Antiemetic Efficacy of the Neurokinin-1 Antagonist, Aprepitant, Plus a $5HT_3$ Antagonist and a Corticosteroid in Patients Receiving Anthracyclines or Cyclophosphamide in Addition to High-Dose Cisplatin

Analysis of Combined Data from Two Phase III Randomized Clinical Trials

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BACKGROUND. The tendency of chemotherapeutic regimens to cause vomiting is dependent on the individual drugs in the regimen. The authors analyzed data combined from 2 Phase III trials to assess the effect of the neurokinin-1 (NK_1) antagonist aprepitant combined with a $5HT_3$ antagonist plus a corticosteroid in a subpopulation receiving $>$ 1 emetogenic chemotherapeutic agent.

METHODS. In the current study, 1043 cisplatin-naive patients (42% were women) receiving cisplatin-based ($\geq$ 70mg/m^2) chemotherapy were assigned randomly to a control regimen (ondansetron [O] 32 mg intravenously and dexamethasone [D] 20 mg orally on Day 1; D 8 mg twice daily on Days 2–4) or an aprepitant (A) regimen (A 125 mg orally plus O 32 mg and D 12 mg on Day 1; A 80 mg and D 8 mg once daily on Days 2–3; and D 8 mg on Day 4). Randomization was stratified for use of concomitant chemotherapy and female gender. The primary end point was complete response (no vomiting and no rescue therapy) on Days 1–5 (0–120 hours). Data were analyzed by a modified intent-to-treat approach, and logistic regression was used to make treatment comparisons among patients receiving the most frequently coadministered emetogenic concomitant chemotherapy (Hesketh level $\geq$ 3).

RESULTS. Among the approximately 13% of patients (n = 81 for A; n = 80 for control) who received additional emetogenic chemotherapy (doxorubicin or cyclophosphamide), the aprepitant regimen provided a 33 percentage-point improvement in the complete response rate compared with the control regimen. Among the general population, the advantage with aprepitant was 20 percentage points.

CONCLUSIONS. The current analysis of $>$ 1000 patients from 2 large randomized trials showed that in the subpopulation at increased risk of chemotherapy-induced nausea and vomiting due to concomitant emetogenic chemotherapy, the addition of aprepitant to standard antiemetics improved protection to an even greater extent than in the general study population. ***Cancer*** **2005;104:864–8.**

KEYWORDS: nausea and vomiting, aprepitant, neurokinin-1 antagonist, cancer, supportive care, antiemetic.

The emergence of scrotonin ($5HT_3$) receptor antagonists for preventive therapy has improved clinicians' ability to manage chemotherapy-induced nausea and vomiting (CINV), but the effectiveness of these drugs is not necessarily sufficient to protect many

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patients. Approximately 50% of patients receiving highly emetogenic chemotherapy such as cisplatin still suffer from CINV.[1–4] So sensitive is the response to the experience of nausea and/or vomiting after chemotherapy that before they have actually received another cycle of chemotherapy, some patients may develop anticipatory CINV in response to a stimulus that reminds them of treatment.[5] CINV continues to be a problem, in part because effective control of it is related to a variety of factors, including younger age, female gender, a history of CINV, and other characteristics.[6–14]

Among predictive factors for CINV, the intrinsic emetogenicity of the chemotherapy regimen has been described as the most important,[15] and combinations of emetogenic drugs may have additive effects on the overall emetogenicity of a regimen.[16] Thus, treatment with more than one emetogenic drug within a regimen is a factor of particular importance in increasing a patient's risk for CINV. The development of classification systems for emetogenicity illustrates the importance of this feature of antineoplastic drugs in planning supportive care.[2,16] Furthermore, the mechanism of emetogenic action varies among different chemotherapeutic drugs,[17,18] suggesting a need for more than one class of antiemetic therapy to correspond with the different emetic stimuli potentially produced by a multidrug chemotherapy regimen.[19] Even a single drug may have an emetogenic potential of complex origin. Cisplatin, for example, stimulates vomiting via a serotonin-mediated peripheral action in the acute phase as well as a substance P-mediated central mechanism in the delayed phase. This is consistent with the improved antiemetic protection achieved when cisplatin-treated patients receive a $5HT_3$ antagonist combined with a substance-P antagonist (aprepitant).[20]

The latest advance in preventive therapy for CINV has been the approval of the neurokinin-1 (NK_1) receptor antagonist aprepitant. In 2 large trials including $>$ 1000 patients, aprepitant substantially improved antiemetic protection when combined with a standard regimen of a $5HT_3$ antagonist plus a corticosteroid, particularly in the 2–5 days after chemotherapy (delayed phase).[21,22] In the current analysis, we assessed data pooled from the two trials to characterize more precisely the benefit of aprepitant in patients at greater risk for CINV due to combinations of emetogenic drugs in their chemotherapy regimens.

MATERIALS AND METHODS

Design

Detailed descriptions of the design and primary efficacy and tolerability results of these identically designed randomized, double-blind, parallel-group, placebo-controlled studies are published elsewhere.[21,22] Written informed consent to participate was obtained from all patients, and all study procedures were conducted in accordance with applicable ethical requirements.

Patients

Cisplatin-naive patients $\geq$ 18 years old with histologically confirmed solid tumors and a Karnofsky score $\geq$ 60, who were scheduled to receive their first cisplatin-based ($\geq$ 70 mg/m^2) chemotherapy, were enrolled. Patients meeting the entry criteria were assigned to 1 of 2 treatment groups as follows: patients in the control group received intravenous ondansetron 32 mg and oral dexamethasone 20 mg on Day 1, followed by oral dexamethasone 8 mg twice daily on Days 2–4. Patients in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg on Day 1, oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on Days 2 and 3, and oral dexamethasone 8 mg on Day 4. Randomization was stratified by gender and use of concomitant chemotherapy categorized by the Hesketh classification.[16]

Patients received either aprepitant or placebo 1 hour before cisplatin infusion. All patients received ondansetron and dexamethasone 30 minutes before cisplatin, which was then infused over a period of $\leq$ 3 hours. Patients receiving docetaxel or paclitaxel in addition to cisplatin were premedicated with 2 doses of dexamethasone 20 mg before paclitaxel or docetaxel infusion. Additional emetogenic chemotherapeutic agents were permitted on Day 1 but were prohibited within 6 days before Day 1 or within 6 days after Day 1. Unless administered as rescue therapy for established nausea or vomiting, additional antiemetics were prohibited within 2 days before Day 1 or between Days 1 and 6 of the study.

Assessments and Statistical Analysis

Patients used a diary to record emetic episodes, severity ratings of nausea using a 100-mm horizontal visual analog scale, and any use of rescue therapy (i.e., medication taken for established nausea or vomiting) on Days 1–5 after the administration of cisplatin. The sponsor managed the data and performed the analyses, and the investigators had access to all of the data and controlled the decision to publish the study results. The efficacy end point for the concomitant emetogenic chemotherapy subgroup post-hoc analyses was the proportion of patients with complete response (CR), defined as no emetic episodes and no rescue therapy in the overall 5-day study period (0–

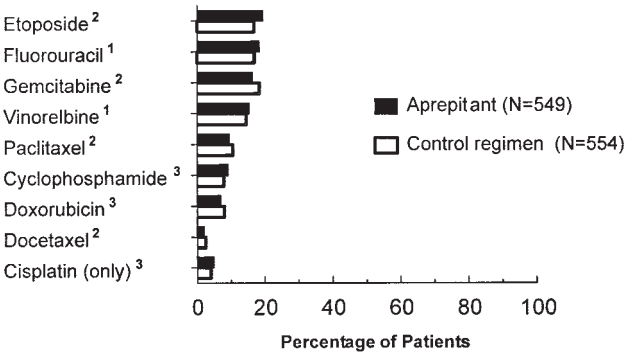

FIGURE 1. Percentages of patients who received concomitant chemotherapy in addition to cisplatin. Emetogenicity was based on the Hesketh system of classification[16]: 1, low/mild emetogenicity; 2, intermediate emetogenicity; 3, high/moderately high emetogenicity.

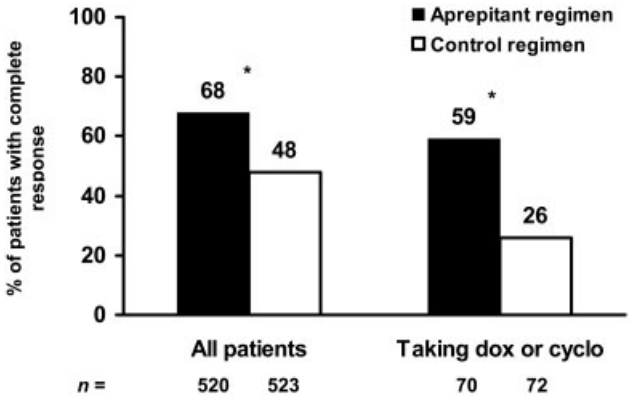

FIGURE 2. Percentages of patients receiving concomitant emetogenic chemotherapy (doxorubicin [Dox] and/or cyclophosphamide [Cyclo]) who had a complete response in the overall 5-day study period, by treatment group. All patients received cisplatin. *$P < 0.001$ vs. the control regimen.

120 hours). A modified intent-to-treat approach was used to analyze the data, and included all patients who received cisplatin, took study drug, and had at least one posttreatment assessment. To avoid confusion regarding levels of emetogenicity of various drugs, the assessment was limited to patients who received the most emetogenic concomitant chemotherapy (Hesketh level ≥ 3) (doxorubicin and/or cyclophosphamide). In the original analysis of combined data, a logistic regression model was used to make treatment comparisons for the CR end point in the general study population. For the subanalysis among patients receiving concomitant emetogenic chemotherapy, the two treatment groups were compared using the Fisher exact test. No adjustment for multiplicity was applied, and nominal P values were reported.

RESULTS

A total of 1043 patients (520 in the aprepitant group and 523 in the standard therapy group) were included in the efficacy analyses. Approximately 95% of patients received some type of concomitant chemotherapy in addition to cisplatin. Figure 1 shows the percentages of patients in each treatment group who received chemotherapeutic agents in addition to cisplatin on ≥ 1 day of the study, along with the emetogenicity of each drug. Doxorubicin and cyclophosphamide were the two most emetogenic agents (moderate to high emetogenicity) given as concomitant chemotherapy in both studies, and as such were the focus of the treatment-comparison analysis. In the aprepitant group, 34 patients (7%) received doxorubicin and 47 (9%) received cyclophosphamide. In the control group, 40 patients (8%) received doxorubicin and 40 (8%) received cyclophosphamide.

Patients Receiving Concomitant Emetogenic Chemotherapy

In the total combined study population regardless of treatment group or use of concomitant chemotherapy, CR was achieved in 58% ($n = 602$) of patients. Analysis by treatment group showed a 20 percentage point superiority for the aprepitant regimen (68% vs. 48%; $P < 0.001$) (Fig. 2). Of the 142 patients who received concomitant emetogenic chemotherapy (i.e., doxorubicin and/or cyclophosphamide), the aprepitant regimen was superior by 33 percentage points (59% vs. 26%; $P < 0.001$) (Fig. 2). Similarly, in separate assessments for the acute and delayed phases among patients receiving concomitant emetogenic chemotherapy, the aprepitant group had significantly higher rates of response in both the acute phase (71% vs. 49%) and particularly the delayed phase (67% vs. 32%) ($P < 0.05$ for both comparisons) (Fig. 3).

DISCUSSION

Patients in these two large trials received a variety of chemotherapeutic regimens. The current analysis evaluated whether the benefit of aprepitant was discernible specifically in the subgroup of patients receiving cisplatin plus at least one other emetogenic drug.

In the two studies, use of concomitant therapy in addition to cisplatin was prevalent among patients in both treatment groups, although the majority of additional drugs were of definitively lower emetogenicity than cisplatin. To limit the evaluation to those patients at greatest risk of CINV due to concomitant chemotherapy, the analysis included only patients receiving the most highly emetogenic drugs in addition to cisplatin. Across both studies, the relevant sub-

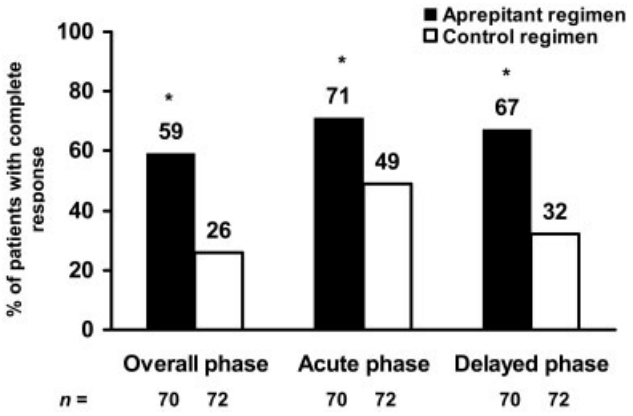

FIGURE 3. Between-treatment comparison of complete response rates in the overall, acute, and delayed phases, in patients taking concomitant emetogenic chemotherapy (doxorubicin and/or cyclophosphamide). *$P < 0.05$ vs. the control regimen.

population was found to have received doxorubicin and/or cyclophosphamide, with similar and relatively low proportions (approximately 13%) of patients in the individual treatment groups receiving either of these drugs. These patients had a distinctly lower rate of antiemetic protection than the general study population, consistent with the expectation for this subpopulation. In 1 previously reported study, concomitant moderately emetogenic chemotherapy was associated with a > 20 percentage-point decrease in antiemetic response rate compared with patients who received only cisplatin.[23]

Regardless of chemotherapy regimen, patients taking aprepitant had significantly superior response rates compared with patients who received only the control regimen. This finding confirmed that the benefit provided by aprepitant in the general study population was preserved in patients whose chemotherapy regimens put them at higher risk for CINV. Moreover, compared with the between-treatment difference in the general study population, the superiority of the aprepitant regimen was even more dramatic among patients taking doxorubicin or cyclophosphamide in addition to cisplatin. This greater benefit with aprepitant may be due to the higher level of emetogenicity produced by combinations of chemotherapeutic agents, as well as by the mechanisms of emetogenicity of the concomitant agents themselves. Cyclophosphamide-induced vomiting, which occurs in a monophasic rather than biphasic pattern and produces a different profile of plasma serotonin levels and urinary excretion of 5-hydroxyindole acetic acid compared with cisplatin,[24,25] may be centrally mediated, possibly involving NK_1 receptors at which aprepitant exerts its antagonistic effect.

In summary, the current analysis of data pooled from two large randomized trials showed that the benefit of aprepitant was not only observable in patients taking more emetogenic chemotherapy, but was actually of greater magnitude specifically in these patients. These findings suggest that aprepitant compensated to some extent for the increased emetogenicity of the chemotherapy, thereby offsetting the higher risk for CINV. This particularly robust efficacy may depend on aprepitant-mediated antagonism of those receptors at which additional chemotherapeutic drugs exert their emetogenic effects. The results of this post-hoc analysis require confirmation in a prespecified controlled trial.

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