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The oral NK_1 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

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Abstract

In early clinical trials, the NK_1 receptor antagonist, aprepitant (EMEND®) was shown to improve the protection provided by the best available therapy (hereafter referred to as 'standard therapy': a 5-HT_3 receptor antagonist and dexamethasone) against chemotherapy-induced nausea and vomiting over multiple cycles of cisplatin-based chemotherapy. To further study the sustainment of antiemetic efficacy of aprepitant plus standard therapy over more than one cycle of chemotherapy, we examined combined data from the multiple cycles extensions of two phase III clinical trials of oral aprepitant plus standard therapy for the prevention of chemotherapy-induced nausea and vomiting. Data were pooled from two multicentre, randomised, double-blind, placebo-controlled studies with identical design and treatment regimens. Cancer patients receiving a first cycle of cisplatin-based ($\geqslant 70$ mg/m^2) chemotherapy were randomised to one of two treatment groups as follows: the standard therapy group received ondansetron 32 mg intravenously (i.v.) and dexamethasone 20 mg on day 1 and dexamethasone 8 mg twice daily (b.i.d.) on days 2–4. The aprepitant group received aprepitant 125 mg, ondansetron 32 mg i.v., and dexamethasone 12 mg on day 1, aprepitant 80 mg and dexamethasone 8 mg on days 2–3, and dexamethasone 8 mg on day 4. Patients had the option to receive the same blinded treatment for up to five additional cycles. The analysis used a combined exploratory endpoint of no emesis and no significant nausea (i.e. nausea which interfered with a patient's normal activities) over the 5 days following cisplatin, for up to six cycles of chemotherapy. A cumulative probabilities approach incorporating a model for transitional probabilities was used to analyse the data. Tolerability was assessed by reported adverse events and physical and laboratory assessments. Baseline characteristics, reasons for discontinuation, and drop-out rates were similar between groups. In every cycle, the estimated probabilities (rates) of no emesis and no significant nausea were significantly higher ($P < 0.006$) in the aprepitant group: in the first cycle, rates were 61% in the aprepitant group ($N = 516$) and 46% in the standard therapy group ($N = 522$), and thereafter, rates for the aprepitant regimen remained higher throughout (59% ($N = 89$) versus 40% ($N = 78$) for the standard therapy, by cycle 6). Repeated dosing with aprepitant over multiple cycles was generally well tolerated. Compared with patients who received standard therapy alone (a 5-HT_3 antagonist plus dexamethasone), those who received aprepitant in addition to standard therapy had consistently better antiemetic protection that was well maintained over multiple cycles of highly emetogenic chemotherapy

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1. Introduction

The prevention of chemotherapy-induced nausea and vomiting (CINV) was greatly improved with the introduction of the selective 5-HT_3 receptor antagonists [1–3] which in combination with a corticosteroid have been shown to prevent acute (day 1) emesis in 70–80% of patients in the first cycle of chemotherapy [4]. Nevertheless, 25–40% of patients still experience vomiting and/or significant nausea in the ensuing 2–5 days (referred to as the delayed phase) of their first cycle of high-dose cisplatin [4,5]. Furthermore, as chemotherapy consists of multiple (generally 4–6) cycles, the efficacy of antiemetic protection must be robust not only throughout the initial cycle, but should be maintained over subsequent cycles.

Few studies have addressed the efficacy of antiemetic drugs over multiple cycles of chemotherapy, and those that have examined this issue have yielded inconsistent findings, possibly due in part to the variation in analytical methods used [6]. Recently, de Wit and colleagues introduced a Markov method for transitional probabilities, which allows the analysis to account for those patients who had partial responses in prior cycles, but who regained complete response in a subsequent cycle [6,7]. When multiple cycles data were analysed using this approach, it appeared that the efficacy of current standard therapy with a 5-HT_3 receptor antagonist and a corticosteroid was not well maintained over multiple cycles, neither in patients receiving cisplatin-based nor in patients receiving non-cisplatin-based chemotherapy [6–8].

The novel neurokinin-1 (NK_1) receptor antagonist, aprepitant, in combination with a 5-HT_3 receptor antagonist and dexamethasone has been shown to provide superior protection in both the acute and delayed phases of CINV during a single cycle of treatment, compared with standard therapy alone [9,10]. In addition, an analysis of phase II multiple cycles data using the transitional probabilities approach showed that in comparison with a standard therapy regimen, the addition of aprepitant conferred improved antiemetic protection that was better maintained over multiple cycles of highly emetogenic, cisplatin-based chemotherapy [11]. To characterise further this sustainment of the antiemetic effect provided by the aprepitant regimen, data from the multiple-cycles extensions of two large phase III studies of aprepitant were pooled for analysis, and the findings are presented here.

2. Patients and methods

2.1. Design

All patients gave their written informed consent to participate in the two multicentre, randomised, double-blind, parallel-group, placebo-controlled trials, which were identical in design and which were conducted in accordance with applicable ethical requirements. A total of 74 sites (15 in the US and 59 outside the US) participated in the studies. In both studies, patients who completed the first cycle and whose continued participation was considered appropriate by the investigator were eligible to receive the same blinded study drug regimen to which they were originally assigned, for a maximum of five additional cycles.

2.2. Patients

Details of enrollment criteria for the individual studies will be the subject of separate publications. Cisplatin-naïve patients over the age of 18 years who had histologically-confirmed solid tumours and who were scheduled to receive their first cisplatin (at a dose of at least $\geqslant 70$ mg/m^2) were enrolled. The primary exclusion criteria included the following: abnormal laboratory values (including white blood count $<3.0\times10^9$ cells/l and absolute neutrophil count $<1.5\times10^9$ cells/l, platelet count $<100\times10^9$/l, aspartate aminotransferase $>2.5\times$upper limit of normal, alanine aminotransferase $>2.5\times$upper limit of normal, bilirubin $>1.5\times$upper limit of normal, or creatinine $>1.5\times$upper limit of normal); active infection or uncontrolled disease which in the opinion of the investigator should exclude the patient for safety reasons; a planned regimen of multiple-day cisplatin-based chemotherapy in a single cycle; radiation therapy to the abdomen or pelvis within 1 week prior to day 1 of the study or between days 1 and 6; or moderately or highly emetogenic chemotherapy on the 6 days prior to and/or following the day of cisplatin infusion. Additional chemotherapeutic agents of high emetogenicity (Hesketh Level $\geqslant 3$) [12] were permitted only on day 1 of each cycle, and additional antiemetics were prohibited within 2 days prior to day 1 or between days 1 and 6 of the study, unless such medications were given as rescue therapy for established nausea or vomiting. Although cisplatin doses initially >70 mg/m^2 could be reduced in subsequent cycles, the minimum dose required in any cycle remained at least 70 mg/m^2 in order for a patient to continue in the study.

2.3. Procedures

Treatment regimens in the two studies were identical. Patients were assigned to one of two treatment groups according to a computer-generated randomisation schedule. On day 1 of each cycle, patients in the standard therapy group received a standard regimen consisting of intravenous (i.v.) ondansetron 32 mg and oral dexamethasone 20 mg, followed by dexamethasone 8 mg twice daily on days 2–4; patients in the aprepitant group received oral aprepitant 125 mg plus a single dose

of i.v. ondansetron 32 mg and oral dexamethasone 12 mg on day 1, aprepitant 80 mg and dexamethasone 8 mg once daily on days 2–3, and dexamethasone 8 mg on day 4.

One hour before each cycle of cisplatin, patients received either aprepitant or placebo. Thirty minutes before cisplatin, patients received ondansetron (infused over 15 min) and dexamethasone; patients receiving docetaxel or paclitaxel in addition to cisplatin were premedicated with two doses of dexamethasone 20 mg before the paclitaxel or docetaxel infusion. Cisplatin was then infused over a period of $\leqslant 3$ h, with the start of infusion designated as T_{zero} (h). On days 2–5 of each cycle, patients took study medications at home (aprepitant and/or ondansetron and the first dose of dexamethasone between 8 and 10 a.m., and the second dose of dexamethasone (or placebo for the aprepitant group) between 5 and 8 p.m. each day). After each cycle, all patients returned to the clinic for a posttreatment visit between days 6 and 8, and for a follow-up safety visit between days 19 and 29, at which time a physical examination and laboratory tests were performed.

2.4. Assessments

In cycle 1, patients recorded emetic episodes and rated nausea daily on a 100-mm visual analogue scale (VAS) headed, 'How much nausea have you had over the last 24 hours?' Zero mm was labelled 'no nausea', and 100 mm was labelled 'nausea as bad as it could be'. Every day between 8 and 10 a.m., patients placed a vertical mark on the scale corresponding to the degree of nausea they experienced in the preceding 24 h. In subsequent cycles, efficacy data were collected at the day 6–8 visit for each cycle, at which time patients completed a simple worksheet containing the following two questions: (1) 'Have you had any episodes of vomiting or retching since your chemotherapy started in this cycle?' and (2) 'Have you had any nausea since your chemotherapy started in this cycle that interfered with your normal activities?' Data were captured as a binary response ('yes' or 'no') for each question. The use of rescue therapy and other concomitant medications was not recorded over multiple cycles. Tolerability was monitored through the reporting of serious adverse events, adverse events leading to discontinuation, or adverse events considered possibly, probably, or definitely related to study drug by the investigator; this approach was preapproved by the regulatory agencies.

Completion of the studies was defined as completion of the days 19–29 visit of cycle 1 or of cycle 6. Patients who completed the day 19–29 visit for any other cycle, but who did not participate in all six cycles were assigned a status of 'completed, but not continuing'. Cessation of the study at any other time was considered a discontinuation.

2.5. Statistical analysis

The analysis used a combined exploratory endpoint of no emesis and no significant nausea. To be considered evaluable, a patient had to have received at least one dose of study drug and cisplatin, and had to have recorded at least one posttreatment efficacy assessment. For cycle 1, data were obtained from the patient diaries, and no significant nausea was defined as a maximum VAS score <25 mm. For cycles 2–6, data were obtained from the two-question worksheet, and no significant nausea was redefined as the absence of nausea that interfered with normal activities. The combined endpoint of no emesis and no significant nausea allowed the use of a three-state model, with the three possible responses to treatment defined as follows: full protection (patient had no emesis and no significant nausea), partial protection (patient had either emesis or significant nausea, but not both), or failure (patient had both emesis and significant nausea). The efficacy measure of interest was the probability (also referred to as a 'rate') of full protection during the 5-day period following each cycle of cisplatin.

The probability of having full protection was calculated for each treatment group in each cycle and displayed graphically. In cycle 1, data were obtained from patients who were randomly allocated to treatment groups, and for cycles 2–6, the data were derived using a transitional probabilities approach based on previous studies [6,7]. Computations for each cycle were based on the number of patients who had had either a full or partial response in the previous cycle. Although patients who failed in a given cycle were not automatically discontinued from the study, their efficacy data were censored in the probability computations for subsequent cycles. Likewise, patients who withdrew or discontinued for reasons other than antiemetic protection failure were not included in the efficacy analysis for subsequent cycles. Therefore, the probability computations for each cycle were based on an evaluable population consisting of those patients who had full protection in the cycle being assessed, and who also had either full or partial protection in all previous cycle(s). This approach allowed for some fluctuation in a patient's level of treatment response from cycle to cycle without exclusion of partial protection as treatment failure. Treatment comparisons for all cycles were performed using the bootstrap method for the calculation of standard error; normal approximation to binomial distribution was applied to obtain Confidence Intervals and P values for proportions of full responders, and nominal P values were reported.

Tolerability assessments during the multiple cycle extension were limited to tabulation of adverse events leading to discontinuation or those considered serious or drug-related by the investigator. The tolerability profile

of interest in the present study was that of repeated dosing with aprepitant (i.e. over at least two cycles of chemotherapy). Data are reported from cycles 2–6; tolerability data from cycle 1 will be reported with the efficacy findings for cycle 1, in a separate publication for each study.

Table 1
Patient baseline characteristics by treatment group, for study protocols #052 and #054

	Aprepitant regimen	Standard therapy regimen
Patients entering cycle 1 (*N*)	547	552
% Female	43	44
Age (years)		
Mean (S.D.)	56 (13)	55 (13)
Range	18–84	18–83
Race (% of patients)		
Black	5	4
White	59	59
Other	36	37
Primary cancer diagnosis (% of patients)		
Non-small cell lung cancer	32	32
Other lung/respiratory	8	6
Urogenital	28	34
Other	32	28
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 units/week (% of patients)		
0	71	73
1–10	20	19
>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
Patients in cycles 2–6 (*N*)	413	438
% Female	44	44
Age (years)		
Mean (S.D.)	56 (13)	55 (13)
Range	18–84	18–81
Race (% of patients)		
Black	5	4
White	55	55
Other	40	41
Primary cancer diagnosis (% of patients)		
Non-small cell lung cancer	29	34
Other lung/respiratory	10	6
Urogenital	32	35
Other	29	25

SD, standard deviation. Aprepitant regimen = oral aprepitant 125 mg plus intravenous (i.v.) ondansetron 32 mg and oral dexamethasone 12 mg on day 1, aprepitant 80 mg plus dexamethasone 8 mg once daily on days 2 and 3, and dexamethasone 8 mg once daily on day 4. Standard therapy = ondansetron 32 mg plus dexamethasone 20 mg on day 1 and dexamethasone 8 mg twice daily on days 2 to 4.

[a] Hesketh Level $\geqslant$3 [12].

3. Results

3.1. Patients

Patients who entered the studies ($N = 1099$), and those who continued into the multiple cycles extensions, were similar with respect to gender, age, and race (Table 1). Fig. 1 shows the disposition of patients as a combined population from both studies. A total of 851 patients (413 in the aprepitant group and 438 in the standard therapy group) entered cycle 2. Attrition rates were similar between the two treatment groups, and were due to similar reasons in each chemotherapy cycle. As the cycles progressed, the mean cisplatin dose declined across the treatment groups in both studies, although the minimum dose of 70 mg/m^2 required by the protocol was maintained through cycles.

3.2. Efficacy

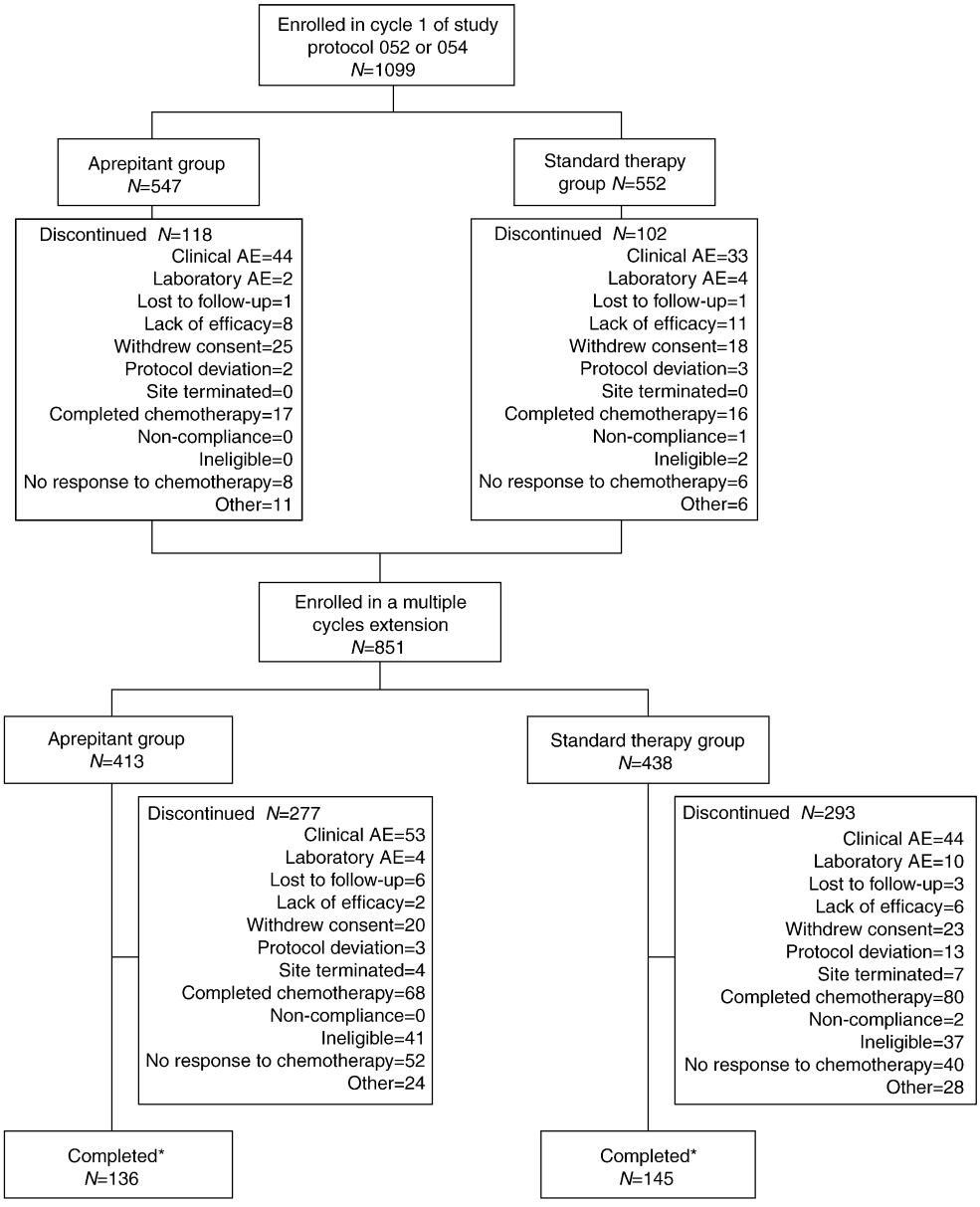
For the combined endpoint of full protection (no emesis and no significant nausea), Table 2 and Fig. 2 depict the probabilities (referred to as 'rates') estimated for each cycle using the transitional probability approach. Assessment of the overall full protection rates (no emesis and no significant nausea on days 1–5) by treatment group over the six cycles showed that there was no change in the full protection rate between cycle 1 and cycle 6 with the aprepitant regimen. In cycle 1, a 15 percentage-point difference between the treatments was noted, and this difference remained consistently above 10 percentage points throughout: in the aprepitant group, the full response rate dropped minimally from 61% ($N = 516$) in cycle 1 to 59% ($N = 89$) in cycle 6, whereas in the standard therapy group, the rate dropped 6 percentage points, from 46% ($N = 522$) in cycle 1 to 40% ($N = 78$) by cycle 6 (Table 2). The aprepitant group maintained rates that were consistently significantly higher than those in the standard therapy group ($P \leqslant 0.006$ for all cycles). In addition, the percentage of failures was calculated for each group as the number of failures over the six cycles, divided by the number of patients in cycle 1. Failures were more prominent in the standard therapy group (51.2%) than in the aprepitant 125/80-mg group (36.3%). No hypothesis was tested regarding this difference.

3.3. Tolerability

The following results refer to data obtained in cycles 2–6; tolerability in cycle 1 of each study will be reported in separate publications. Tolerability in the multiple cycles extension was limited to assessment of reported clinical adverse events that caused study discontinuation or that were considered by the investigators to be serious (defined according to regulatory standards) or

drug-related. The clinical and laboratory adverse event data from both phase III studies were pooled for comparisons here (Table 3). Serious adverse events, drug-related adverse events, and adverse events leading to discontinuation occurred in similar proportions of patients in each treatment group, with between-treatment differences of 1–2 percentage points (Table 3). Of the 38 deaths that occurred during the multiple cycles extensions, 18 (7%) were in the aprepitant group and 20 (5%) were in the standard therapy group. One death (due to perforating duodenal ulcer in a patient in the aprepitant group) was considered possibly related to study drug by the investigator. The patient had a history of gastritis and had taken chronic non-steroidal anti-inflammatory drugs (NSAID) therapy for over 4 months prior to developing the ulcer; the investigator considered that the death could have been related to aprepitant, dexamethasone, or diclofenac.

Serious laboratory adverse events were reported for 6 patients. Serious laboratory adverse events resulted in discontinuation for 1 patient in each treatment group; only in the case of the patient on standard therapy was the adverse event (hyperglycaemia) considered probably related to the study drug. Although no formal statistical comparisons were made with regard to patterns of National Cancer Institute (NCI) toxicity grade-3 or



*A patient was considered to have completed the study if he/she completed the day 19-29 visit of cycle 6.

Fig. 1. Study flow chart.

grade-4 changes in laboratory values, inspection of the data indicated that the pattern of abnormal haematological toxicity was comparable across both treatment groups, as were patterns of toxicity grade-3 or -4 changes in alanine aminotransferase (seen in no more than 3% of patients at any posttreatment assessment), aspartate aminotransferase (seen in no more than 0.6% of patients), or serum creatinine (seen in no more than 0.3% of patients).

4. Discussion

In clinical trials of antiemetic therapy for the prevention of CINV, evaluations of efficacy have been derived almost exclusively from studies of a single (initial) cycle of chemotherapy. Because chemotherapy usually consists of 4–6 cycles of treatment, it is of clinical importance to optimise antiemetic protection throughout all cycles of treatment. There is a tendency for CINV to

Table 2
Responses to treatment in the aprepitant group and the standard therapy group by cycle of cisplatin, and estimated probabilities of full response[a]

	Cycle					
	1 ($N=1038$)	2 ($N=589$)	3 ($N=448$)	4 ($N=312$)	5 ($N=212$)	6 ($N=167$)
Aprepitant regimen						
Estimated probability of full response	*0.61*[c]	*0.66*[c]	*0.65*[c]	*0.59*[c]	*0.57*[d]	*0.59*[c]
Patients in cycle (n)[b]						
Patients with full response (n)	317	248	203	140	97	79
Patients with partial response (n)	110	43	22	22	17	9
Patients with treatment failure (n)	89	17	20	8	3	1
Patients with incomplete data (n)	0	2	3	1	1	1
Number of withdrawals	0	206	62	77	54	28
Standard therapy						
Estimated probability of full response	*0.46*	*0.54*	*0.47*	*0.46*	*0.46*	*0.40*
Patients in cycle (n)[b]	522	281	203	142	95	78
Patients with full response (n)	238	219	157	115	80	58
Patients with partial response (n)	123	35	29	21	13	11
Patients with treatment failure (n)	161	27	17	6	2	9
Patients with incomplete data (n)	0	1	3	4	3	1
Number of withdrawals	0	240	77	60	48	19

[a] Full response = no emesis and no significant nausea (for cycle 1, maximum visual analogue scale (VAS) < 25; for cycles 2–5, no nausea that interfered with patient's daily activities). Partial response = either ⩾1 emetic episodes, but no significant nausea, or significant nausea, but no emesis. Failure = ⩾1 emetic episodes and significant nausea. Intermittent missingness = missing data for the previous or current cycle, without withdrawal from the study. Withdrawal included failures from the previous cycle and patients no longer in the study.

[b] Includes only those patients included in the modified intent-to-treat analysis (i.e. those who received at least one dose of study drug and cisplatin, and recorded at least one posttreatment efficacy assessment); small numbers of patients who enrolled in a cycle may not have met criteria to be considered evaluable for that cycle.

[c] $P<0.001$ versus standard therapy (standard error calculated using the bootstrap method).

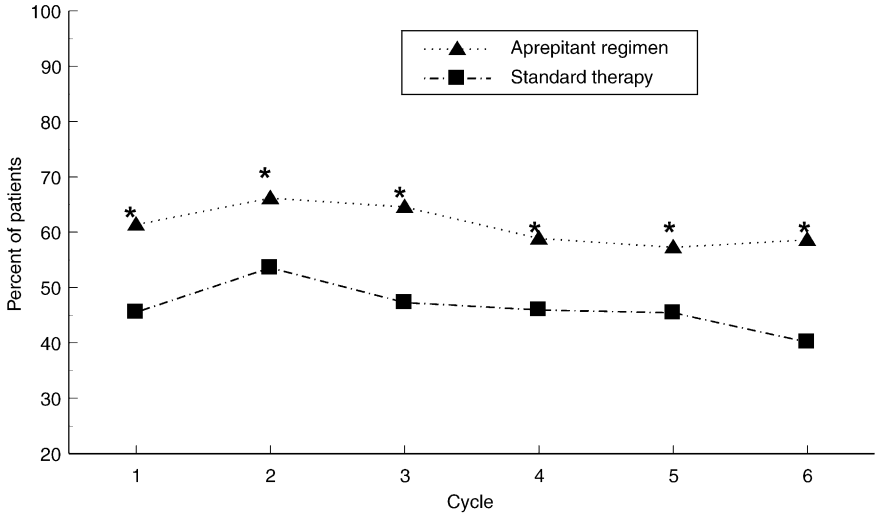
[d] $P=0.006$ versus standard therapy (standard error calculated using the bootstrap method).

Table 3
Summary of adverse events in cycles 2–6 of phase III multiple cycles extensions

Patients (%)[b]	Aprepitant regimen ($N=413$)	Standard therapy ($N=438$)
With drug-related[a] clinical adverse events	6	4
With serious clinical adverse events	19	18
Discontinued due to a clinical adverse event	12	10
With drug-related laboratory adverse events	1	1
With serious laboratory adverse events	1	1
Discontinued due to a laboratory adverse event	1	2
Who died	7	5

[a] Adverse events considered by the investigator to be possibly, probably, or definitely related to study drug. Statistical testing was not performed.

[b] For laboratory values, percentages refer to patients with at least one laboratory test postbaseline.



	N	N	N	N	N	N
Aprepitant regimen	516	308	245	170	117	89
Standard therapy	522	281	203	142	95	78

*$P \leq 0.001$ versus standard therapy in cycles 1–6; $P=0.006$ in cycle 5 (standard error calculated using the bootstrap method).

Fig. 2. Overall full response rates (estimated probabilities) for the aprepitant regimen and for standard therapy, by cycle of cisplatin: a transitional probabilities analysis of phase III data.

become progressively more severe with repeated administration of chemotherapy, and for the efficacy of 5-HT_3 antagonists (with or without concomitant corticosteroids) to decline during repeat cycles of chemotherapy [6–8]. These observations emphasise the clinical importance of antiemetic therapy with efficacy that is sustained over multiple cycles.

A need exists not only for more data on antiemetic therapy over multiple cycles, but also for a more consistent and reliable approach to the analysis of those data. The evaluation of antiemetic therapy during repeat cycles is considerably more complex than in a single cycle because of the potentially variable response between different cycles. For example, a patient may be emesis-free in cycles 1 and 2, vomit once in cycle 3 or 4, but may then return to an emesis-free course by cycles 5 and 6. Another feature of multiple cycles studies which can complicate the analysis is the attrition rate—patients discontinue therapy for various reasons including side-effects or lack of efficacy of chemotherapy. A Kaplan–Meier approach considers only 2 possible responses to treatment (success or failure), and categorises a partial response to treatment, such as one or two emetic episodes or a brief period of nausea in a given cycle, as a failure. By discounting partially successful responses, this approach may underestimate the true antiemetic protection rate over time, and by assessing only data obtained from within a given cycle, the Kaplan–Meier approach does not account for what may have occurred in prior cycles. Another method that has been adopted involves conditional analysis, which considers in each cycle's success rate only those data from patients who had successful protection in all previous cycles, thereby resulting in patient selection. By eliminating prior failures in the sum of failures for the evaluable patient population over subsequent cycles, this method overestimates the true response rates.

In order to take into consideration the attrition rate and the potentially variable response between cycles, a transitional probabilities approach allowing three states (i.e. fluctuation in response among full protection, partial protection, or treatment failure) was recently applied to the assessment of antiemetic efficacy in multiple cycles at the Rotterdam Cancer Institute [6,7]. This model accounts for patients who have partial protection in prior cycles, but may regain full protection in a subsequent cycle. Even with the use of dual therapy with 5-HT_3 receptor antagonist plus dexamethasone during 6 subsequent days, efficacy was not sustained [6]. The same method was adopted in an analysis of data from an earlier clinical trial with aprepitant [11]. The endpoint of interest in that analysis was complete response, defined as no emesis and no use of rescue therapy, with the three possible response outcomes defined in terms of number of emetic episodes and use of rescue therapy, which served as a surrogate measure of nausea control [11]. The aprepitant regimen was observed to provide better antiemetic protection that was sustained over

multiple cycles, whereas standard therapy not only conferred a lesser degree of protection, but also appeared to diminish in efficacy over multiple cycles [11].

These initial findings with aprepitant were further explored in the present combined analysis of multiple-cycles data pooled from two phase III studies of identical design. A new endpoint was used in order to allow for a simpler method of capturing data during multiple cycles. Based on input from participants in the phase II multiple cycles study, the diary was eliminated due to the complicated logistics of its use over 5 days of multiple cycles of chemotherapy. In place of the diary, patients in the present study were required to answer two yes/no questions about efficacy for the entire 5-day period of each cycle. Using transitional probabilities and the new composite endpoint, we analysed the data from a total of 589 patients who participated in the phase III multiple cycles extensions. The aprepitant regimen provided significantly greater antiemetic efficacy that was clearly maintained over multiple cycles, although it did not increase over time as observed in the original phase II analysis. Of note, the slightly higher full protection rate in cycle 2 for both treatments may be explained by the fact that it reflects the sum of both full and partial protection; this phenomenon has been observed in previous studies using the transitional probabilities approach [7].

As observed in the multiple cycles extension of the phase II study, the incidence and profile of adverse events in the present analysis were consistent with a population of patients with cancer receiving high-dose cisplatin-based chemotherapy, and were comparable between the treatment groups. Similarly low percentages of patients in each group had drug-related adverse events or serious adverse events. The number of deaths and the number of adverse events leading to discontinuation were also similar between groups, as were the profiles of laboratory adverse events.

In summary, we evaluated the antiemetic efficacy of the aprepitant regimen in a large population of patients receiving multiple cycles of highly emetogenic chemotherapy. The analysis was performed using a transitional probabilities approach. The effectiveness of the aprepitant regimen observed during the initial cycle of chemotherapy was well maintained during subsequent cycles, and was consistently and significantly better than that of dual therapy with a 5-HT_3 receptor antagonist and dexamethasone. These data show that the addition of aprepitant to standard antiemetic therapy represents an important advance in supportive care for patients receiving multiple cycles of highly emetogenic chemotherapy.

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