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

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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 antracycline 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/m² 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.

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 extensive antiemetic treatment against CINV and those who do 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-naive 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-naive 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 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].

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

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