was not significantly different for the 3 groups, but Apr-Gra and Apr-Pal were superior to Gra only. CC in the delayed phase for Gra only, Apr-Gra, and Apr-Pal was 29.1%, 51.7%, and 46.2%, respectively. CC in the delayed phase was not significantly different for the 3 groups, but Apr-Gra and Apr-Pal were superior to Gra only (Figure 2). Patients with DM and HBV carriers showed similar responses to the antiemetics. No patients discontinued or postponed chemotherapy agents because of nausea and vomiting. Therefore, we suggest that the dose of AC regimen may not be reduced. There was no incidence of HBV reactivation in this study and in patients with DM, blood sugar levels and HbA1c were well controlled.

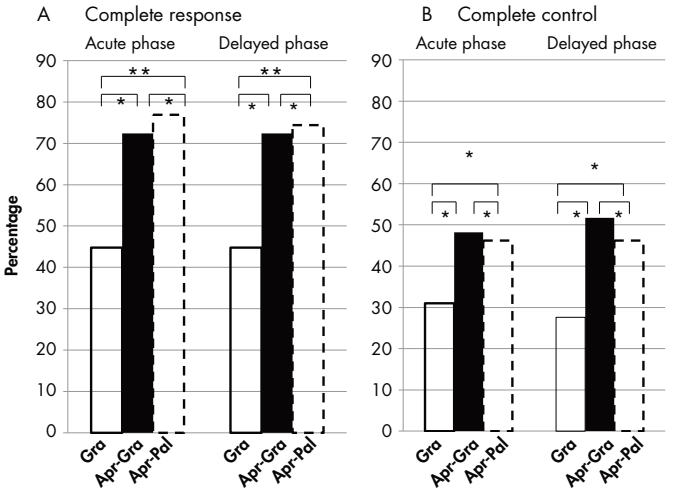

FIGURE 2 A, Complete response and B, complete control in the acute[a] and delayed[b] phases

Apr-Gra, aprepitant and granisetron; Apr-Pal, aprepitant and palonpsetron; Gra, granisetron

[a]0-<24 hours after chemotherapy. [b]24-120 hours after chemotherapy.

*Not significant. $^{**}P < .05$.

Discussion

Anthracycline- and cyclophosphamide-containing regimens are highly emetogenic chemotherapy, therefore the NCCN 2012 and ASCO guidelines recommend combination regimens with NK1 receptor antagonists, 5-HT3 receptor antagonists, and corticossteroids for prevention of acute- and delayed-phase nausea and vomiting. In a retrospective study, CR and CC was about 20% higher for

a dexamethasone-containing regimen than for the non-dexamethasone regimen in both the acute and delayed phases.[5] However, dexamethasone often has a negative effect on the control of HBV and DM, so it is recommended that its use is avoided in HBV carriers or patients who have DM.

In this study, CR and CC in both the acute and delayed phases were higher if dexamethasone was omitted from the regimen than if it had been included. In addition, no patients discontinued or postponed the dose of chemotherapy agents because of nausea and vomiting. And there was no incidence of HBV reactivation in this study. DM patients were able to control their blood sugar levels and HbA1c in this study. Although HBV carriers or patients who have DM prefer to avoid dexamethasone as antiemetic, they need not also avoid anthracycline-containing regimens.

In conclusion, patients with HBV or DM may not require a steroid antiemetic therapy with counseling that their chance of experiencing chemotherapy-induced nausea and vomiting is higher. Instead, omission of dexamethasone in antiemetic treatment is tolerable when anthracycline- and cyclophosphamide-containing chemotherapy is administered to breast cancer patients who are HBV carriers or have DM. Further investigations are warranted for improving CR and CC in DM patients and HBV carriers who are treated with when anthracycline- and cyclophosphamide-containing regimens.

References

1. Early Breast Cancer Trialist's Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-years survival: an overview of the randomized trials. Lancet Oncol. 2005;365:1687-1717.
2. NCCN Clinical Practice Guidelines in Oncology-Antiemesis-ver. 1, 2012. https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed April 26, 2016.
3. Ioannidis JP, Hesketh PJ, Lau J. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. J Clin Oncol. 2000;18:3409-3422.
4. Jantunen IT, Kataja VV, Muhonen TT. An overview of randomized studies comparing 5-HT3 receptor antagonists to conventional antiemetics in the prophylaxis of acute chemotherapy-induced vomiting. Eur J Cancer. 1997;33:66-74.
5. Nakayama Y, Ito Y, Tanabe M, Takahashi S, Hatake K. A combination of aprepitant, palonosetron, and dexamethasone prevents emesis associated with anthracycline-containing regimens for patients with breast cancer. A retrospective study. Breast Cancer. 2013;22:177-184.
6. Gralla RJ, Warr DG, Cardies AD. Effect of aprepitant on antiemetic protection in patients receiving moderately emetogenic chemotherapy plus high-dose cisplatin: Analysis of combined data from 2 phase III randomized clinical trials [ASCO abstract 8137]. J Clin Oncol. 2004;22(14S). 8137-
7. Roila F, Warr D, Clark-Snow RA, et al. Delayed emesis: moderately emetogenic chemotherapy. Support Care Cancer. 2005;13:104-108.
8. Saito M, Aogi K, Sekine I, et al. Palonosetoron plus dexamethasone versus grenisetoron plus dexamethasone. Lancet Oncol. 2009;10:115-124.
9. Wands JR, Chura CM, Roll FJ, Maddrey WC. Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. Gastroenterology. 1975;68:105-112.
10. Xunrong L, Yan AW, Liang R, Lau GK. Hepatitis B virus (HBV) reactivation after cytotoxic or immunosuppressive therapy- pathogenesis and management. Rev Med Virol. 2001;11:287-299.
11. Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology. 2006;43:209-220.
12. Yeo W, Zee B, Zhong S, et al. Comprehensive analysis of risk factor associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer. 2004;90:1306-1311.
13. Tappy L, Randin D, Vollenweider P, et al. Mechanisms of dexamethasone-induced insulin resistance in healthy humans. J Clin Endocrinol Metab. 1994;79:1063-1069.
14. Takeuchi H, Saeki T, Aiba K, et al. Japanese Society of Clinical Oncology clinical practice guidelines 2010 for antiemesis in oncology: executive summary. Int J Clin Oncol. 2016;21:1-12.
15. Yeo W, Chan PK, Zhong S, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol. 2000;62:299-307.
16. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology. 1991;100:182-188.