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Functional relevance of antiemetic control: experience using the FLIE questionnaire in a randomised study of the NK-1 antagonist aprepitant

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Abstract

Little information exists on the functional impact of effective antiemetic protection. In the present study, the Functional Living Index—Emesis (FLIE), was used to assess patient-reported impact of chemotherapy-induced nausea and vomiting (CINV) after administration of a new NK-1 receptor antagonist (aprepitant). Cisplatin-treated patients in a double-blind randomised trial received either aprepitant + dexamethasone + ondansetron on day 1 and aprepitant + dexamethasone on days 2–5 or standard antiemetic therapy (dexamethasone and ondansetron on day 1 and dexamethasone on days 2–5). Emetic events, nausea ratings and rescue medications were recorded in a 5-day diary and the FLIE was completed on day 6. Compared with standard therapy, significantly more patients treated with the high dose aprepitant regimen achieved a Complete Response (71 vs 44%, $P < 0.001$) and also reported no impact on daily life as indicated by the FLIE total score (84 vs 66%, $P < 0.01$). Use of the FLIE demonstrated that improved control of emesis was highly effective in reducing the impact of CINV on patients' daily lives.

Keywords: Patient-reported outcomes; Nausea; Vomiting; Quality of life; FLIE; Antiemetics

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) continue to be some of the most feared side-effects of cancer treatment [1,2]. The incidence of CINV varies according to treatment factors, as well as patient demographics. However, regardless of age or gender, nearly 100% of patients receiving cisplatin-based chemotherapy will experience CINV during the acute and delayed phases if not treated with antiemetic therapy [3]. The acute phase of CINV occurs during the first 24 h and the delayed phase during days 2–5 following the chemotherapy infusion [3]. CINV, especially during the delayed phase, can lead to significant problems for patients such as an inability to perform daily activities and a lack of interest in eating and drinking. However, the impact of CINV on these patient-reported outcomes has not been well characterised [4–6].

A new class of antiemetics, the neurokinin-1 (NK-1) receptor antagonists, have been demonstrated to be particularly effective in decreasing the incidence of delayed nausea and vomiting [7–10]. The objective of this analysis was to use the Functional Living Index-Emesis (FLIE), a validated nausea- and vomiting-specific patient-reported outcome measure, to evaluate the patient-reported impact of CINV on daily life after the administration of a new, more effective antiemetic regimen compared with standard antiemetic therapy.

2. Patients and methods

The development of the FLIE and measurement characteristics of a modified version with 5-day recall

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have been previously described in Refs. [4,11]. The FLIE instrument was modelled after the Functional Living Index-Cancer, a patient-completed multidimensional quality of life evaluative instrument [12]. The FLIE is a validated nausea- and vomiting-specific patient-reported outcome (PRO) instrument comprised of 2 domains (vomiting and nausea) with 9 identical items in each domain. The first item in each domain asks the patient to rate how much nausea (vomiting) he/she experienced over the past 5 days. The remaining 8 items assess the impact of nausea [vomiting] on the following aspects of a patient's daily life: ability to enjoy meals/liquids, prepare meals/do household tasks, perform daily functions, perform usual recreation/leisure activities, willingness to spend time with family and friends, and the extent to which the side-effect has caused personal hardship and hardship on others.

Each item is answered using a 100 mm (1–7 points) visual analogue scale (VAS) with anchors corresponding to "none"/"not at all" and "a great deal" with tick marks dividing the scale into six equal segments (Fig. 1). Items within the domain are weighted equally, reversed as required for some items and summed to create the domain score according to the instrument's Scoring and Interpretation Manual. The two domain scores are then summed to create a total score. Higher scores are more favourable and reflect less impact on daily life and hence a greater ability to maintain daily functioning. We have developed a binary endpoint for reporting FLIE scores. Termed "no impact on daily life" (NIDL), it is defined as an average FLIE item score of >6 on the 7-point scale as shown in Fig. 1. A patient whose average item response is >6 reflects his/her explicit choice to use the best category, anchored by "none" or "not at all", to describe the level of impact of CINV on his/her daily life.

The present study was a companion study to a large, multi-national, double-blind, randomised, parallel-group, controlled, Phase IIb clinical trial of a novel oral NK-1 receptor antagonist (aprepitant) [13]. Patients of at least 18 years of age, scheduled to receive cisplatin $\geqslant 70$ mg/m^2 for the first time, were enrolled in the study. Patients were excluded if they were mentally incapacitated, used any illicit drugs including marijuana or excessive alcohol, were scheduled to receive stem cell rescue therapy, had received an investigational drug within the last 4 weeks, were scheduled to receive multiple-day chemotherapy with cisplatin, had vomited within the 24 h prior to the study start, were scheduled to receive radiotherapy to the abdomen or pelvis, had a symptomatic primary or metastatic central nervous system (CNS) malignancy, or had a contra-indication to the administration of the study medication due to current medical status or concomitant medications. Table 1 outlines the treatment regimen for patients included in the clinical study.

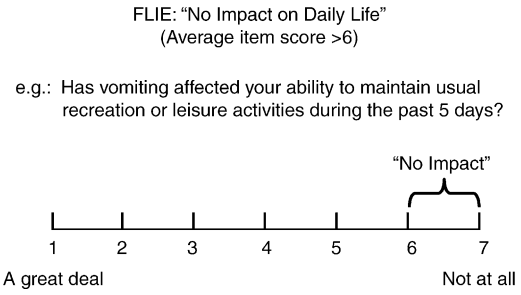

Fig. 1. Sample item from the FLIE questionnaire.

The number of emetic episodes, nausea ratings on a 100 mm visual analogue scale (VAS), and use of rescue medications were recorded by the patients in a 5-day daily diary.

The primary efficacy endpoint of the clinical trial was Complete Response, which was defined as no vomiting and no use of rescue medications over the 5 days (acute and delayed phases combined) following chemotherapy during cycle one. The primary patient-reported outcome endpoint evaluated in the present study was "no impact on daily life" (NIDL), which was assessed using the modified version of the FLIE with 5-day recall [11] scored according to the FLIE Scoring and Interpretation Manual. Patients completed the FLIE questionnaire on day 1 for training purposes and again on day 6 during their first cycle of chemotherapy. Ethical committee approval and informed consent was obtained prior to enrolling patients in the study.

Data from the day 6 FLIE were used for all analyses. The proportion of patients reporting NIDL was calculated for each treatment group. Treatment group comparisons of the proportion of patients achieving NIDL were made in the context of logistic regression models adjusting for investigator site (region), gender and concomitant chemotherapy. Analyses of treatment group differences were completed separately for the total score, nausea and vomiting domain scores and for each individual item.

A modified intent-to-treat approach was used for all FLIE analyses. That is, all patients were included in the

Table 1
Treatment regimens

Group	Day 1	Days 2–5
I	*Aprepitant p.o. (125 mg)* Ondansetron i.v. (32 mg) Dexamethasone p.o. (20 mg)	*Aprepitant p.o. (80 mg)* Dexamethasone p.o. (8 mg)
II	*Aprepitant p.o. (40 mg)* Ondansetron i.v. (32 mg) Dexamethasone p.o. (20 mg)	*Aprepitant p.o. (25 mg)* Dexamethasone p.o. (8 mg)
III	Ondansetron i.v. (32 mg) Dexamethasone p.o. (20 mg)	Dexamethasone p.o. (8 mg)

p.o. orally; i.v., intravenously.

analyses in the treatment group to which they were assigned, regardless of any protocol violation as long as the patient received cisplatin, had taken at least one dose of the study drug and had at least one post-treatment assessment. This approach was also used in analysing the clinical endpoints. No adjustment for multiplicity was made to determine significance in the analyses. Nominal *P*-values are reported.

Because some patients may have answered one or more items incorrectly due to reversed scale anchors on some questions, a sensitivity analysis was performed according to the FLIE Scoring and Interpretation Manual whereby "invalid" item scores were set to missing before calculating the domain and total scores. A response on one of the reversed items was considered invalid if the item score was ± 50 mm or more from the mean score of the remaining items from the same domain.

Measurement characteristics of the FLIE have been previously reported in Ref. [11]. However, the discriminant validity of the FLIE was assessed here in terms of a responder analysis among patients achieving the primary endpoint of Complete Response.

3. Results

Baseline patient characteristics by treatment group are presented in Table 2. The treatment groups overall were comparable and did not differ in terms of mean cisplatin dose, concurrent emetogenic chemotherapy or primary cancer diagnosis.

During the 5 days post-chemotherapy, 71% of the patients in the aprepitant 125/80 mg group and 59% of the patients in the aprepitant 40/25 mg group reported a Complete Response. For the standard therapy group, 44% of the patients reported a Complete Response. Both the aprepitant 125/80 mg and 40/25 mg groups had statistically significantly higher rates of Complete Response than the standard therapy group ($P < 0.001$ and $P = 0.014$, respectively, adjusted for gender, region and use of concomitant chemotherapy). These results indicated that the regimens containing aprepitant were more effective in controlling CINV than the standard therapy regimen.

Of the clinical trial sample, 93% ($n = 355$; mean age 56 years, 44% female) completed the FLIE questionnaire with less than 2% missing questions/item data. The results of the modified intent-to-treat analysis of the FLIE by treatment group are presented in Table 3 and Figs. 2–4. The results of the sensitivity analysis were no different from the intention-to-treat data and so the observed proportions are displayed in the tables.

There was a nearly eighteen percentage point difference in the proportion reporting NIDL between patients receiving the aprepitant 125/80 mg regimen and those on standard anti-emetic therapy (84 vs 66%) as assessed by the FLIE Total score, paralleling the Complete Response rates for these regimens. The domain scores and individual items were highly significantly better ($P < 0.01$) for the aprepitant 125/80 mg group compared with the standard therapy group except for one item within the nausea domain, "hardship on others" which did not reach statistical significance (83 vs. 75%, $P = 0.0559$).

Figs. 2 and 3 present the cumulative distribution curves of the FLIE nausea and vomiting domain scores by treatment group.

The results of the responder analysis showed the FLIE data were consistent with the clinical endpoint of Complete Response (and support the instrument's discriminant validity). A significantly greater proportion of patients who achieved a Complete Response reported NIDL as assessed by the FLIE total score compared with those who experienced vomiting or used rescue medication over the 5 days post-chemotherapy (96% vs 49%, $P < 0.01$) (Fig. 4).

Table 2
Baseline patient characteristics by treatment group

	Aprepitant regimen plus standard therapy		Standard therapy ($N = 127$)	Total ($N = 381$)
	125/80 mg ($N = 134$) *n* (%)	40/25 mg ($N = 120$) *n* (%)	*n* (%)	*n* (%)
Gender				
Female	61 (46)	51 (43)	54 (43)	166 (44)
Age (years) mean (range)	56.0 (18, 81)	58.4 (20, 81)	53.7 (18, 87)	56.0 (18, 87)
Race				
Black	7 (5)	8 (7)	9 (7)	24 (6)
Caucasian	78 (58)	72 (60)	73 (58)	223 (59)
Hispanic	12 (9)	8 (7)	12 (9)	32 (8)
Other	37 (28)	32 (27)	33 (26)	102 (27)
Cisplatin dose				
Mean dose	79.9	81.2	82.1	81.0

Table 3
Observed percent of patients with "no impact on daily life" (NIDL)[a] by treatment group, intent-to-treat population

FLIE item (question No.)	Aprepitant regimen plus standard therapy		
	125/80 mg n/m[b] (%)	40/25 mg n/m (%)	Standard therapy n/m (%)
Primary			
Total score	106/126 (84)**	81/110 (74)	79/119 (66)
Secondary			
Nausea domain score	98/126 (78)**	79/110 (72)	72/119 (61)
'had nausea' [1]	90/126 (71)**	77/110 (70)*	68/119 (57)
'rec or leisure activities' [2]	108/126 (86)**	81/110 (74)	78/119 (66)
'make meal/do tasks' [3]	106/126 (84)**	81/110 (74)	82/117 (70)
'ability to enjoy meal' [4]	99/126 (79)**	79/110 (72)**	66/119 (56)
'enjoy drinking fluids' [5]	104/126 (83)**	86/110 (78)*	79/119 (66)
'see family/friends' [6]	105/126 (83)**	83/110 (76)	80/119 (67)
'daily functioning' [7]	105/126 (83)**	82/110 (75)	78/119 (66)
'personal hardship' [8]	101/126 (80)**	80/110 (73)	78/119 (66)
'hardship on others' [9]	105/126 (83)	84/110 (76)	89/119 (75)
Vomiting fomain Score	117/126 (93)**	86/110 (78)	80/119 (67)
'vomited' [10]	118/126 (94)**	92/110 (84)**	76/119 (64)
'rec or leisure activities' [1]	117/126 (93)**	89/110 (81)	90/119 (76)
'make meal/do tasks' [12]	121/126 (96)**	93/110 (85)*	89/119 (75)
'ability to enjoy meal' [13]	118/126 (94)**	90/110 (82)	85/119 (71)
'enjoy drinking fluids' [14]	119/125 (95)**	92/110 (84)*	86/119 (72)
'see family/friends' [15]	118/126 (94)**	89/109 (82)	89/119 (75)
'daily functioning' [16]	120/126 (95)**	90/109 (83)	87/119 (73)
'personal hardship' [17]	121/126 (96)**	88/109 (81)	85/119 (71)
'hardship on others' [18]	117/126 (93)**	86/109 (79)	92/119 (77)

rec, recreational. *$P<0.05$, **$P<0.01$ compared with the standard therapy group.
[a] NIDL ("No impact on daily life") defined as average FLIE item score >6 on a 7-point scale.
[b] n/m = number of patients with NIDL/number of patients included in time point.

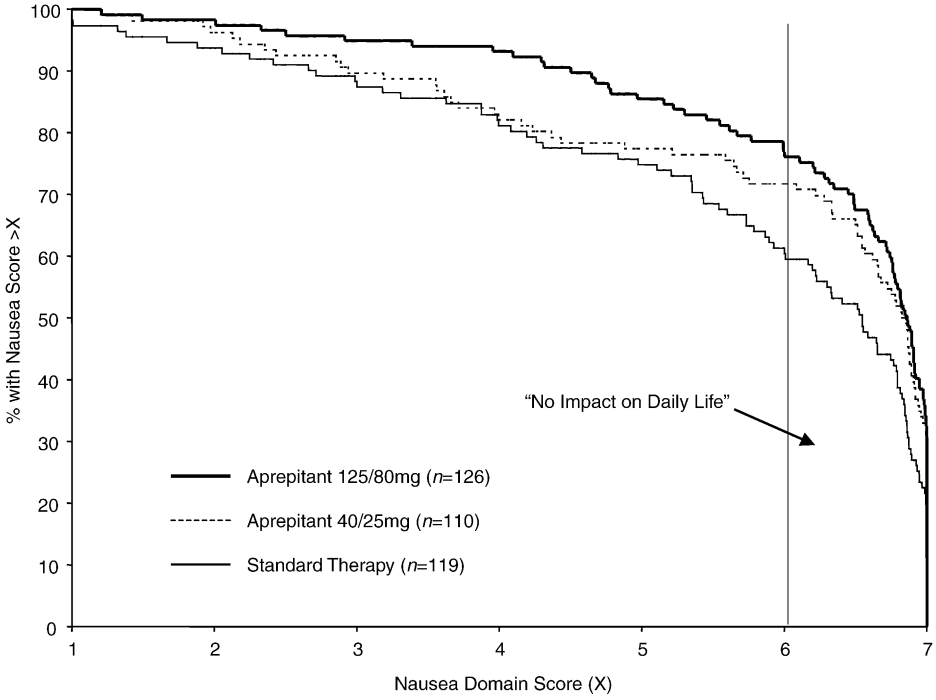

Fig. 2. Cumulative distribution of FLIE nausea domain scores, by treatment group.

4. Discussion

The results of this study show that the FLIE can demonstrate both the negative impact of CINV on patients' daily lives and the benefit to patients when CINV is controlled. While nausea and vomiting are seldom life-threatening side-effects of cancer chemotherapy, they are among the more important issues and concerns facing cancer patients and their families. The impact of CINV on patients, nurses, and caregivers has fueled the research and development of antiemetics [1,2,4–6]. The introduction of the first 5HT3 antiemetics in 1991 was a breakthrough in the prevention of acute vomiting following chemotherapy and provided enhanced patient care [14]. However, the occurrence of nausea and vomiting following infusion of highly emetogenic chemotherapy remains a problem for 10–30% of patients in the acute phase and to an even greater extent in the delayed phase, despite the use of current standard antiemetic therapy [3,15].

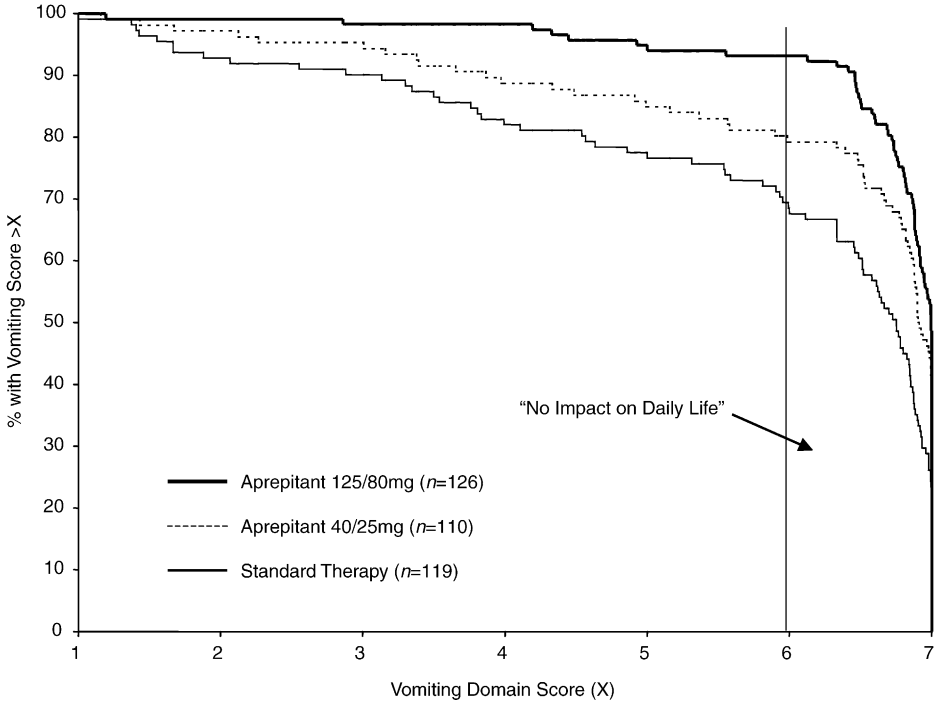

Fig. 3. Cumulative distribution of FLIE vomiting domain scores by treatment group.

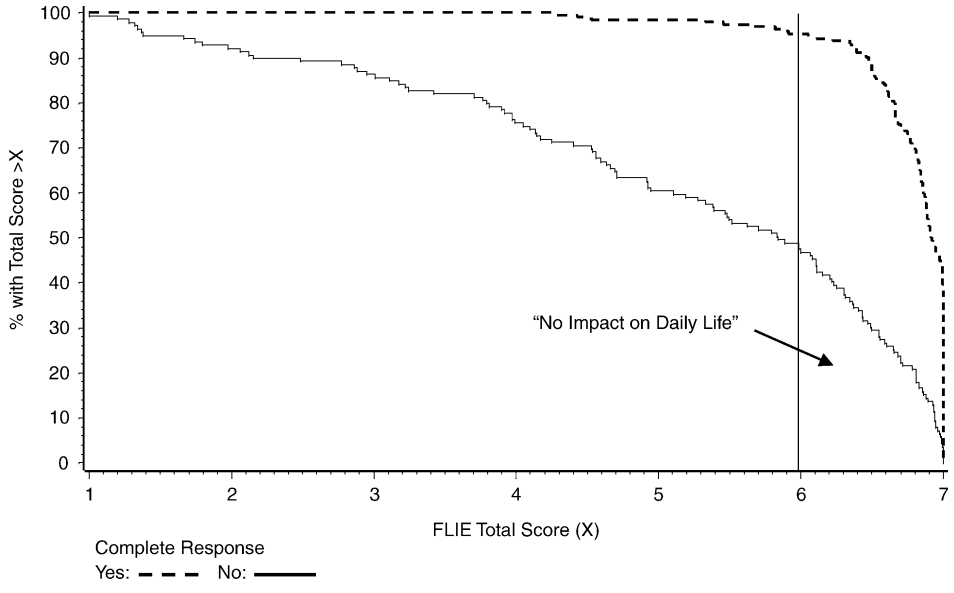

Fig. 4. Cumulative distribution of FLIE total scores by response group.

The FLIE questionnaire was used in this study to assess the impact of CINV on the daily life of cancer chemotherapy patients receiving highly emetogenic chemotherapy who were randomised to receive either a regimen containing aprepitant or standard antiemetic therapy. The clinical results clearly indicated the benefit of the aprepitant 125/80 mg regimen to patients during the combined acute and delayed phases. The aprepitant 125/80 mg regimen was also highly effective in reducing the impact of both nausea and vomiting on patients' daily life activities based on the FLIE domain scores. In a previous antiemetic study of ondansetron vs prochlorperazine, significant treatment group differences were observed in the FLIE vomiting domain scores, however, no difference was observed for the nausea domain [16]. The present study is unique in that the investigational regimen was shown to also be highly effective in controlling the impact of nausea on patients' daily lives.

The importance of these results is twofold. First, these results add value to the efficacy endpoints commonly assessed by clinicians. While patient-reported counts of emetic episodes and ratings of nausea demonstrate the clinical efficacy of an antiemetic, these measures do not fully describe the benefits to patients of preventing CINV. The ability to maintain normal activity may have a direct impact on patients' future health-care decisions. Use of the FLIE questionnaire adds a measure of functional status to the evaluation schema [17]. Second, the FLIE analysis suggests that an effective antiemetic can be beneficial by helping patients to maintain their level of daily function, thereby reducing the indirect cost to caregivers and family members who might otherwise lose time at work or other activities to perform such tasks for the patient. Patients who have caregiving responsibilities themselves may also be less likely to need additional help if they are able to maintain their level of daily function.

Some caution should be used in the interpretation of the results presented here. While the FLIE questionnaire is a nausea- and vomiting- specific questionnaire, some researchers have argued that patients may not be able to discern CINV from other chemotherapy-related side-effects such as fatigue as the root cause of problems with daily functions [5]. While this may be the case to an extent, the results presented here demonstrated a clear association between emetic control and responses on the FLIE questionnaire in the direction expected, i.e., patients with a better control of nausea and vomiting reported less impact on daily life activities. A second caution is that the analyses performed here did not control for baseline FLIE scores as suggested by Osoba [18]. This procedure was not followed because the FLIE questionnaire, in the context of this clinical trial, was used to assess the ability of effective antiemetic therapy to prevent a negative impact of CINV on patients' daily lives. In this context, the FLIE was not used to assess changes from the baseline in patients' functional status following treatment. Rather, the aim was to assess the between-group difference in the proportion achieving the set cut-off of an average item score >6 on the 7-point FLIE scale (i.e., NIDL). Additionally, because only patients naïve to highly emetogenic chemotherapy were eligible for inclusion in this trial and because the first administration of the questionnaire was used for training purposes, adjustment for baseline FLIE scores was deemed inappropriate. Finally, as Soukoup and colleagues have cautioned, patient recall of the impact of symptoms may be inaccurate [19]. While patient reports of symptom frequency and severity in a daily diary are likely to be accurate, recall of the impact of symptoms over a cumulative period of 5 days may be biased towards the days closest to the assessment. While recall bias is always a possibility with patient-completed questionnaires, the measurement characteristics of the 5-day recall version of the FLIE were found to be acceptable and consistent with those of the original version [11].

Based on the FLIE data from patients in this Phase IIb clinical trial, those treated with a more objectively effective antiemetic regimen were better able to maintain their daily lives over the combined acute and delayed periods. Specifically, the results from this analysis suggest that improved emetic control through inclusion of an NK-1 antagonist in the antiemetic regimen allows a higher percentage of patients to maintain their functional status over the 5-day period following administration of highly emetogenic chemotherapy.

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