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NK-1 Receptor Antagonists: Who Truly Need them and their Cost-Effectiveness Analysis?

Akihito Kubo[1*], Ikuto Tsukiyama[2], Sumiyo Tsukiyama[2], Masayuki Ejiri[2], Katsuhiko Matsuura[2], Etsuro Yamaguchi[1] and Masahiko Ando[3]

[1]*Division of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine, Yazakokarimata, Nagakute, Aichi 480-1195, Japan*

[2]*Department of Pharmacy, Aichi Medical University Hospital, Japan*

[3]*Center for Advanced Medical and Clinical Research, Nagoya University Hospital, Japan*

***Corresponding author:** Akihito Kubo, Department of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan, Tel:+81-561-62-3311; Fax: +81-561-62-4652; E-mail: kuboa@aichi-med-u.ac.jp

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Introduction

Chemotherapy Induced Nausea and Vomiting (CINV) remains a major adverse effect of chemotherapy. While the incidence of CINV is declining with the development of antiemetic agents and improvement in various guidelines for the prevention and treatment of CINV, it still has a serious impact on cancer patients' well-being and adherence to chemotherapy.

CINV is categorized as acute (<24 hours after chemotherapy initiation), delayed (24 hours or later), or anticipatory (before chemotherapy). The vomiting reaction occurs by stimulation of the vomiting center in the medulla oblongata through three main pathways: via the path through the fourth ventricle chemoreceptor trigger zone; via afferent vagal nerves from the gastrointestinal tract; and via the cerebral cortex induced by memories or impressions [1-3]. Substance P induces vomiting by binding to the neurokinin-1 (NK-1) receptor, which is highly expressed in the solitary tract nucleus and is part of the vomiting center of the brainstem. NK-1 receptor antagonists (RAs) have been shown to be effective for delayed emesis, which is often regarded as emesis that is difficult to control by conventional antiemetic therapies, and are recommended in antiemetic guidelines in many countries. The level of substance P release by anticancer agents has also been reported to increase on day 2 or later of chemotherapy, explaining the effectiveness of NK-1RAs against delayed emesis.

Antiemetic guidelines classify anticancer agents into four classes according to the risk of emetogenesis: high, moderate, low, and minimum emetogenic agents. For highly emetogenic chemotherapy (HEC), a three-drug preventive antiemetic combination consisting of an NK-1RA, a 5-hydroxytryptamine (5-HT3) receptor antagonist, and a corticosteroid has been recommended. In moderately emetogenic chemotherapy (MEC), this three-drug antiemetic combination is also recommended for patients receiving anthracycline and cyclophosphamide combination chemotherapy [4-6].

While the preventive effect of NK-1RAs in combination with 5-HT3RAs and corticosteroids for CINV has been widely accepted, the cost-effectiveness of aprepitant, the first approved NK-1RA, remains under debate [7-13].

Here in this short review we briefly discuss the utility of NK-1RAs, their cost-effectiveness, and the risk factors of CINV based on published studies.

Cost-effectiveness of NK-1 receptor antagonists

Aprepitant was the first NK-1RA approved in 2003 by the FDA following the results of phase III studies where the preventive effect of aprepitant against CINV in patients receiving HEC was shown [14-16]. Aprepitant is also recommended by various guidelines for MEC regimens of anthracyclines plus cyclophosphamide [4-6]. Based on the results of these phase III studies, antiemetic guidelines recommend the uniform use of aprepitant in combination with 5-HT3RAs and corticosteroids against HEC. The use of NK-1RAs according to demographic factors is not recommended in most guidelines for antiemetic prophylaxis. However, increasing medical cost due to uniform use of NK-1RAs is a concern. In a recent population-based study of patients who received platinum-based chemotherapy after diagnosis of lung cancer from 2001 to 2007, Gomez et al. reported a low adherence to antiemetic guidelines. In 4,566 patients analyzed, adherence rates for receiving NK-1RAs were less than 10%, while compliance rates of 60–90% were seen with a 5-HT3RA and dexamethasone [17].

To date, six studies have compared the cost-effectiveness ratio of antiemetic regimens consisting of aprepitant, a 5-HT3RA, and a corticosteroid with that of a conventional regimen comprising a 5-HT3RA and a corticosteroid for CINV prevention in HEC and in anthracyclines plus cyclophosphamide therapy [7-9,11-13]. Based on the data from published phase III trials of aprepitant [15,16,18-20], these studies calculated the incremental cost-effectiveness ratio (ICER), which is a ratio of the incremental cost per quality adjusted life years (QALY), as the primary index of cost-effectiveness in a putative setting according to each country's economic status.

Moore et al. developed the Markov model with five cycles of cisplatin (70 mg/m^2 or less)–based chemotherapy to compare costs and clinical outcomes associated with an aprepitant-containing three-drug antiemetic regimen and a conventional two-drug regimen. Data from a published clinical trial with a high-dose cisplatin regimen [15] were used to calculate probabilities of each clinical outcome (presence or absence of acute and delayed CINV), and costs were determined from the perspective of the payer. The ICER of the three-drug regimen over the conventional two-drug regimen was determined as 97,429 USD/QALY, which is higher than the commonly accepted threshold of 50,000 USD/QALY. The authors concluded that aprepitant provides only modest benefit and would be cost-effective only when the

likelihood of delayed CINV or the cost of rescue medications was high [7].

Another five studies from Germany, Belgium, the United Kingdom, Hong Kong, and Singapore used a decision analytical model and data from published clinical trials of HEC or MEC of anthracycline plus cyclophosphamide to calculate the probabilities of each of the following health states: complete protection (CP, defined as no emesis, no rescue medication, and maximum nausea less than 25 mm on a 100-mm visual analog scale (VAS)); complete response at best (CRB, defined as no emesis, no rescue medication, and maximum nausea of 25 mm or greater on a 100-mm VAS); or incomplete response (IR, the complement of CP and CRB). ICER was shown to be below the threshold level of each country or the threshold endorsed by the World Health Organization of up to three times gross domestic product per capita per QALY gained. In one report by Annemann et al., the aprepitant-based regimen was reported to be more effective and less expensive (dominant) than the non-aprepitant-based regimen [9].

These economic studies, all with aprepitant, have shown that incremental costs in aprepitant-containing antiemetic regimens are at least partially offset by reduced costs in patient management, rescue medication, and hospitalization (Figure 1). Further studies evaluating the cost-utility of other NK-1RAs and in different economic circumstances are warranted.

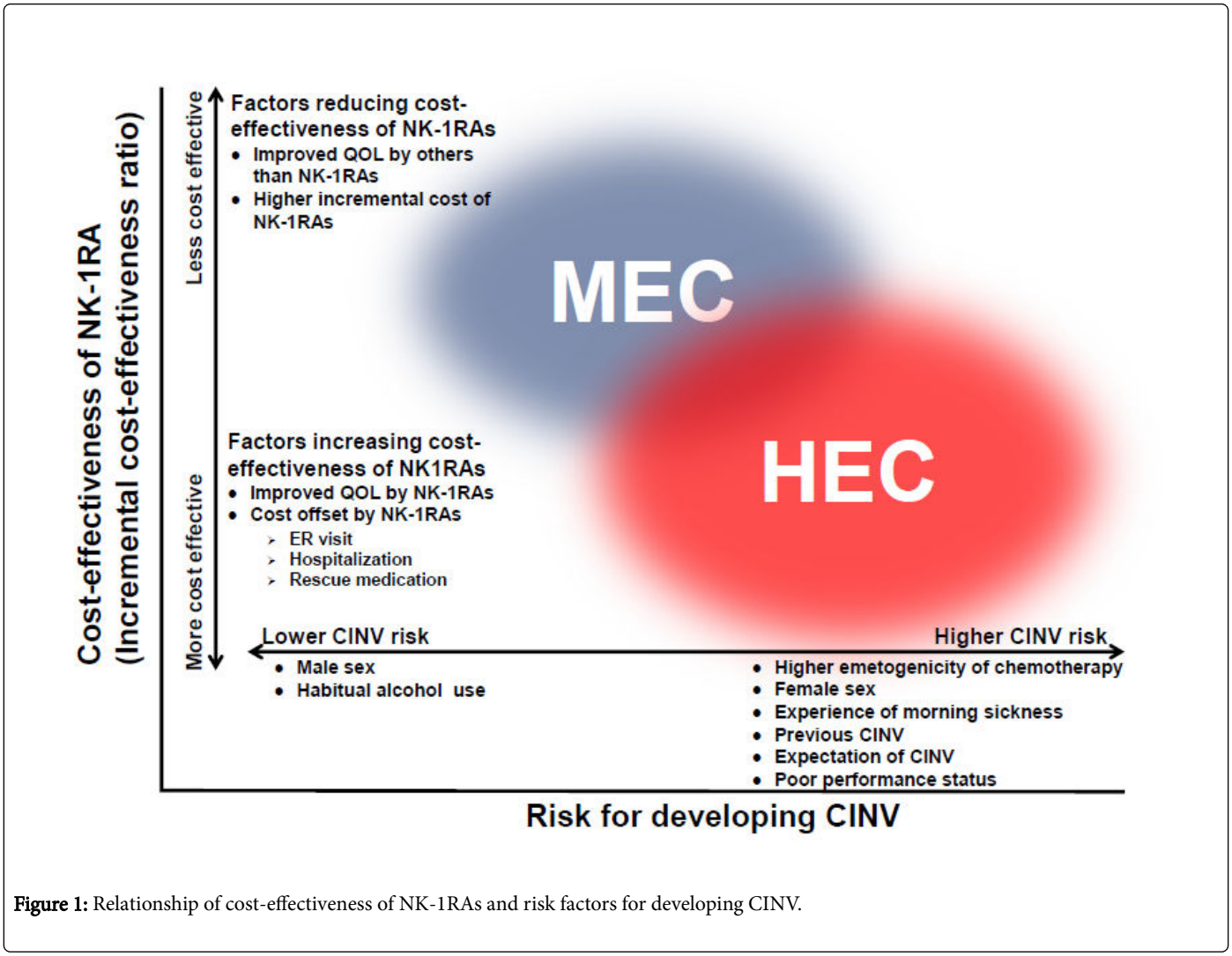

Figure 1: Relationship of cost-effectiveness of NK-1RAs and risk factors for developing CINV.

Who truly need NK-1 receptor antagonists?

Before the introduction of NK-1RAs into the clinic, it was shown that CINV is well controlled by conventional two-drug antiemetic regimens with no NK-1RAs in 40-70% of patients treated with HEC [15,16,19-21]. Thus, whether all patients who are undergoing HEC truly need NK-1RAs remains unclear. While the uniform prophylactic use of aprepitant is recommended in guidelines regardless of demographic risk factors, increased medical costs owing to the uniform use of NK-1RAs are a concern.

When aprepitant was approved and antiemetic guidelines were updated in Japan in 2010, questions and concerns regarding how and whether the uniform prophylactic administration of aprepitant was truly needed were raised in the oncology clinic in Aichi Medical University Hospital (AMUH). To determine the proportion of patients who truly need aprepitant, we prospectively examined 96 consecutive patients with thoracic malignancies who received HEC or MEC with conventional antiemetic prophylaxis with the 5-HT3RA, granisetron, and a corticosteroid. The study was carried out on an in-patient basis after the approval of the institutional review board of AMUH. A

patient who needed aprepitant was defined as a patient who experienced CINV and received aprepitant for therapeutic intent and/or received aprepitant for prophylactic intent in the subsequent courses of chemotherapy. Aprepitant was then administered to patients who needed it to treat CINV in the first course when CINV occurred, or to prevent CINV in the second course. Among 77 patients assessable, aprepitant was not needed in 57% of patients who received HEC, and in 88% of patients who received MEC. Eighteen patients needed aprepitant, and the therapeutic use of aprepitant decreased the average scores in the numerical rating scale for nausea from 7.44 to 5.44 (p=0.10, n=9), and the average frequency of vomiting per day from 2.11 to 0.11 (p=0.03). Prophylactic use of aprepitant in the second course (n=18) increased the proportion of patients with no significant nausea from 6% (first course) to 50% (second course; p=0.007), and those with no vomiting from 33% to 89% (p=0.002). Aprepitant use also significantly improved quality of life with respect to CINV in the second course. The total drug costs for antiemetic therapy were calculated in the first two courses of chemotherapy. The cost of aprepitant was the biggest difference in the total cost of antiemetics between patients who did and did not need aprepitant. Patients who did not experience CINV when using conventional two-drug antiemetics did not need further medical expense involving CINV treatment, and their quality of life was not influenced by CINV. On the other hand, patients who needed aprepitant required further antiemetic therapy, and their quality of life was considerably disrupted by CINV. The results of this study suggested that aprepitant is highly effective against CINV for those who truly need it, while it has little effect for those who do not need it [22]. Further research is warranted to discriminate, before chemotherapy, between patients who need extensive antiemetic treatment against CINV and those who do not.

Risk factors for developing CINV

Since the strongest factor for the development of CINV is the emetogenic potential of the therapeutic regimen, prophylaxis for CINV has been established according to the emetogenicity of anticancer agents that have been categorized into four levels [4-6]. Many potential risk factors of CINV occurrence related to patients have been reported including female sex, younger age, experience of morning sickness during pregnancy, a previous experience to CINV, expectation of CINV, poor performance status, and low alcohol consumption [23-29]. The influence of patient demographic background on CINV is not clearly understood, and a demographic background-based antiemetic strategy is not recommended in CINV guidelines [4-6]. Successful assessment of patients according to the risk of CINV occurrence would help to reduce the prevalence and severity of CINV (Figure 1).

Risk factors for chemotherapy induced nausea (CIN) and those for chemotherapy induced vomiting (CIV) may not be the same, and risk factors for acute CINV and those for delayed CINV may also differ, which may partially reflect a difference in the mechanism of occurrence. Before the introduction of NK-1RAs, Osoba et al. performed an intensive assessment of CINV in 832 chemotherapy-naïve patients receiving HEC or MEC. In multivariate analysis, the variables remaining in the final model included low social functioning, prechemotherapy nausea, female sex, HEC, and the lack of maintenance antiemetics (5-HT3RAs with or without dexamethasone) after chemotherapy. A history of low alcohol use was also associated with CIV, whereas increased fatigue and lower performance status were associated with CIN [26]. Before the introduction of aprepitant in Japan, Sekine et al. examined risk factors for acute and delayed CINV in 1,549 chemotherapy-naïve patients in phase II or phase III trials of palonosetron and showed that female sex (odds ratio, 95% confidence interval: 2.96, 2.09–4.20), age <55 years (2.56, 1.94–3.37), non-habitual alcohol intake (1.90, 1.43–2.51), and non-smoker (1.40, 1.04–1.90) were associated with treatment failure in the acute phase. In contrast, only female sex (1.88, 1.34–2.64) was associated with treatment failure in the delayed phase [30]. While risk factors for developing CINV have been intensively studied, these factors need re-evaluation according to the development of new treatment options and changes in the social healthcare environment. Indeed, addition of aprepitant to a conventional antiemetic regimen improved the CR rate and eliminated or reduced the risk factors of CINV occurrence, such as younger age, female sex, and low alcohol consumption [28,29].

From the patients' perspective

The cost-effectiveness analyses of NK-1RAs reported to date are all from the perspective of the payer or healthcare system, and outcomes were measured using CINV-related health status (i.e., rates of CP, CR, and IR) [7-9,11-13]. Regarding medical costs of CINV, all of these reports included only direct medical costs of CINV, and did not analyze indirect costs. However, in the real-world setting of patients receiving emetogenic chemotherapy, indirect costs due to loss of productivity are also critical, not only from the viewpoint of individual patient lives, but also from a socioeconomic standpoint. Haiderali et al. analyzed 178 patients who underwent HEC (n=53) or MEC (n=125) in the US real-world setting during 2007 to 2008, which was the period after approval of aprepitant. The total direct and indirect medical costs on average associated with CINV were 732.14 USD and 46.39 USD, respectively. However, for patients who were employed at the time and missed work hours, the average indirect costs were higher (180.02 USD in total: 112.40 USD for missed work and 67.62 USD for reduced productivity) [31].

To better understand patient health, evaluation of patient conditions using only CINV-related health status is not sufficient, and an understanding of changes in the health status of the patients during the treatment course is also important. Patient reported outcome measures (PROMs) are designed to obtain the patients' views of their symptoms, functional status, and health-related quality of life, and to compare patient health at different times. In England, PROMs are used nationwide, particularly for performance comparisons, and in Sweden they are used to support clinical practice [32]. Considering that CINV is often underestimated by healthcare professionals, assessment of outcomes of CINV therapy from the patients' perspective is expected to help further improve the performance of antiemetic treatment.

Conclusion

While CINV therapy has significantly improved over the past decade, challenges remain. Considering the rapidly expanding medical costs and limited budgets worldwide, health economic evaluation is becoming much more critical. To further improve cost-effectiveness, necessary treatment should only be delivered to patients who truly, or at least likely, need it. Improving risk factor assessment will be important for identification of patients at higher risk of CINV. To better ascertain the patients' views of their symptoms, functional status, and health-related quality of life, and to further improve the healthcare system, introduction of newer technologies such as PROMs may also need to be considered. Regarding medical costs, not only direct costs incurred by CINV but also indirect costs due to reduced productivity should be considered in health economic evaluation.

Although a combination of the above discussed evaluations is complicated, it is important in order to deliver finely-tuned CINV treatment.

References

1. Hesketh PJ (2008) Chemotherapy-induced nausea and vomiting. N Engl J Med 358: 2482-2494.
2. Navari RM (2009) Antiemetic control: toward a new standard of care for emetogenic chemotherapy. Expert Opin Pharmacother 10: 629-644.
3. Bayo J, Fonseca PJ, Hernando S, Servitja S, Calvo A, et al. (2012) Chemotherapy-induced nausea and vomiting: pathophysiology and therapeutic principles. Clin Transl Oncol 14: 413-422.
4. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, et al. (2010) Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 21 Suppl 5: v232-243.
5. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, et al. (2011) Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 29: 4189-4198.
6. http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf
7. Moore S, Tumeh J, Wojtanowski S, Flowers C (2007) Cost-effectiveness of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy. Value Health 10: 23-31.
8. Lordick F, Ehlken B, Ihbe-Heffinger A, Berger K, Krobot KJ, et al. (2007) Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. Eur J Cancer 43: 299-307.
9. Annemans L, Strens D, Lox E, Petit C, Malonne H (2008) Cost-effectiveness analysis of aprepitant in the prevention of chemotherapy-induced nausea and vomiting in Belgium. Support Care Cancer 16: 905-915.
10. Langford P, Chrisp P (2010) Fosaprepitant and aprepitant: an update of the evidence for their place in the prevention of chemotherapy-induced nausea and vomiting. Core Evid 5: 77-90.
11. Lopes G, Burke T, Pellissier J, Zhang XH, Dedhiya S, et al. (2012) Aprepitant for Patients Receiving Highly Emetogenic Chemotherapy: An Economic Analysis for Singapore. Value Health Regional Issues 1: 66-74.
12. Humphreys S, Pellissier J, Jones A (2013) Cost-effectiveness of an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer in the UK. Cancer Manag Res 5: 215-224.
13. Chan SL, Jen J, Burke T, Pellissier J (2014) Economic analysis of aprepitant-containing regimen to prevent chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy in Hong Kong. Asia Pac J Clin Oncol 10: 80-91.
14. Chawla SP, Grunberg SM, Gralla RJ, Hesketh PJ, Rittenberg C, et al. (2003) Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Cancer 97: 2290-2300.
15. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, et al. (2003) The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group. J Clin Oncol 21: 4112-4119.
16. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie Ma G, Eldridge K, et al. (2003) Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 97: 3090-3098.
17. Gomez DR, Liao KP, Giordano S, Nguyen H, Smith BD, et al. (2013) Adherence to national guidelines for antiemesis prophylaxis in patients undergoing chemotherapy for lung cancer: a population-based study. Cancer 119: 1428-1436.
18. Herrstedt J, Muss HB, Warr DG, Hesketh PJ, Eisenberg PD, et al. (2005) Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. Cancer 104: 1548-1555.
19. Schmoll HJ, Aapro MS, Poli-Bigelli S, Kim HK, Park K, et al. (2006) Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 17: 1000-1006.
20. Rapoport BL, Jordan K, Boice JA, Taylor A, Brown C, et al. (2010) Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer 18: 423-431.
21. Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, et al. (2005) Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 23: 2822-2830.
22. Ito S, Tsukiyama I, Ando M, Katakami M, Hamanaka R, et al. (2015) Therapeutic and preventive antiemetic effect of aprepitant in Japanese patients with thoracic malignancies who truly need it. Support Care Cancer 23: 905-912.
23. Roila F, Tonato M, Basurto C, Bella M, Passalacqua R, et al. (1987) Antiemetic activity of high doses of metoclopramide combined with methylprednisolone versus metoclopramide alone in cisplatin-treated cancer patients: a randomized double-blind trial of the Italian Oncology Group for Clinical Research. J Clin Oncol 5: 141-149.
24. du Bois A, Meerpohl HG, Vach W, Kommoss FG, Fenzl E, et al. (1992) Course, patterns, and risk-factors for chemotherapy-induced emesis in cisplatin-pretreated patients: a study with ondansetron. Eur J Cancer 28: 450-457.
25. Hesketh P, Navari R, Grote T, Gralla R, Hainsworth J, et al. (1996) Double-blind, randomized comparison of the antiemetic efficacy of intravenous dolasetron mesylate and intravenous ondansetron in the prevention of acute cisplatin-induced emesis in patients with cancer. Dolasetron Comparative Chemotherapy-induced Emesis Prevention Group. J Clin Oncol 14: 2242-2249.
26. Osoba D, Zee B, Pater J, Warr D, Latreille J, et al. (1997) Determinants of postchemotherapy nausea and vomiting in patients with cancer. Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 15: 116-123.
27. Roscoe JA, Bushunow P, Morrow GR, Hickok JT, Kuebler PJ, et al. (2004) Patient expectation is a strong predictor of severe nausea after chemotherapy: a University of Rochester Community Clinical Oncology Program study of patients with breast carcinoma. Cancer 101: 2701-2708.
28. Hesketh PJ, Aapro M, Street JC, Carides AD (2010) Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. Support Care Cancer 18: 1171-1177.
29. Warr DG, Street JC, Carides AD (2011) Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of phase 3 trial of aprepitant in patients receiving adriamycin-cyclophosphamide-based chemotherapy. Support Care Cancer 19: 807-813.
30. Sekine I, Segawa Y, Kubota K, Saeki T (2013) Risk factors of chemotherapy-induced nausea and vomiting: index for personalized antiemetic prophylaxis. Cancer Sci 104: 711-717.
31. Haiderali A, Menditto L, Good M, Teitelbaum A, Wegner J (2011) Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a U.S. population. Support Care Cancer 19: 843-851.
32. Black N (2013) Patient reported outcome measures could help transform healthcare. BMJ 346: f167.