ELSEVIER

European Journal of Cancer 41 (2005) 1278–1285

European Journal of Cancer

www.ejconline.com

The oral NK_1 antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: Pooled data from 2 randomised, double-blind, placebo controlled trials

David G. Warr [a,*], Steven M. Grunberg [b,1], Richard J. Gralla [c,2], Paul J. Hesketh [d,3], Fausto Roila [e,4], Ronald de Wit [f,5], Alexandra D. Carides [g,6], Arlene Taylor [g,7], Judith K. Evans [g,8], Kevin J. Horgan [g,9]

[a] *Princess Margaret Hospital, 610 University Avenue, Toronto, Ont., Canada M5G 2M9*
[b] *University of Vermont, UHC Campus/St. Joseph 3400, Burlington, VT 05405, USA*
[c] *New York Lung Cancer Alliance, 459 Columbus Avenue, PMB-187, New York, NY 10027, USA*
[d] *Caritas St. Elizabeth's Medical Center, 736 Cambridge Street, Brighton, MA 02135-2997, USA*
[e] *Policlinico Monteluce, Divisione Oncologica Medica Ospedale Policlinico, Perugia 06100, Italy*
[f] *Rotterdam Cancer Institute and University Hospital, Groene Hilledijk 301, 3075 EA Rotterdam, Netherlands*
[g] *Merck Research Laboratories, BL 3-2, 10 Sentry Parkway, Blue Bell, PA 19422, USA*

Received 11 October 2004; received in revised form 3 December 2004; accepted 27 January 2005

Abstract

In this work, data from two phase III studies were pooled to further evaluate the NK_1 antagonist aprepitant for prevention of cisplatin induced nausea and vomiting.

One thousand and forty three patients receiving cisplatin ($\geqslant 70$ mg/m^2) were randomised to receive either a control regimen (32 mg intravenous ondansetron [O] and 20 mg oral dexamethasone [D] on day 1; 8 mg D twice daily on days 2–4) or an aprepitant (A) regimen (125 mg A plus 32 mg O and 12 mg D on day 1, 80 mg A and 8 mg D once daily on days 2–3, and 8 mg D on day 4). The primary endpoint was no emesis and no rescue therapy. Potential correlations between acute and delayed emesis were assessed, as were frequency of emetic episodes by time interval and effects on nausea and quality of life as measured by the functional living index emesis (FLIE) questionnaire. In the aprepitant group, there was statistically significantly less nausea over the study period

* Corresponding author. Tel.: +1 416 946 2260; fax: +1 416 946 6546.
E-mail addresses: david.warr@uhn.on.ca (D.G. Warr), steven.grunberg@vtmednet.org (S.M. Grunberg), rgralla@hotmail.com (R.J. Gralla), phesketh@massmed.org (P.J. Hesketh), roila.fausto@libero.it (Fausto Roila), r.dewit@erasmusmc.nl (R.de Wit), alexandra_carides@merck.com (A.D. Carides), arlene_taylor@merck.com (A. Taylor), judith_evans@merck.com (Judith K. Evans), kevin_horgan@merck.com (K.J. Horgan).
[1] Tel.: +802 847 3827; fax: +802 847 5946.
[2] Tel.: +212 579 5084; fax: +801 365 6442.
[3] Tel.: +617 789 2317; fax: +617 789 2959.
[4] Tel.: +11 39 075 578 3456; fax: +11 39 075 572 0990.
[5] Tel.: +11 31 10 4391760; fax: +11 31 10 439 1003.
[6] Tel.: +484 344 7016; fax: +484 344 2931.
[7] Tel.: +484 344 2867; fax: +484 344 2931.
[8] Tel.: +484 344 3634; fax: +484 344 4049.
[9] Tel.: +484 344 7264; fax: +484 344 2956.

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.01.024

as well as higher functioning on the FLIE questionnaire in both the nausea and vomiting domains. Patients without acute emesis were more likely to have no emesis in the delayed phase. Compared with control, the aprepitant regimen improved prevention of delayed emesis by 16% points in patients without acute emesis, and by 17% points in patients with acute emesis. Among patients who did not have complete response, the frequency of emesis at various intervals over 5 days was consistently lower in patients receiving aprepitant.

Analyses of this combined Phase III population further characterized the clinical profile of the aprepitant regimen, showing that delayed emesis is correlated with, but not entirely dependent on, the presence of acute emesis, and that aprepitant has a favorable effect against nausea throughout 5 days postchemotherapy. In addition, even among patients who had emesis or needed rescue therapy, aprepitant was associated with a lower frequency of these events compared with the control regimen.

Keywords: Aprepitant; NK_1 antagonist; Antiemetic; Nausea; Vomiting; Clinical trial

1. Introduction

Two identically designed Phase III trials have been previously reported describing the addition of the NK_1 antagonist aprepitant to a control regimen (a $5HT_3$ antagonist and dexamethasone) for the prevention of cisplatin-based chemotherapy induced nausea and vomiting (CINV) [1,2]. The aprepitant regimen was significantly superior to the control regimen in the overall 5-day study period, the first 24 h postchemotherapy (day 1, the acute phase of CINV), and particularly days 2–5 (the delayed phase). The reports of the individual phase III studies established that aprepitant was generally well tolerated and made a large impact on the likelihood of vomiting following high dose cisplatin. The impact of NK_1 receptor antagonists on the important symptom of nausea, however, was less clear. There was a statistically significant difference in the proportion of patients with no nausea in only one of the two phase III trials. Non-statistically significant trends were reported for the proportion of patients with nausea visual analog scores less than 25 mm. No tests of statistical significance were reported for the functional living index emesis (FLIE) questionnaire, nor were the results for the nausea and vomiting domains of that questionnaire reported separately. This paper aims to expand upon the results for the nausea outcomes in the pooled dataset.

Another topic that appears in the antiemetic literature is the relationship between acute and delayed emesis. Consistent with current belief that the most important risk factor for delayed emesis is poor control of acute emesis [3], in both phase III studies, the likelihood of delayed emesis was lower in patients who had not experienced acute emesis [1,2]. It has been suggested that the pharmacologic benefit of aprepitant in the delayed phase is not strictly a carryover effect from the acute phase [4,5]. In this study, we have analysed data pooled from the Phase III studies to determine the extent to which the results in the first 24 h predict the results in the delayed phase.

2. Patients and methods

2.1. Design

Two identically designed multicenter, randomised, double-blind, parallel-group, placebo-controlled trials were conducted. Written informed consent to participate was obtained from every patient, and was approved by the Institutional Review Board of each participating site. Detailed descriptions of the design (including enrollment criteria), as well as the primary efficacy and tolerability results of the individual studies, are published elsewhere [1,2].

2.2. Patients

The studies enrolled cisplatin-naïve patients who were scheduled to receive their first cycle of chemotherapy including cisplatin $\geqslant 70$ mg/m^2. Randomisation to 1 of 2 treatment groups was stratified by gender and use of concomitant emetogenic chemotherapy categorized by the Hesketh classification [6]. 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. Due to the known interaction between aprepitant and dexamethasone which results in increased plasma levels of the corticosteroid, the dexamethasone dose was reduced in the aprepitant group so that plasma levels would be more closely matched between groups [8]. In the aprepitant containing group, the dose of oral dexamethasone was 12 mg on day 1 and 8 mg daily on days 2–4. The oral aprepitant dose was 125 mg on day 1 and 80 mg on days 2 and 3. Matching placebos were given to maintain blinding. Patients were given a take home prescription for PRN antiemetics to be used as needed in case of nausea or vomiting.

2.3. Assessments and statistical analysis

On the first 5 days, patients used a diary to record the occurrence of emetic episodes, any use of rescue therapy,

and daily ratings of nausea severity using a 100-mm horizontal visual analogue scale (VAS). On day 6 patients also completed the functional living index emesis (FLIE) questionnaire, a validated 18 item VAS-based, patient-reported outcome measure that captures information about the effect of CINV on patients' daily lives [9,10]. FLIE has separate domains for the impact of nausea and vomiting on functioning.

The study sponsor (Merck Research Laboratories) managed the data and performed the analysis, which included data only from cycle 1 of both studies. Results of the analysis of the combined data from the multiple-cycles extensions of both studies are published elsewhere [11]. The primary endpoint was complete response (defined as no emetic episodes and no rescue therapy) in the overall 5-day study period. Other endpoints assessed included (1) complete response in the acute phase (0–24 h postcisplatin) and delayed phase (days 2–5); (2) no emesis; (3) no nausea (VAS score <5 mm); (4) no significant nausea (VAS score <25 mm); (5) complete protection (no emesis, no rescue therapy, and no significant nausea [VAS score <25 mm]) and (6) the impact of CINV on daily life (as measured by a FLIE total score >108 out of a maximum possible 126) [10]. Analysis of all endpoints other than complete response from 0 to 5 days and complete response in the acute phase (0–24 h postcisplatin) were posthoc. At time of study design, the individual studies were considered underpowered (52%) to test the endpoint of complete response in the first 24 h. An analysis of combined data was therefore prespecified with the assumption of a conservative difference of 8% between the treatment groups. Although in both studies the aprepitant regimen was in fact significantly superior for acute-phase complete response, the combined analysis was performed as originally planned for this endpoint.

The modified intent-to-treat analysis included all patients who received cisplatin, took study drug, and had at least one posttreatment assessment. For treatment comparisons, logistic regression models were used which included terms for treatment allocation, gender and use of concomitant chemotherapy. Treatment-by-factor interactions were assessed at the 10% significance level with logistic models, and if appropriate, with Gail and Simon's test at the 5% significance level to assess whether any interactions were qualitative. Each study had 90% power to detect a 15% point difference in complete response rates over days 1 to 5 based on a 2-sided test at a significance level $\alpha = 0.05$, with a sample size of 470 evaluable patients (235 per treatment group). Interaction between the 2 studies was assessed by use of a difference estimator from the 2 independent logistic models, before combining the studies. The combined treatment effect was estimated using the average of treatment effect estimator from the 2 independent logistic models.

The relationship between acute and delayed emesis and treatment response was assessed by categorising patients according to the presence or absence of acute emesis, then comparing the incidence of delayed emesis in each category. This procedure was carried out for the entire study population regardless of treatment, and again for each treatment group. In addition, Kaplan–Meier test was used to display the time to first emesis for the 2 treatment groups.

The subgroup of patients who did not achieve a complete response (i.e., those who had emesis or required rescue medication for nausea or emesis) was also considered. Counts of patients in each treatment group who had emesis (1 episode in a given interval and >1 episode in a given interval) were plotted by 4-h increments up to 24 h, and by 8-h increments over 24–120 h. Patients could be counted more than once, as their emetic episodes may have occurred at discontinuous time intervals. In addition, the overall frequency of emetic episodes per patient was calculated for each treatment group, with each patient only counted once according to the total number of emetic episodes he or she had over the entire 120-h study period. Those patients who did not have emesis but did require rescue therapy were also counted for each treatment group.

3. Results

3.1. Patients

Details of patient accounting for the individual studies are published elsewhere [1,2]. Combined data from 1099 patients were assessed for baseline characteristics (Table 1). As shown in the table, baseline characteristics were similar between the treatment groups. A total of 1043 patients (520 in the aprepitant group and 523 in the control group) were included in the efficacy analyses.

3.2. Efficacy

Fig. 1 and Table 2 show results of the efficacy analyses. No statistically significant interaction between the 2 studies was observed for any of the endpoints assessed, in any phase ($P \geqslant 0.121$). As expected based on the consistency of results between the individual studies [1,2], the percentage of patients with complete response (no emesis and no use of rescue therapy) in the pooled sample was significantly higher with the aprepitant regimen *vs*. the control regimen in the acute phase (86% *vs*. 73%; $P < 0.001$) (Fig. 1), as well as in the post hoc analyses for the delayed phase (72% *vs*. 51%; $P < 0.001$) and the overall 5-day study period (68% *vs*. 48%; $P < 0.001$).

The results of analyses for other efficacy endpoints are shown in Table 2. The percentage of patients in the aprepitant group with no emesis was significantly

Table 1
Patient baseline characteristics by treatment group

	Aprepitant regimen ($N = 547$)	Control regimen ($N = 552$)
% Female	42	43
Age (years)		
Mean [SD]	56 [13]	55 [13]
Range	18–84	18–83
Race (%)		
Black	5	4
White	59	59
Other	36	37
Use of concurrent emetogenic chemotherapy[a] (% of patients)	16	17
Cisplatin dose		
$\geqslant$70 to 100 mg/m^2 (% of patients)	76	76
Mean dose (mg/m^2)	80	80
Alcoholic drinks/week (% of patients)		
0	71	72
1–10	20	20
>10	9	8
History of morning sickness (% of patients)	9	6
History of motion sickness (% of patients)	6	4
History of chemotherapy (% of patients)	11	12
History of CINV (% of patients)	6	6
Primary cancer diagnosis (% of patients)		
Respiratory	40	38
Urogenital	28	34
Digestive	13	10
Eyes/ears/nose/throat	9	7
Other	10	11

[a] Hesketh level $\geqslant$ 3.

higher ($P < 0.0001$) than that for the control group, in all three phases of the study. For the endpoint of no nausea (VAS score <5 mm), the aprepitant regimen was statistically significantly superior in the overall 5-day study period ($P < 0.05$) and the delayed phase ($P < 0.01$) but not the acute phase. Similarly, the endpoint of no significant nausea (VAS score <25 mm) was significantly superior in the aprepitant group in the overall study period ($P < 0.05$), the delayed study period ($P < 0.05$), and the acute phase ($P < 0.01$). The aprepitant group also had a higher percentage of patients with the stringent endpoint of complete protection (no emesis, no rescue, and no significant nausea) in all 3 study phases ($P < 0.001$). When the percentage of patients with no emesis was plotted for each treatment group over the 5-day study period, a higher percentage of patients in the aprepitant group remained protected from emesis, beginning at approximately 12–16 h post-cisplatin (Fig. 2). As shown in Table 3, tolerability results were consistent with those of the individual studies [1,2].

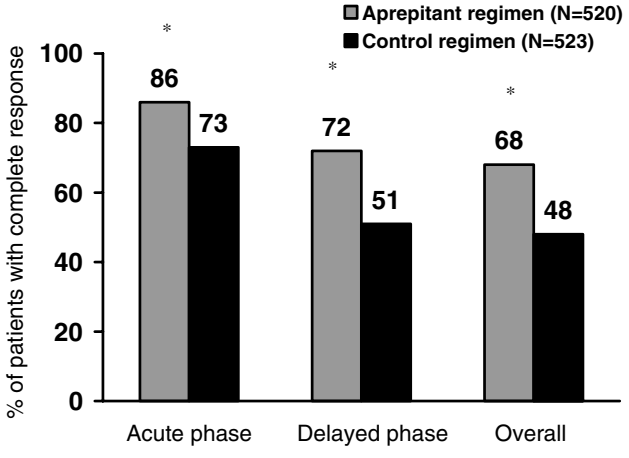

Fig. 1. Percentage of patients with complete response (no emesis and no use of rescue therapy) in the acute phase (0–24 h), the delayed phase (24–120 h), and the overall 5-day study period, by treatment group (data combined from 2 identically designed Phase III studies). *$P < 0.001$ for aprepitant regimen *vs.* control in all 3 phases; analysis was prespecified for the acute phase and post hoc for the delayed phase and overall study period.

Based on the FLIE total score, significantly more patients in the aprepitant group (74%) reported minimal or no impact of CINV on daily life over 5 days compared with patients on the control regimen (64%) ($P < 0.01$) [12] (analysis not adjusted for multiplicity). The FLIE total score is composed of domains for both nausea and vomiting that can be scored separately. 70% of patients in the aprepitant group *vs.* 61% in the control group ($P < 0.05$) met the definition of minimal or no impact of CINV on daily life for the nausea domain, and 84% in the aprepitant group *vs.* 69% in the control group ($P < 0.05$) met the definition for the vomiting domain [12].

Across both treatment groups, acute emesis occurred in 20% of patients, and delayed emesis occurred in 35% of patients. To evaluate the relationship between acute and delayed emesis, patients were first categorised according to the presence or absence of acute emesis, and the resulting 2 categories of patients were then compared according to the presence or absence of delayed emesis. Among all patients who had acute emesis, 80% also had delayed emesis, and among all patients who did not have acute emesis, 24% had delayed emesis (Fig. 3). A similar categorisation was done for each treatment group. Among the 13% of patients in the aprepitant group who had acute emesis, 68% of this subset also had delayed emesis. By contrast, among the 26% of patients in the control group who had acute emesis, 85% of this subset also had delayed emesis. Among the 87% of patients in the aprepitant group who did not have acute emesis, 17% of this subset had delayed emesis, and among the 74% of patients in the control group who did not have acute emesis, 33% of this subset had delayed emesis (Fig. 3).

A total of 405 patients (146 in the aprepitant group and 259 in the control group) experienced at least one emetic episode in the 5-day study period. Fig. 4 shows the numbers of patients who had emesis in each treatment

Table 2
Percentages of patients reaching efficacy endpoints in post hoc analyses, by study phase and treatment group

Endpoint	Overall (days 1–5)		Acute (day 1)		Delayed (days 2–5)	
	Aprepitant regimen ($N = 520$)[a]	Control regimen ($N = 523$)[a]	Aprepitant regimen ($N = 520$)[a]	Control regimen ($N = 523$)[a]	Aprepitant regimen ($N = 520$)[a]	Control regimen ($N = 523$)[a]
No emesis	72[b]	50	87[b]	74	76[b]	54
Complete protection	60[b]	45	82[b]	70	64[b]	48
No nausea	48[c]	42	70	68	52[b]	44
No significant nausea	72[c]	65	91[b]	85	74[c]	67

No nausea = VAS score <5 mm.
No significant nausea = VAS score <25 mm.
Complete protection = no emesis, no rescue therapy, and no significant nausea.
[a] Because not every patient provided complete efficacy data, very slight variability (1–4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ *vs.* control regimen.
[c] $P < 0.05$ *vs.* control regimen.

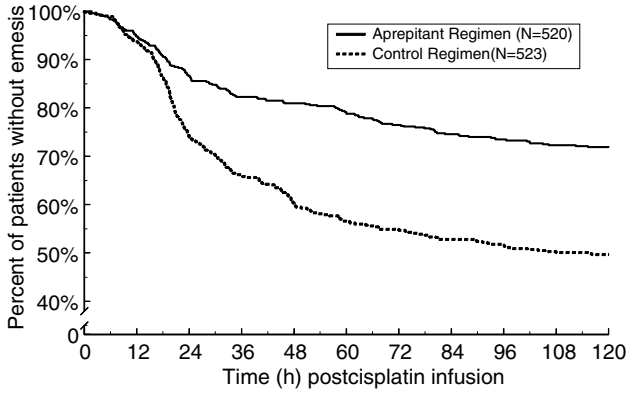

Fig. 2. Percent of patients without emesis in each treatment group, over the 5-day study period (0–120 h post-cisplatin) (data combined from 2 identically designed Phase III studies). Reproduced with permission from Wolters Kluwer Health, *Am J Cancer* 2005, **4** (1), 35–48.

group, plotted according to the time interval in which the emesis occurred. For each 4-h interval over the first 24 h, and for each 8-h interval thereafter, Fig. 4(a) shows how many patients had a single emetic episode in that interval. These numbers were similar between treatment groups (4–13 patients) for the first 3 intervals (i.e., 0–4, 4–8 and 8–12 h). Over the ensuing days, the numbers of patients in the aprepitant group who had a single episode of emesis remained at about 20–30 patients per interval. By contrast, the numbers of patients with a single episode of emesis in the control group increased from 10 patients at the 8–12 h interval to 28 patients at the 12–16 h interval and 66 patients in the 20–24-h interval. Over the succeeding 8-h intervals, the numbers peaked at the 40–48 h interval (80 patients) and remained at >30 patients until approximately 104 h. Six patients in each treatment group had a single episode of emesis in the final interval (112–120 h).

Fig. 4(b) shows numbers of patients who had >1 episode of emesis in a given time interval. In the early 4-h intervals, up to 12 h, fewer than 20 patients in either treatment group had >1 emetic episode. The number

Table 3
Summary of adverse events

Percent of patients	Aprepitant regimen $N = 544$[a]	Control regimen $N = 550$[a]
With ⩾1 clinical adverse event	69	67
With drug-related clinical adverse events[b]	17	13
With serious clinical adverse events	13	14
Discontinued due to a clinical adverse event	8	6
With ⩾1 laboratory adverse event	22	20
With drug-related laboratory adverse events	4	3
With most common clinical adverse events[c]		
Anorexia	10	9
Asthenia/fatigue	18	12
Constipation	10	12
Diarrhea	10	7
Hiccups	11	6
Nausea	13	12
With prespecified adverse event of interest		
Febrile neutropenia[d]	1.7	1.3
Infection-related serious adverse event	3.7	2.4
Dehydration	5.9	5.1
Fever	2.9	3.5
Infections	12.5	10.4
Hypertension	1.8	1.3
Hematologic/lymphatic system adverse event	11.6	11.1
Hyperglycemia	1.7	1.8
Hypokalemia	2.6	2.7

[a] For laboratory data, $N = 539$ in the aprepitant group and $N = 543$ in the control group.
[b] Adverse events considered by the investigator to be possibly, probably, or definitely related to study drug.
[c] ⩾10% in at least one treatment group; nausea and vomiting were considered adverse events if they occurred after day 5 of the study, or at any time if determined by the investigator to be serious, drug-related, or result in discontinuation.
[d] Investigator-determined.

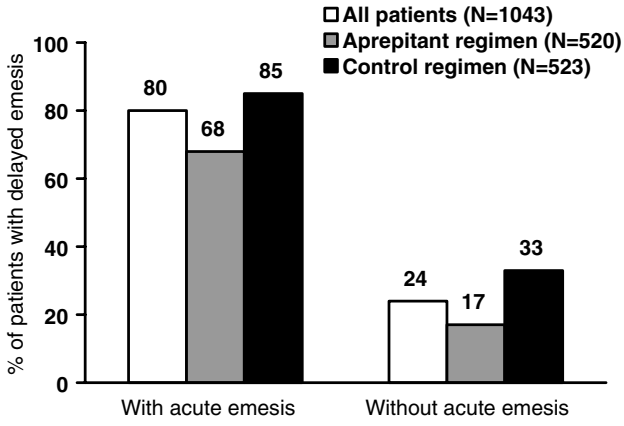

Fig. 3. Incidence of delayed emesis in patients with and without acute emesis, by treatment group (data combined from 2 identically designed Phase III studies).

of patients in the aprepitant group who had >1 emetic episode remained at 30–40 patients over most of the intervals in the ensuing days, whereas the number of patients in the control group increased to about 35 patients at the 12–16 h interval, >70 patients at the 16–20 h interval and about 95 patients at the 20–24 h interval. Over the succeeding 8-h intervals, the numbers of patients with emesis peaked at the 40–48 h interval (>110 patients) and remained between 40 and 80 patients until approximately 104 h. Numbers of patients with >1 emetic episode declined to similar counts (<40 patients) in both treatment groups after about 104 h.

The frequency of emesis was also examined by categorising each patient according to the total number of emetic episodes he or she had throughout the study. It was observed that in both treatment groups, 65% of patients who had emesis (95/146 patients in the aprepitant group and 167/259 patients in the control group) had a total of 5 or fewer emetic episodes. The groups were also similar in terms of patients who had 3 or fewer emetic episodes (49% of patients [71/146] in the aprepitant group and 47% of patients [123/259] in the control group). Among all patients who had emesis, 24% of patients (35/146) in the aprepitant group and 21% of patients (55/259) in the control group had 1 emetic episode.

In addition to patients who had emesis, a total of 32 patients (22 in the aprepitant group and 10 in the control group) did not have emesis but did require rescue medication. In the first 24 h postchemotherapy, 2 of the 22 patients in the aprepitant group and 0 of the 10 patients in the control group took rescue therapy. In the next 24 h (i.e., the interval between 24 and 48 h postchemotherapy), 8 of 22 patients in the aprepitant group and 3 of 10 in the control group took their rescue therapy.

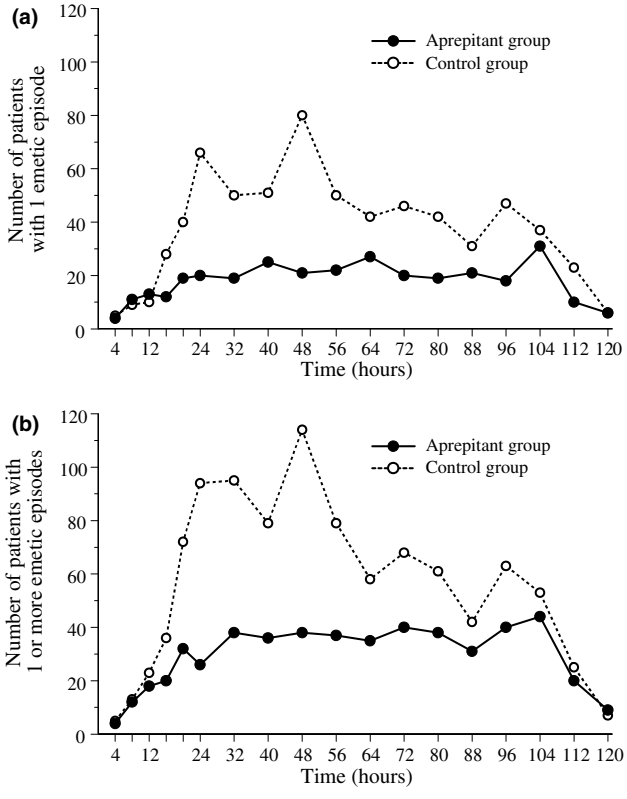

Fig. 4. Number of patients with 1 emetic episode and with >1 emetic episode at discrete time intervals over 5 days, by treatment group.

4. Discussion

The efficacy of currently recommended therapeutic regimens, which include a $5HT_3$ antagonist combined with a corticosteroid, has been well established for the acute phase of CINV (especially up to about 16 h post cisplatin), but these agents have not been nearly as effective in the delayed phase [3,13,14].

As anticipated, based on the consistency of results between the individual studies [1,2], the present efficacy findings based on the pooled Phase III data confirmed that the aprepitant regimen was superior to the control regimen in the acute phase, notably in the delayed phase, and in the overall 5-day study period. Whereas in the individual studies the aprepitant regimen produced numerically greater response rates for nausea endpoints and in exploratory analyses some of the differences reached statistical significance [2], the individual studies did not include a large enough sample size to make a definitive assessment. In the combined dataset the aprepitant regimen was significantly superior for nausea measurements at nearly all time points, confirming the trends observed in each study. These results support the potential clinical benefit against nausea as previously suggested by the complete response endpoint, which includes use of rescue therapy as a surrogate measure of nausea.

Data obtained with the Functional Living Index Emesis, a questionnaire which focused exclusively on the effect of nausea and vomiting on daily life, showed that a significantly higher percentage of patients reported "minimal or no impact of CINV on daily life" in the aprepitant group compared with patients in the control group. This result was consistent whether treatments were compared by total score or by scores for the individual domains of nausea and vomiting. Thus apart from the percentage of patients with no nausea on day 1, all endpoints related to nausea demonstrated a statistically significant difference in favour of the aprepitant regimen. The absolute differences for the nausea-related outcomes in the overall period (no nausea, no significant nausea and the nausea domain) were 6–9% indicating a modest but consistent impact of aprepitant in reducing nausea.

Another aspect explored in this analysis was the relationship between acute and delayed emesis. As has been recognized in guidelines for management of CINV, delayed emesis occurred more frequently in patients who experienced acute emesis than in those who did not, regardless of treatment group (Fig. 3). Among patients with acute emesis, the incidence of delayed emesis was higher by approximately 56% points than among patients who did not have acute emesis. However, while emesis in the acute phase is unquestionably associated with a greater likelihood of emesis in the delayed phase, 20% of patients who had emesis in the acute phase did not have subsequent emesis in the delayed phase, and one quarter of the patient population who did not have acute emesis nevertheless went on to have delayed emesis. These findings emphasize that emesis in the acute phase does not necessarily mean that a patient will have emesis in the delayed phase, nor does protection in the acute phase guarantee protection in the delayed phase.

Within each treatment group, the incidence of delayed emesis was higher among patients who had acute emesis than among those who did not. The magnitude of this difference within each group (51% points with aprepitant and 50% points with control) was consistent with the 56%-point difference seen in the general study population. However, regardless of whether patients had acute emesis, the incidence of delayed emesis was consistently lower in aprepitant-treated patients than in control-treated patients. Among patients who suffered acute emesis (13% in the aprepitant group and 26% in the control group), the incidence of subsequent delayed emesis was 17% points lower with aprepitant *vs*. control (68% *vs*. 85%, compared with 80% in the general study population). Likewise, in the absence of acute emesis, the incidence of delayed emesis was again lower with aprepitant by 16% points (17% *vs*. 33%, compared with 24% in the general study population). Thus aprepitant conferred a similar degree of improvement in delayed-phase protection irrespective of acute emesis; this finding demonstrates that the decrease in delayed emesis cannot be attributed to a "carryover" effect resulting from decreased acute emesis, but instead was largely due to a direct pharmacologic effect of aprepitant [1,2,5].

While complete response was the primary endpoint of interest and the most favorable clinical goal, it was also of interest to examine potential patterns of response among patients who failed to achieve the primary endpoint (i.e., those who either had emesis or needed rescue therapy). Among patients who had emesis at any time during the 5-day study period, approximately one-third were in the aprepitant group and two-thirds were in the control group, consistent with the enhanced antiemetic protection conferred by aprepitant when added to the control regimen. In addition, dramatic between-treatment differences were observed in numbers of patients who had single or multiple episodes of emesis at specified time intervals across the entire 120-h study period. For the initial 12 h postchemotherapy, the number of patients who had a single episode of emesis was similar between treatment groups. However, after 12 h, the number of patients in the aprepitant group remained relatively consistent (20–30 patients) for the ensuing intervals, whereas numbers in the control group increased sharply, peaking (80 patients) at 48 h or day 2 postchemotherapy and remaining between 30 and 50 over the ensuing intervals, declining below 30 only after the onset of day 5. A similar between-treatment pattern was noted in terms of numbers of patients who had >1 emetic episode in a given time interval. Thus, even among patients who did not achieve complete response (CR), fewer patients had emesis (single or multiple episodes) over the 5 days postchemotherapy if they were taking aprepitant. Furthermore, over time the likelihood of emesis in the aprepitant group remained relatively consistent, without sharp peaks. The likelihood of emesis was consistently greater in the control group, in which the number of patients with 1 or more emetic episodes increased over time, peaked dramatically at 48 h, and also showed more fluctuation in succeeding days, suggesting less predictability of antiemetic control compared with the aprepitant regimen.

The frequency of emesis in each patient was assessed; in both treatment groups, 95% of patients with emesis had 5 or fewer episodes. The treatment groups were also similar in terms of the percentage of patients with emesis who had a single emetic episode and those who had 3 or fewer episodes. In addition, 32 patients required rescue therapy despite having not had emesis, and were therefore also considered to have failed to achieve the primary endpoint of CR. Ten of the 22 patients taking aprepitant and 3 of the 10 patients taking control required rescue therapy in the first 48 h, consistent with the peak time observed for emesis and/or nausea.

Although these analyses demonstrate a favorable impact of aprepitant upon both nausea and delayed eme-

sis, as well as on the likelihood of emesis at various time intervals following chemotherapy, the multimechanistic nature of these problems means that further interventions are required to optimise antiemetic control.

Conflict of interest statement

Drs. Carides, Evans, and Horgan are employees of Merck Research Laboratories. Drs. Warr, Grunberg, Gralla, Hesketh, Roila, and de Wit have received funding from Merck Research Laboratories for the conduct of clinical studies of aprepitant. The studies described in this paper were funded by Merck Research Laboratories, manufacturers of aprepitant.

References

1. Hesketh PJ, Grunberg SM, Gralla RJ, *et al*. The oral NK1 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. *J Clin Oncol* 2003, **21**(22), 4112–4119.
2. Poli-Bigelli S, Rodriguez-Pereira J, Guoguang-Ma J, *et al*. Addition of the NK1 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* 2003, **97**(12), 3090–3098.
3. Gralla RJ, Osoba D, Kris MG, *et al*. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. *J Clin Oncol* 1999, **17**(9), 2971–2994.
4. Hesketh PJ, Van Belle S, Aapro M, *et al*. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur J Cancer* 2003, **39**, 1074–1080.
5. Grunberg SM, Hesketh PJ, Carides AD, *et al*. Relationships between the incidence and control of cisplatin-induced acute vomiting and delayed vomiting: analysis of pooled data from two phase III studies of the NK-1 antagonist aprepitant. *Proc Am Soc Clin Oncol* 2003, **22**, 729.
6. Hesketh PJ, Kris MG, Grunberg SM, *et al*. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997, **15**(1), 103–109.
8. McCrea JB, Majumdar A, Goldberg MR, *et al*. Effects of the neurokinin 1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther* 2003, **74**(1), 17–24.
9. Lindley CM, Hirsch JD, O'Neill CV, *et al*. Quality of life consequences of chemotherapy-induced emesis. *Qual Life Res* 1992, **1**(5), 331–340.
10. Martin AR, Pearson JD, Cai B, *et al*. Validation of a 5-day recall version of the Functional Living Index-Emesis (FLIE) quality of life questionnaire for chemotherapy-induced emesis. *Qual Life Res* 2000, **9**, 18.
11. de Wit R, Herrstedt J, Rapoport BL, *et al*. The oral NK1 antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. *Eur J Cancer* 2004, **40**, 403–410.
12. Martin AR, Ma JG, Carides AD, *et al*. Superiority of aprepitant, an oral NK1 antagonist, over standard antiemetic therapy: reducing the impact of nausea and vomiting on patients' daily lives. *Eur J Cancer* 2003, **1**(5), S282.
13. Cubeddu LX. Serotonin mechanisms in chemotherapy-induced emesis in cancer patients. *Oncology* 1996, **53**(Suppl. 1), 18–25.
14. Tavorath R, Hesketh PJ. Drug treatment of chemotherapy-induced delayed emesis. *Drugs* 1996, **52**(5), 639–648.