PERGAMON

European Journal of Cancer 37 (2001) 835–842

European Journal of Cancer

www.ejconline.com

Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis

V. Cocquyt [a], S. Van Belle [a,*], R.R. Reinhardt [b], M.L.A. Decramer [c], M. O'Brien [d], J.H.M. Schellens [e], M. Borms [a], L. Verbeke [a], F. Van Aelst [a], M. De Smet [f], A.D. Carides [b], K. Eldridge [b], B.J. Gertz [b]

[a] *Vlaamse Oncologische Studiegroep, Ghent, Belgium*
[b] *Merck Research Laboratories, Rahway, NJ, USA*
[c] *UZ Gasthuisberg, Leuven, Belgium*
[d] *Mid-Kent Oncology Centre, Kent, UK*
[e] *The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[f] *Merck Research Laboratories Europe, Brussels, Belgium*

Received 31 May 2000; received in revised form 29 September 2000; accepted 15 November 2000

Abstract

Substance P is localised in brainstem regions associated with emesis. Based on studies in the ferret, it was postulated that a neurokinin-1 (NK_1) receptor antagonist would have antiemetic activity as monotherapy in humans receiving chemotherapy. L-758,298 is a water-soluble, intravenous (i.v.) prodrug for L-754,030, a potent and selective NK_1 receptor antagonist. This double-blind, randomised, active-agent (ondansetron)-controlled study enrolled 53 cisplatin-naïve patients and evaluated the prevention of both acute (0–24 h) and delayed (days 2–7) emesis after cisplatin treatment (50–100 mg/m^2). All patients received i.v. L-758,298 (60 or 100 mg) ($n=30$) or ondansetron (32 mg) ($n=23$) before cisplatin and efficacy was evaluated up to day 7 post-cisplatin. Nausea was assessed by means of a four-point ordinal scale at intervals over the 7 day period. In the acute period, the proportion of patients without emesis in the L-758,298 and ondansetron groups was 37 and 52%, respectively (no significant difference between the groups). Comparing the distribution of average nausea scores over the entire first 24 h revealed no significant difference between the groups. In the delayed period, the proportion of patients without emesis in the L-758,298 and ondansetron treatment groups was 72 and 30%, respectively ($P=0.005$). The distribution of average nausea scores in the delayed period was lower in the L-758,298 group compared with the ondansetron group ($P=0.15$ for the entire delayed period and $P=0.043$ for day 2 only). No serious adverse events were attributed to L-758,298. A single dose of L-758,298 substantially suppressed the delayed nausea and vomiting characteristic of high dose cisplatin and also appeared to reduce acute emesis post-cisplatin. The data also support the proposition that the underlying mechanism(s) of acute and delayed emesis are different.

Keywords: Antiemetic; Cancer; Substance P; Neurokinin

1. Introduction

Chemotherapy-induced nausea and vomiting are among the most intolerable side-effects of treatment [1–3]. The specific chemotherapeutic agent, dosage and administration protocol determine both the intensity and pattern of chemotherapy-induced emesis [4]. Cisplatin, for example, is most commonly associated with intense nausea and vomiting which follows a particular pattern including both an acute (first 24 h) and a delayed period (several days post chemotherapy) [5]. Acute emesis occurs in virtually all patients who receive cisplatin doses $\geqslant 50$ mg/m^2 in the absence of prophylactic antiemetics [6]; delayed emesis has been reported in 57–89% [7–9] with maximal intensity on days 2 and 3 after chemotherapy [10,11].

* Corresponding author at University Hospital Gent, De Pintelaan 185, B-9000 Gent, Belgium. Tel.: +32-9-240-2692; fax: +32-9-240-3843.

E-mail address: simon.vanbelle@rug.ac.be (S. Van Belle).

0959-8049/01/$ - see front matter
PII: S0959-8049(00)00416-0

Initial therapeutic attempts to prevent chemotherapy-induced emesis involved antagonising brainstem neurotransmitter receptors in the vomiting centre and on interrupting vagal afferent input to this centre. Chemotherapeutic agents stimulate the chemoreceptor trigger zone in the area postrema to transmit impulses to the vomiting centre [12]. Dopamine antagonists, corticosteroids, and, most recently, the 5-HT_3 antagonists were found to significantly reduce chemotherapy-induced emesis [13–17].

While 5-HT_3 antagonists by themselves improved the prevention of acute chemotherapy-induced emesis [15–17], better control was achieved with the combination of a 5-HT_3 antagonist and dexamethasone [18–20]. However, the 5-HT_3 antagonists are not very effective in preventing delayed emesis [21,22]. The most effective therapy to prevent delayed emesis is the combination of a 5-HT_3 antagonist or metoclopramide with dexamethasone (no emesis in 52–69% of patients) [23,24]. However, these regimens may require dosing two to four times a day and metoclopramide can be associated with sedation and extrapyramidal side-effects. Thus, there is a need for a simpler and more effective therapy for the prevention of delayed emesis.

Substance P is one of four mammalian tachykinins found in neurones, particularly in vagal afferent fibres innervating the brainstem nucleus tractus solitarius (which sends impulses into the vomiting centre) and the area postrema. Exogenous substance P applied to cells in the nucleus tractus solitarius induces emesis [25]. Substance P acts via the G-protein coupled neurokinin-1 (NK_1) receptor to generate an inositol phosphate second messenger, and thereby exert its biological effects [26].

L-758,298 is the water soluble pro-drug of L-754,030, a potent and selective non-peptide NK_1-receptor antagonist [27]. L-758,298 can be formulated for intravenous (i.v.) administration whereas L-754,030 can be given orally. It has been shown that NK_1-receptor antagonists (including L-758,298/L-754,030) are antiemetic in the ferret and central nervous system penetration is required for such activity [28–30]. L-758,298 produced dose-dependent inhibition of cisplatin-induced vomiting in both an acute and delayed emesis model in the ferret [31]. It has recently been shown that oral L-754,030 added to a regimen of granisetron plus dexamethasone prior to cisplatin confers more effective protection against acute emesis than the latter two agents alone [32]. Furthermore, the addition of L-754,030 reduced the incidence of delayed emesis post-cisplatin [32]. However, the antiemetic characteristics of this NK_1 antagonist by itself were not examined in that clinical trial.

The primary objectives of the present study were to evaluate the activity of a single dose of a NK_1-receptor antagonist as monotherapy for the prevention of acute emesis secondary to cisplatin, and to assess the safety and tolerability of L-758,298 in patients receiving chemotherapy. The secondary objective was to determine whether a single dose of L-758,298 given prior to cisplatin had efficacy in the prevention of delayed emesis.

2. Patients and methods

2.1. Study design

This double-blind, randomised, active-agent (ondansetron)-controlled study was conducted at seven centres in cisplatin-naïve male and female patients with cancer. Patients were assigned to one of two treatment groups according to a computer-generated, randomised allocation schedule (with an approximate 1.5:1 ratio of L-758,298 to ondansetron) which incorporated stratification for both gender and the administration of additional highly emetogenic chemotherapy (Fig. 1). The chemotherapy included in this highly emetogenic category was based on a published categorisation [33]. All additional emetogenic chemotherapy was only administered on day 1. The study protocol was approved by the local ethical committee in each of the participating centres and all patients signed an informed consent form. The patients were recruited for the trial between 1996 and 1997.

All patients received i.v. treatment with L-758,298 (60 or 100 mg) or ondansetron (32 mg) infused over 30 min, beginning 60 min prior to cisplatin (50 to 100 mg/m^2

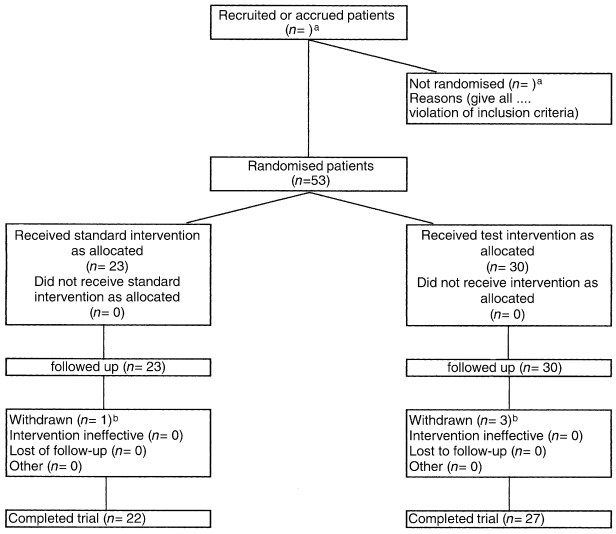

Fig. 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwoods, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639.)

[a]Not recorded in the clinical study.

[b]The 4 subjects who withdrew form the study, were all included in the efficacy analysis (up to day 7).

infused up to 2 h) and were monitored for 7 days post-cisplatin. Fig. 2 provides a diagram of the study and its procedures. Blinding was maintained by preparation of i.v. medication by a pharmacist uninvolved with other aspects of the trial including patient monitoring. The first nine patients assigned to the L-758,298 group received 60 mg. Their results were summarised by the study statistician without identification of individual subjects as predefined in the protocol. Based on the less than complete control of emesis observed, the dose of L-758,298 was increased to 100 mg for subsequent patients, while maintaining the blinding of the study for the investigators. Medical supervision in the hospital was continued up to 24 h post-cisplatin and at home on days 2 to 7 post-cisplatin. Rescue therapy (as defined by the investigator) was permitted in the first 24 h after three emetic episodes. On days 2 to 7, rescue medication was allowed for all patients who needed or requested it, irrespective of the occurrence of emesis.

2.2. Patient eligibility

Patients ($\geqslant$18 years old) scheduled to receive their first course of cisplatin-based chemotherapy at a dose of 50 to 100 mg/m^2 were enrolled. Female patients of reproductive potential demonstrated a negative test for serum β-human chorionic gonadotropin (HCG) at the prestudy visit. Primary criteria for exclusion included: a Karnofsky score <60; use of another antiemetic agent within 1 week of study day 1 (serotonin antagonists, phenothiazines, butyrophenones, cannabinoids, metoclopramide, corticosteroids, or benzodiazepines); an episode of vomiting or retching within 1 week of the start of the cisplatin infusion on study day 1; severe concurrent illness other than neoplasia; known brain metastasis, gastrointestinal obstruction or an active peptic ulcer; radiation therapy to the abdomen or pelvis within 1 week prior to or following study day 1; and a laboratory measurement as follows: haemoglobin (Hb) <100 g/l, white blood cells (WBC) $<3.5\times10^9$/l, platelets $<100\times10^9$/l, aspartate aminotransferase (AST) >2 times the upper limit of normal alanine aminotransferase (ALT) >2 times the upper limit of normal, bilirubin >2 times the upper limit of normal, alkaline phosphatase >2 times the upper limit of normal, albumin <3.0 g/l, prothrombin time >3 s above control, and creatinine >176.8 μmol/l.

2.3. Assessments

Episodes of vomiting or retching (date, time and number of episodes) were recorded on diary cards. An emetic episode was defined as a single vomit or retch, or any number of continuous vomits or retches; distinct episodes were separated by at least 1 min. The primary efficacy parameter was the proportion of patients who had no emetic episodes in the acute period (initial 24 h postinitiation of cisplatin infusion). Emetic episodes were also recorded in the delayed period (days 2 to 7). Emetic episodes were recorded on the diary card by the nurse while the patient was in the hospital and by the patient while at home.

Patients also rated their degree of nausea and their global satisfaction with emetic prophylaxis. Nausea (four-point scale: 0 = none, 1 = mild (does not interfere with normal daily life), 2 = moderate (interferes with normal daily life) and 3 = severe (bedridden due to nau-

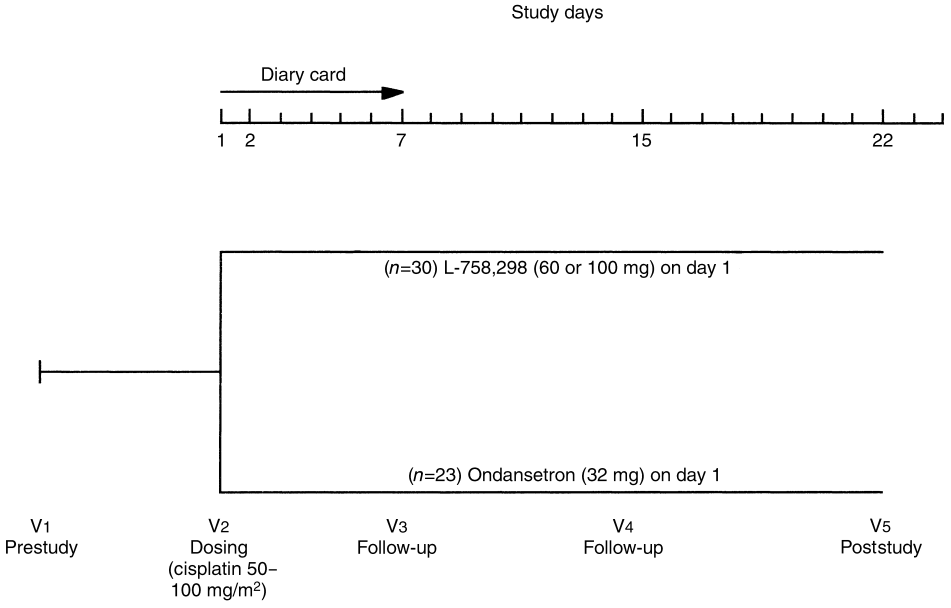

Fig. 2. Schematic of study design. Patients ($n=53$) were randomised to prophylactic treatment with either ondansetron ($n=23$) on L-758,298 ($n=30$). The first 24 h post-cisplatin constituted the acute period and days 2 to 7 the delayed period for the analyses of emetic episodes and nausea.

sea)) was recorded every 2 h while awake during the first 24 h post-cisplatin. Patients recorded nausea ratings on the diary card every 8 h on days 2 through to 7 post-cisplatin. At each entry (2:00 p.m., 10:00 p.m. and 6:00 a.m. or awakening), patients recorded the number and time of emetic episodes they experienced in the preceding 8 h and rated their nausea. Global satisfaction with the antiemetic treatment was assessed by the patient at 24 h post-cisplatin using a horizontal 100-mm visual analogue scale. The scale was headed: ''How satisfied are you with your antiemetic treatment?'' 0 mm on the scale was labelled ''not at all satisfied''; 100 mm was labelled ''completely satisfied''.

Adverse events other than episodes of vomiting and nausea were recorded by the patients on their diary cards from study day 1 to 7. Adverse events from study day 8 to their post study visit (study day 22) were recorded. Patients were also evaluated at 24 h and on study days 7, 15 and 22 for laboratory safety (routine haematology and serum chemistry; urinalysis), electrocardiograms (ECGs) and physical examinations.

2.4. Statistical analysis

The statistical analysis approach was based on intent-to-treat data. All patients that had emesis data after receiving cisplatin were included. The study compared the incidence of acute and delayed emesis in the L-758,298 (combined 60 and 100 mg treatments) and ondansetron groups. The use of rescue medication in both periods was also evaluated. Fisher's Exact Test was used to compare the incidence of emesis between the two treatment groups. Data are reported on the proportion of patients without emesis. In addition to the primary efficacy parameter, data are provided on the proportion of patients with 1–2 emetic episodes, and those without emesis or use of rescue therapy. A 95% exact two-sided confidence interval (CI) was calculated for the difference in the proportions of patients for each of the relevant comparisons.

A secondary efficacy parameter was the patient's self-assessment of nausea. In the analysis for the acute (day 1) and delayed periods (days 2 to 7), an average score was computed for each patient using the four-point scale values over the given interval, while the analysis for day 2 used only the average of the three values recorded on day 2 for each patient. Non-parametric analyses were performed on the ranked scores due to a non-normal distribution of values. For the days 2 to 7 analysis, the distributions of these average scores were compared among the treatment groups, using the Wilcoxon test, and the median values for these distributions are reported. In addition, comparisons were performed for the proportions of patients that had no nausea for the acute period (day 1), days 2 to 7 and day 2 only using the Fisher's Exact Test (defined *post hoc* as a four-point scale average rating = 0 over the corresponding time period).

An exploratory parameter was patient's global satisfaction with the antiemetic therapy recorded at 24 h post-cisplatin. The two treatment groups were compared using a non-parametric analysis on the ranked VAS ratings. The median values for the distributions of the global satisfaction ratings in the two treatment groups are reported. All statistical comparisons were two-tailed with significance set at $P < 0.05$.

3. Results

A total of 53 patients took part in the study; none was excluded from the acute analysis, while 1 patient was excluded from the delayed analysis (in the L-758,298 group, as she did not return her diary). Both treatment groups had similar baseline characteristics (Table 1).

3.1. Emesis prevention

During the acute period, the proportion of patients without emesis was 37% in the L-758,298 group and 52% in the ondansetron group (Table 2) ($P = 0.28$). The difference in the proportion of patients without emesis (L-758,298 minus ondansetron) was −15 percentage points (95% CI for the difference: −45 to 12%). The frequency with which patients had no emesis or use of rescue medication in the L-758,298 and ondansetron groups was 37 and 48%, respectively (Table 2; $P = 0.57$). The difference in the proportion of patients without emesis or use of rescue (L-758,298 minus ondansetron) was −11 percentage points (95% CI for the difference: −41 to 16%). When considering 0–2 emetic episodes, frequencies in the L-758,298 and ondansetron groups were 57 and 65%, respectively ($P = 0.58$). During the first 8 h post-cisplatin, the proportion of patients without emesis in the L-758,298 and ondansetron groups was 37 and 83%, respectively ($P = 0.001$). During the delayed period, superior control of emesis was achieved following a single dose of L-758,298 on day 1 (Table 2). Prevention of delayed emesis in the L-758,298 group was significantly better than in the ondansetron group (proportion of patients without delayed emesis was 72% versus 30%; $P = 0.005$). The difference between the two groups in the frequency with which patients had no emesis (L-758,298 minus ondansetron) was 42 percentage points (95% CI for the difference: 14 to 68%). Similarly, comparison of the L-758,298 and ondansetron groups revealed differences in the proportion of patients reporting no emesis or use of rescue medication (Table 2; 48% versus 17%; $P < 0.04$). The difference in the frequency with which patients reported no emesis or use of rescue in the delayed period was 31 percentage

Table 1
Patient characteristics

	Treatment group	
	L-758,298	Ondansetron
No. of patients	30	23
Male *n* (%):female *n* (%)	16 (53):14 (47)	12 (52):11 (48)
Age (years)[a]	57 (±8)	55 (±9)
Cisplatin dose (mg/m^2)[a]	77 (±15)	79 (±16)
Additional emetogenic chemotherapy *n* (%)	7 (23)[b]	8 (35)[c]
60/100 mg L-758,298 (*n*)	9/21	–
Type of cancer *n* (%)		
Lung	7 (23)	2 (9)
Gastrointestinal	7 (23)	6 (26)
Head and neck	4 (14)	4 (17)
Genitourinary	9 (30)	9 (39)
Other	3 (10)	2 (9)

[a] Mean± standard deviation (S.D.).
[b] Type of additional emetogenic chemotherapy + dose and (number of subjects): ifosfamide 1200 mg/m^2 + vindesine 2.4 mg/m^2 ($n=1$); cyclophosphamide 750 mg/m^2 ($n=2$); cyclophosphamide 500 mg/m^2 + doxorubicin 50 mg/m^2 ($n=2$); doxorubicin 30 mg/m^2 + methotrexate 30 mg/m^2 + vinblastine 3 mg/m^2 ($n=2$).
[c] Type of additional emetogenic chemotherapy + dose and (number of subjects): ifosfamide 1200 mg/m^2 + vindesine 2.4 mg/m^2 ($n=1$); cyclophosphamide 750 mg/m^2 ($n=3$); cyclophosphamide 500 mg/m2 + doxorubicin 50 mg/m^2 ($n=2$); epirubicin 50 mg/m^2 ($n=1$); epirubicin 60 mg/m^2 + 5-fluorouracil 200 mg/m^2 ($n=1$).

points (95% CI for the difference: 4 to 58%). In addition, significantly fewer patients used rescue medication when receiving L-758,298 than ondansetron (38% versus 74%; $P=0.013$). When considering 0–2 emetic episodes in the delayed period, frequencies in the L-758,298 and ondansetron groups were 79 and 48%, respectively ($P=0.022$).

3.2. Nausea assessment

For the acute period, the median values for the distribution of nausea scores were slightly lower in the ondansetron group than in the L-758,298 group (median = 0 in the ondansetron group versus 0.3 in the L-758,298 group), but the difference was not statistically significant (Table 3; $P=0.11$). Fig. 2 depicts the mean nausea scores for the acute and delayed periods by timepoint; it appears that nausea was more effectively prevented by ondansetron over the initial 8 h post-cisplatin, and this trend tends to reverse after that time with numerically lower scores in the L-758,298 group (Fig. 3a).

Over the delayed period of days 2 to 7, the distribution of nausea scores in the L-758,298 group was lower than in the ondansetron group but the difference was not statistically significant ($P=0.15$). For the day 2 analysis only, nausea scores in the L-758,298 group were significantly lower than in the ondansetron group ($P=0.043$). The frequency with which patients reported no nausea (defined as a four-point scale average rating of 0 over the corresponding time period) for the entire delayed period in the L-758,298 and ondansetron groups was 28 and 17%, respectively ($P=0.51$), while for day 2, the frequencies were 52 and 22%, respectively ($P=0.044$).

3.3. Global satisfaction assessment

Although the median global satisfaction rating obtained after the acute period was higher for the

Table 2
Proportion of patients without emesis and without emesis or use of rescue medication in the acute and delayed periods

Acute period (day 1)				Delayed period (days 2–7)		
Treatment	*n*	No emesis *n* (%)	No emesis or use of rescue medication[a] *n* (%)	*n*	No emesis *n* (%)	No emesis or use of rescue medication[a] *n* (%)
L-758,298	30	11 (37)	11 (37)	29	21 (72)†	14 (48)*
Ondansetron	23	12 (52)	11 (48)	23	7 (30)	4 (17)

[a] The percentage of patients who had no emesis and did not receive any rescue medication for any reason.
*$P<0.04$ versus ondansetron. †$P=0.005$ versus ondansetron.

Table 3
Median nausea scores in the acute and delayed periods

Treatment	Median		
	Acute period (day 1)	Delayed period (day 2–7)	Delayed period (day 2)
L-758,298	0.3	0.4	0.0*
Ondansetron	0.0	0.8	1.3

*$P = 0.043$ versus ondansetron.

ondansetron group than for the L-758,298 group (91 versus 68), the difference in the distribution of the ranked visual analogue scale (VAS) ratings between the two treatment groups approached, but did not achieve significance ($P = 0.10$).

3.4. Safety

All 53 patients were included in the safety analysis. Table 4 lists the most frequent adverse events (occurring in $\geqslant 10\%$ of patients) through to day 7 (6 days after the initial dose of study medication). The most commonly reported clinical adverse events were asthenia, headache, constipation, diarrhoea, abdominal pain, and anorexia. There was an increased incidence of diarrhoea in the L-758,298 group. No significant differences were observed between the two treatment groups with respect to laboratory indices of safety. The same pattern in the clinical and laboratory adverse experiences emerged when looking at the entire study period (day 1 through to the last study visit on day 22). No serious adverse events were considered by the investigators to be study drug related.

Table 4
Clinical and laboratory adverse events[a]

	Randomisation group	
	L-758,298	Ondansetron
Adverse event[a]		
Constipation	12 (40)	9 (39)
Diarrhoea	18 (60)	2 (9)
Anorexia	12 (40)	8 (35)
Headache	14 (47)	9 (39)
Abdominal pain	5 (17)	2 (9)
Asthenia	12 (40)	7 (30)
Haematological decreases[b]		
Total white blood cells (WBC)	1 (3)	0
Neutrophils	1 (3)	0
Transaminase elevations[c]		
AST	0	0
ALT	1 (3)	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a] Numbers (percentage) of patients in each group with adverse events from study days 1 to 7 regardless of relationship to study drug. Only the most common ($\geqslant 10\%$ of patients) adverse clinical events are listed.

[b] Transient changes for WBC $< 2.0 \times 10^9$/l and neutrophils/bands $< 1.0 \times 10^9$/l, in patients who had normal or above-normal baseline values (National Cancer Institute toxicity grades III or IV) [34].

[c] Transient increases to greater than 2.5 times the upper limit of the normal range in patients who had normal or below-normal baseline values (National Cancer Institute toxicity grades II, III or IV) [34].

4. Discussion

The 5-HT_3 antagonists have been found to greatly reduce acute chemotherapy-induced emesis (especially when used in combination with dexamethasone), but have had less of an impact on delayed vomiting result-

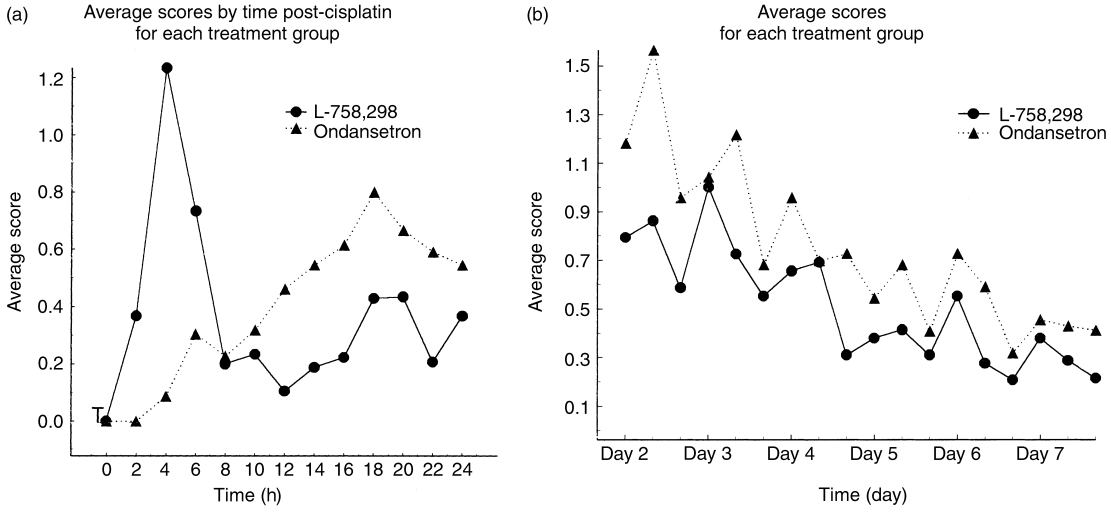

Fig. 3. Mean nausea scores in the acute (a) (day 1) and delayed (b) (days 2 to 7) periods. There was no significant difference in the average nausea score distributions over the acute period. For the day 2 analysis, the distribution of the average nausea scores in the L-758,298 group was significantly lower than in the ondansetron group ($P = 0.043$). The first point on (b) on day 2 reflects the initial 8 h assessment on day 2, whereas the 24 h point on (a) reflects the immediately preceding 2 h time frame.

ing from the administration of highly emetogenic agents such as cisplatin [18–24]. Recently, the addition of the selective NK_1-antagonist, L-754,030, to a 5-HT_3 antagonist plus dexamethasone was found to provide substantial benefit in reducing both acute and delayed emesis post-cisplatin [32]. The results of the present trial suggest that L-758,298, the i.v. prodrug for L-754,030, given as monotherapy has activity for the prevention of acute emesis and significantly reduces delayed emesis compared with ondansetron.

L-758,298 was generally similar to ondansetron when considering the proportion of patients without emesis, the extent of nausea, and the global satisfaction rating over the initial 24 h post-cisplatin. Although the numerical superiority of ondansetron to L-758,298 for the prevention of acute emesis (15 percentage points) was not statistically significant, the small size of the trial could have missed a true difference. This is reflected in the relatively wide confidence intervals for the difference in the proportion of patients without emesis. Furthermore, the proportion of patients without emesis in the L-758,298 group (37%), was less than that reported with the 5-HT_3 antagonist/dexamethasone combination [7–9]. This suggests that L-758,298 will need to be used in combination with another antiemetic such as dexamethasone and/or a 5-HT_3 antagonist for optimal control of acute emesis. Indeed, when L-754,030 was given orally along with granisetron plus dexamethasone, nearly 93% of patients had no acute emetic episodes [32]. However, the present data support L-758,298 as an effective antiemetic as monotherapy in the acute period since virtually all patients receiving the doses of cisplatin utilised in this study would have been expected to vomit had they received no prophylactic antiemetic treatment [6]. A more detailed examination of the initial 24 h period suggests that ondansetron may be more effective in the initial 8 h post-cisplatin. As others have suggested, this may indicate that the 'transition' from the acute to delayed period of emesis may actually begin sooner than 24 h [24].

For the delayed period (defined as days 2 to 7 in this trial), a single dose of L-758,298 on day 1 resulted in a proportion of patients without emesis approximately 42 percentage points higher (72% versus 30%) than that following the single dose of ondansetron and up to 20 percentage points better than the best reported dual therapy regimen dosed continuously throughout the delayed period (a 5-HT_3 antagonist or metoclopramide plus dexamethasone which yielded no emesis frequencies of 52–69%) [23,24]. Based on the findings of this study, it would be of interest to compare the effect of a NK-1 antagonist with the effect of what has now become a recommended antiemetic regimen for delayed emesis (dexamethasone with or without metoclopramide or a 5-HT-3 antagonist) [35]. Given the lack of superiority of L-758,298 alone in preventing acute emesis, the advantage in preventing delayed emesis can not be attributed to a carry-over effect from the acute period. This observation suggests the underlying mechanism(s) of acute and delayed emesis are different and that the prevention of delayed vomiting observed in the present trial was not simply the result of controlling emesis in the acute period. In addition, patients had less delayed nausea in the L-758,298 group, especially on day 2, which tends to be the day of maximal intensity [10,11].

L-758,298 was generally well tolerated with clinical and laboratory adverse events similar to the ondansetron group except for a higher incidence of diarrhoea. However, cisplatin has been shown to cause diarrhoea in up to 60% of patients when not given with other antiemetics [36] while antiemetic trials with 5-HT_3 antagonists have resulted in a lower incidence of diarrhoea suggesting a constipating effect for the 5-HT_3 antagonists [37]. L-758,298 administration has not resulted in diarrhoea in normal volunteer studies (data on file; Merck Research Laboratories).

In summary, single i.v. doses of the NK_1-antagonist prodrug, L-758,298, appeared to be generally similar to a 5-HT_3 antagonist given alone for the prevention of acute emesis and markedly suppressed delayed emesis following high-dose cisplatin therapy. This study also provides convincing additional support for the proposal that there are fundamental differences in the underlying mechanism(s) of acute and delayed emesis following chemotherapy. Further trials are required to establish the appropriate regimen of NK_1-antagonists for the prevention of chemotherapy-induced nausea and vomiting.

References

1. Griffin AM, Butow PN, Coates AS, *et al*. On the receiving end V: patient perceptions of the side effects of cancer chemotherapy. *Ann Oncol* 1997, **7**, 189–195.
2. Osoba D, Zee B, Warr D, Kaizer L, Latreille J, Pater J. Quality of life studies in chemotherapy-induced emesis. *Oncology* 1996, **53**(Suppl. 1), 92–95.
3. Laszlo J, Lucas VSJ. Emesis as a critical problem in chemotherapy. *N Engl J Med* 1981, **305**, 948–949.
4. Gralla RJ. Controlling emesis in patients receiving cancer chemotherapy. *Recent Results Cancer Res* 1991, **121**, 68–82.
5. Gralla RJ, Tyson LB, Kris MG, Clark A. The management of chemotherapy-induced nausea and vomiting. *Med Clin North Am* 1987, **71**, 289–301.
6. Kris MG, Cubeddu LX, Gralla RJ, *et al*. Are more antiemetic trials with a placebo necessary? Report of patient data from randomized trials of placebo antiemetics with cisplatin. *Cancer* 1996, **78**, 2193–2198.
7. Passalacqua R, Cocconi G, Bella M, *et al*. Double-blind, randomized trial for the control of delayed emesis in patients receiving cisplatin: comparison of placebo vs adrenocorticotropic hormone (ACTH). *Ann Oncol* 1992, **3**, 481–485.
8. Gandara DR, Harvey WH, Monaghan GG, Perez EA, Hesketh PJ. Delayed emesis following high-dose cisplatin: a double-blind randomized comparative trial of ondansetron (GR 38032F) versus placebo. *Eur J Cancer* 1993, **29A**(Suppl. 1), S35–S38.

9. Kris MG, Gralla RJ, Tyson LB, Clark RA, Cirrincione C, Groshen S. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989, **7**, 108–114.
10. Kris MG, Gralla RJ, Clark RA, *et al*. Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. *J Clin Oncol* 1985, **3**, 1379–1384.
11. Navari RM, Madajewicz S, Anderson N, *et al*. Oral ondansetron for the control of cisplatin-induced delayed emesis: a large, multicenter, double-blind, randomized comparative trial of ondansetron versus placebo. *J Clin Oncol* 1995, **13**, 2408–2416.
12. Borison HL, McCarthy LE. Neuropharmacology of chemotherapy induced emesis. *Drugs* 1983, **25**, 8.
13. Ireland SJ, Straughan DW, Tyers MB. Influence of 5-HT uptake on the apparent 5-HT antagonist potency of metoclopramide on the rat isolated superior cervical ganglion. *Br J Pharmacol* 1987, **90**, 151–160.
14. Kris MG, Gralla RJ, Tyson LB, *et al*. Improved control of cisplatin-induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone, and diphenhydramine. Results of consecutive trials in 255 patients. *Cancer* 1985, **55**, 527–534.
15. De Mulder PH, Seynaeve C, Vermorken JB, *et al*. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. A multicenter, randomized, double-blind, crossover study. *Ann Intern Med* 1990, **113**, 834–840.
16. Kris MG. Phase II trials of ondansetron with high-dose cisplatin. *Seminars Oncol* 1992, **19**, 23–27.
17. Ruff P, Paska W, Goedhals L, *et al*. Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: a multicenter double-blind, randomized, parallel-group study. *Oncology* 1994, **51**, 113–118.
18. Roila F, Tonato M, Cognetti F, *et al*. Prevention of cisplatin-induced emesis: a double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. *J Clin Oncol* 1991, **9**, 675–678.
19. Smith DB, Newlands ES, Rustin GJS, *et al*. Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 1991, **338**, 487–490.
20. Hesketh PJ, Harvey WH, Harker WG, *et al*. A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. *J Clin Oncol* 1994, **12**, 596–600.
21. Roila F, Bracardia S, Tonato M, *et al*. Ondansetron in the prophylaxis of acute and delayed cisplatin-induced emesis. *Clin Oncol* 1990, **2**, 268–272.
22. Hesketh P. Management of cisplatin-induced delayed emesis. *Oncology* 1996, **53**(Supp. 1), 78–85.
23. Kris MG, Gralla RJ, Tyson LB, Clark RA, Cirrincione C, Groshen S. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989, **7**, 108–114.
24. Gralla RJ, Rittenberg C, Peralta M, Lettow L, Cronin M. Cisplatin and emesis: aspects of treatment and a new trial for delayed emesis using oral dexamethasone plus ondansetron beginning at 16 hours after cisplatin. *Oncology* 1996, **53**(Suppl. 1), 86–91.
25. Gardner CJ, Bountra C, Bunce KT, *et al*. Anti-emetic activity of neurokinin NK1 receptor antagonists is mediated centrally in the ferret. *Br J Pharmacol* 1996, **112**, 516P.
26. Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. *Physiol Rev* 1993, **73**, 229–308.
27. Hale JJ, Mills SG, MacCoss M, *et al*. Structural optimization affording 2-(R)-(1-(R)-3,5-bis(trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4(3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a potent, orally active, long-acting morpholine acetal human NK-1 receptor antagonist. *J Med Chem* 1998, **41**, 4607–4614.
28. Tattersall FD, Rycroft W, Francis B, *et al*. Tachykinin NK_1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. *Neuropharmacol* 1996, **35**, 1121–1129.
29. Gardner CJ, Armour DR, Beattie DT, *et al*. GR205171: a novel antagonist with high affinity for the tachykinin NK_1 receptor, and potent broad-spectrum anti-emetic activity. *Regulatory Peptides* 1996, **65**, 45–53.
30. Singh L, Field MJ, Hughes J, *et al*. The tachykinin NK_1 receptor antagonist PD 154075 blocks cisplatin-induced delayed emesis in the ferret. *Eur J Pharmacol* 1997, **321**, 209–216.
31. Tattersall FD, Rycroft W, Hale JJ, *et al*. The NK_1 receptor antagonist L-754,030 and its N-phosphoryl prodrug L-758,298 inhibit acute and delayed cisplatin-induced emesis in the ferret. *Proc ASCO* 1998, **17**, 253a.
32. Navari RM, Reinhardt RR, Gralla RJ, *et al*. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. *N Engl J Med* 1999, **340**, 190.
33. Hesketh PJ, Kris MG, Grunberg SM, *et al*. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997, **15**, 103–109.
34. Cancer Therapy Evaluation Program. *Common Toxicity Criteria*, version 2.0. DCTD, NCI, NIH, DHHS, 1998.
35. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the Perugia Consensus. *Conference Ann Oncol* 1998, **9**, 811–819.
36. Gralla RJ, Itri LM, Pisko SE, *et al*. Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *N Engl J Med* 1981, **305**, 905–909.
37. *Physicians Desk Reference*, 52nd edn. Montvale, Medical Economics Co., 1998, 2836–2838.