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ORIGINAL ARTICLE

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Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the Functional Living Index—Emesis (FLIE) with 5-day recall

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Abstract *Background:* The Functional Living Index—Emesis (FLIE), a patient-reported outcome measure, was originally developed to assess the impact of chemotherapy-induced nausea and vomiting (CINV) on patients' daily lives over the 3 days following chemotherapy. More recent studies of CINV include assessments covering the 5 days following chemotherapy in an effort to capture information during both the acute (within 24 h) and delayed (up to 5–7 days) phases of CINV. *Goals:* To assess the measurement characteristics of a modified version of the FLIE with 5-day recall. Instrument reliability, validity, and missing data were assessed. *Patients and methods:* Data were collected from 183 patients receiving cisplatin ≥70 mg/m^2 as part of a phase IIb antiemetic trial of an NK-1 receptor antagonist (MK-0869). Patients recorded the number of vomiting episodes and nausea ratings in a 5-day daily diary. *Results:* The 5-day FLIE had: (1) excellent internal consistency within FLIE Nausea and Vomiting domains (Cronbach's alpha 0.77–0.78), (2) acceptable construct validity shown by FLIE item-total correlations stronger within domains (r=0.74–0.97) than across domains (r=0.52–0.76), and (3) acceptable convergent validity as shown by moderate to strong correlations between FLIE domain scores and independent endpoints of emetic episodes, nausea ratings, and use of rescue medications. The extent of missing data was within acceptable limits with less than 2% of patients missing data. *Conclusion:* The 5-day FLIE had adequate measurement characteristics for studying the impact of CINV on patients' daily lives during the period covering both the acute and delayed phases.

Keywords Patient-reported outcomes · Chemotherapy-induced nausea and vomiting · Health-related quality of life · FLIE

Introduction

Cancer chemotherapy is associated with a predictable spectrum of dose-related toxic effects including nausea and vomiting, which may be present for up to 5–7 days after dosing. Symptoms that occur within 24 h after the initiation of chemotherapy are traditionally defined as acute; those that occur after 24 h are defined as delayed [10, 11].

Cisplatin is one of the most emetogenic chemotherapeutic agents. High-dose cisplatin (>50 mg/m^2) predictably evokes acute vomiting in approximately 100% of patients and delayed vomiting in approximately 70%–90% of patients in the absence of preventive therapy. Cisplatin has been used as the benchmark chemotherapy in the evaluation of the efficacy of antiemetic therapies.

While current antiemetic treatments have resulted in much improved control of chemotherapy-induced nausea and vomiting (CINV) especially during the acute phase, many cancer patients still experience these complications [14], either because of failure of antiemetic treatments or

Table 1 Treatment regimens

Group	Day 1	Days 2 to 5
I	MK-0869 orally (375 mg) Ondansetron i.v. (32 mg) Dexamethasone orally (20 mg)	MK-0869 orally (250 mg) Dexamethasone orally (8 mg)
II	MK-0869 orally (125 mg) Ondansetron i.v. (32 mg) Dexamethasone orally (20 mg)	MK-0869 orally (80 mg) Dexamethasone orally (8 mg)
III	Ondansetron i.v. (32 mg) Dexamethasone orally (20 mg)	 Dexamethasone orally (8 mg)

because of failure to prescribe appropriate antiemetic therapy. CINV, especially during the delayed phase, can lead to significant problems for patients such as an inability to perform daily activities and difficulties with eating and drinking. In some cases, patients experiencing severe CINV are unable to eat during the week following treatment, may require intravenous volume replacement therapy or delay future treatment [14]. Patients consistently rank nausea and vomiting as one of the most distressing side effects of cancer chemotherapy [9, 12].

At the time of this study, only one patient-completed instrument, the Functional Living Index—Emesis (FLIE), existed to directly assess the impact of CINV on patients' daily lives. Other methods and instruments have been used to assess the overall impact of chemotherapy on patients' well-being or to assess treatment burden, but these methods are not specific to nausea and vomiting [2, 3]. As originally developed by Lindley et al., the FLIE was used with a 3-day recall period [13]. The purpose of this analysis was to assess the measurement characteristics of the FLIE instrument using a longer recall period of 5 days in order to quantify the impact of CINV throughout the acute and delayed phases following chemotherapy initiation. The measurement characteristics of the 5-day recall version were also compared to those for the original 3-day version.

Patients and methods

The development of the FLIE has been described previously by Lindley et al. [13]. The FLIE instrument was modeled after the Functional Living Index—Cancer, a patient-completed multidimensional quality-of-life evaluative instrument [15]. The FLIE is a validated nausea and vomiting-specific patient-reported outcome instrument comprising two domains (Vomiting and Nausea) with nine identical items in each domain. The first item in each domain asks the patient to rate how much nausea (vomiting) he/she has experienced over the past 5 days. The remaining eight items assess the impact of nausea (vomiting) on the following aspects of a patient's daily life: ability to enjoy meals/liquids, ability to prepare meals/do household tasks, ability to perform daily functions, ability to perform usual recreation/leisure activities, willingness to spend time with family and friends, extent to which the side effect has caused personal hardship and hardship on others.

Each item is answered using a 100-mm (1 to 7 points) visual analog scale (VAS) with anchors corresponding to "none"/"not at all" and "a great deal" and tick-marks dividing the scale into six equal

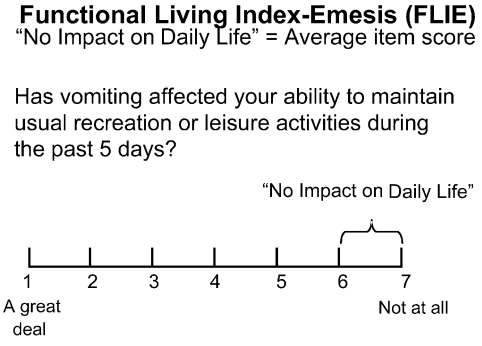

Fig. 1 Example of a FLIE item with definition of "No Impact on Daily Life

categories (Fig. 1). Items within the domain are weighted equally and summed to create the domain score. The two domain scores are then summed to create a total score. Higher scores are more favorable and indicate greater ability to maintain daily life. The endpoint, "no impact on daily life", is operationally defined as an average item score of >6 on the seven-point scale. This cut-off was chosen based on face validity. A patient whose average item response is >6 has explicitly chosen the highest category anchored by "none" or "not at all" to describe the level of impact on daily life.

The modified version with 5-day recall was used to assess the overall impact of CINV on patients' daily lives following their first round of highly emetogenic chemotherapy. Data from a large, multinational, double-blind, randomized, parallel-group, controlled, phase IIb clinical trial of a novel oral NK-1 receptor antagonist (MK-0869, aprepitant; 3-[[(2*R*,3*S*)-3-(*p*-fluorophenyl)-2-[[(*R*)-methyl-3,5-bis(trifluoromethyl)benzyl]oxy]morpholino]methyl]-3-1,2,4-triazolin-5-one tachykinin receptor antagonist) were used for these analyses. Patients of at least 18 years of age, scheduled to receive cisplatin ≥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 to receive stem cell rescue therapy, had received an investigational drug within the last 4 weeks, were to receive multiple-day chemotherapy with cisplatin, had vomited within the 24 hours prior to the start of the study, were to receive therapy to the abdomen or pelvis, had a symptomatic primary or metastatic CNS malignancy, or the study medication was contraindicated due to the patient's current medical status or concomitant medications. Table 1 outlines the treatment regimens for patients included in this analysis.

Data were pooled across treatment groups for all analyses. The number of emetic episodes, nausea ratings on a 100-mm VAS, and use of rescue medications were recorded by the patients in a 5-day daily diary. The patients also completed the 5-day recall version of the FLIE questionnaire on day 1, for training purposes only, and again on day 6 during their first cycle of chemotherapy.

Measurement characteristics

Reliability

Two aspects of instrument reliability are routinely assessed as part of questionnaire development. The first, also termed reproducibility or test-retest reliability, is assessed through repeated administrations of the instrument to patients with stable disease. The second, internal consistency or scale reliability, refers to the degree to which questions within a domain measure the same concept. Due to the fluctuation in frequency and severity of CINV during the first cycle of chemotherapy, it was not possible to assess reproducibility. Internal consistency of the FLIE was assessed by Cronbach's alpha [7]. Alpha values above 0.75 indicate excellent internal consistency, although values above 0.95 may imply redundancy [17].

Validity

Two types of instrument validity, construct and convergent, were assessed. Correlations between items and domain scores using Spearman's correlation were used to assess construct validity, the relative appropriateness of item groupings within each domain. Acceptable construct validity is demonstrated by item-domain correlations stronger within domains than across domains. The degree to which a measure reflects the disease severity (convergent validity), was explored by assessing the correlation between FLIE total and domain scores and independent clinical endpoints such as number of emetic episodes, nausea ratings, and use of rescue medications. FLIE total and domain scores were expected to be moderately correlated to the severity of nausea, frequency of vomiting episodes and use of rescue medications. Additionally, the proportion of patients reporting "no impact on daily life" (average domain item score of >6 on the seven-point scale) on the Total score was compared (Pearson chi-square) among patients with and without Total Control. Total control was defined as no vomiting, no use of rescue medication and no nausea (<5 mm on the VAS) during the 5 days after chemotherapy.

Missing data

Finally, as part of the assessment of this new version, the frequency of missing data for individual questions or sections of the questionnaire was evaluated.

Results

The patient demographics and clinical characteristics are presented in Table 2. Patients included in this analysis were primarily Caucasian (73.8%) and male (62.8%) with a mean age of 57 years. Of the full clinical trial sample completing cycle 1, 93% of the patients (187 of 202) completed the questionnaire. Of those completed, 4 were excluded from the analysis because they were completed outside the allowable time-frame (i.e., completed after day 8), leaving 183 patients for this analysis.

Reliability

Internal consistency assessed by Cronbach's alpha was 0.79 for both the Nausea and Vomiting domains. According to the guidelines established by Streiner [17], the internal consistency of the original 3-day version (alpha values above 0.9) [13] would appear to indicate some level of redundancy; however, both domains in this modified version were found to have excellent internal consistency.

Validity

Table 3 presents the item-domain correlation coefficients for each item in each domain. Acceptable construct validity was observed with item-domain correlations stronger within domains (r=0.74 to 0.97) than across domains (r=0.52 to 0.76).

Table 2 Baseline patient demographics and clinical characteristics

Female (n/%)	68	37.2
Male (n/%)	115	62.8
Age (years)		
Mean	57.3	
Range	20–80	
Race (n/%)		
Caucasian	135	73.8
Black	7	3.8
Hispanic	8	4.4
Other	33	18.0
Cisplatin dose (mean, mg/m^2)	81	
US (n/%)	85	46.4
Non-US (n/%)	98	53.6

Table 3 Item-domain correlations for construct validity

FLIE item	Correlation with domain	
	Nausea	Vomiting
Nausea domain (n=181)		
Item 1: "how much nausea"	0.90**	0.66**
Item 2: "recreation/leisure activities"	0.92**	0.68**
Item 3: "make meal/do tasks"	0.80**	0.58**
Item 4: "enjoy meals"	0.89**	0.67**
Item 5: "enjoy fluids"	0.88**	0.59**
Item 6: "see family/friends"	0.86**	0.67**
Item 7: "daily functioning"	0.94**	0.72**
Item 8: "personal hardship"	0.95**	0.72**
Item 9: "hardship on others"	0.84**	0.69**
Vomiting domain (n=183)		
Item 10: "how much vomiting"	0.62**	0.87**
Item 11: "recreation/leisure activities"	0.58**	0.84**
Item 12: "make meal/do tasks"	0.67**	0.90**
Item 13: "enjoy meals"	0.72**	0.93**
Item 14: "enjoy fluids"	0.74**	0.91**
Item 15: "see family/friends"	0.68**	0.88**
Item 16: "daily functioning"	0.75**	0.95**
Item 17: "personal hardship"	0.76**	0.97**
Item 18: "hardship on others"	0.52**	0.74**

**P<0.0001

Table 4 Correlations between domain scores and clinical endpoints for concurrent validity (n=183)

Domain	Average no. of emetic episodes	Average nausea (VAS)	Rescue medication (yes/no)
Nausea	–0.61**	–0.86**	–0.55**
Vomiting	–0.68**	–0.68**	–0.42**

**P<0.0001

Table 5 Proportion of patients reporting "no impact on daily life" among patients with and without CINV (n=182)

	Vomiting				No vomiting			
	Nausea (n=53)		No nausea (n=7)		Nausea (n=35)		No nausea (n=87)	
	No.	%	No.	%	No.	%	No.	%
FLIE total score	20	37.7	7	100	23	65.7	84	96.6
Nausea domain	14	26.4	7	100	20	57.1	84	96.6
Vomiting domain	24	45.3	7	100	32	91.4	85	97.7

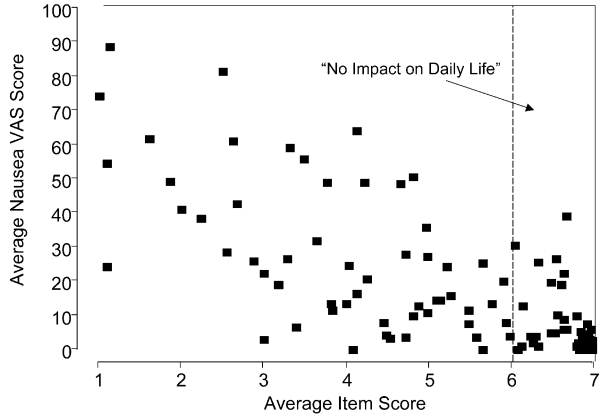

Fig. 2 Distribution of FLIE scores by nausea VAS score: less nausea associated with higher average FLIE Nausea Domain item score

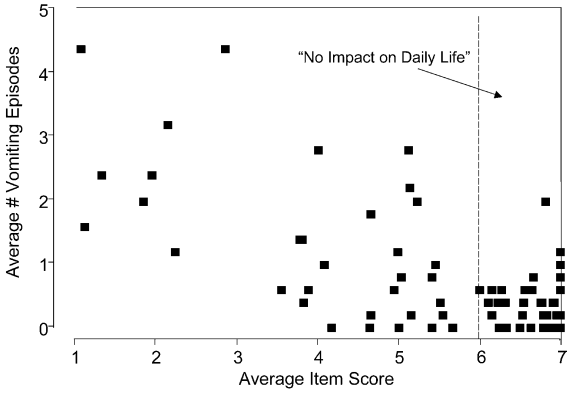

Fig. 3 Distribution of FLIE scores by vomiting episodes: less vomiting associated with higher average FLIE Vomiting Domain item score

The correlations presented in Table 4 support the convergent validity of each domain. The correlations were moderately strong and negative indicating that patients experiencing less nausea and vomiting were more likely to report favorable outcomes as assessed by the FLIE questionnaire. These results are consistent with those of the original version with 3-day recall wherein correlations of –0.65 and –0.68 were observed between FLIE scores and patient reports of nausea and vomiting, respectively. Likewise, the percentage of patients reporting no impact on daily life as assessed by the FLIE 5 days after chemotherapy was significantly smaller among those experiencing either nausea or vomiting or both compared to those with no nausea or vomiting (Table 5).

Figures 2 and 3 present scatter plots of the FLIE Nausea and Vomiting domain scores by average nausea VAS score, and average number of emetic episodes, respectively, during the 5 days after chemotherapy. Patients reporting more severe and frequent nausea and vomiting reported more impact of their CINV on daily life compared to those with less severe symptoms. Finally, Fig. 4 presents the cumulative distribution of FLIE Total scores by level of CINV control. The proportion of patients with an average item score >6 (i.e., "no impact on daily life") in the Total Control group was significantly greater than among those without Total Control (96.6% vs 52.1%; P<0.01). Fewer than 5% of the patients who reported no nausea, no vomiting and no use of rescue medication had average item FLIE scores ≤6 versus nearly 50% of those who reported some nausea, vomiting or rescue medication use over the 5 days.

Missing data

Finally, the analysis of missing data showed excellent compliance to the questionnaire instructions. Two of the

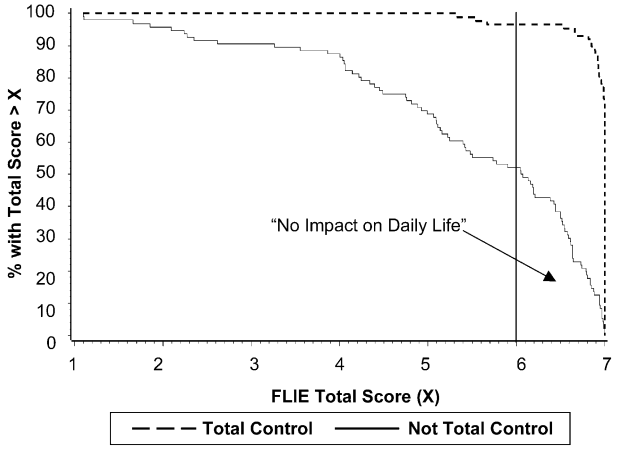

Fig. 4 Cumulative distribution of FLIE Total scores by CINV control (*n*=183)

183 patients who completed the questionnaire according to the protocol missed two and three questions on the FLIE, respectively. According to the scoring guidelines, a domain score may be computed if at least five items in each domain are completed. Among the study sample, all patients had the required number to calculate both domain scores.

Discussion

Though enumeration of vomiting episodes and ratings of nausea are useful for evaluating the clinical efficacy of antiemetics, these measures do not assess the full impact of CINV on the daily life of patients (e.g., daily functioning, appetite, family life, etc.) and thus are not capable of demonstrating the broader impact of treatment. The value of including a patient-reported outcome that assesses the impact of CINV on patients' everyday lives in antiemetic clinical trials is to supplement the information obtained from clinical endpoints. The factors most important to patients may have direct impact on their future health-care decisions and willingness to continue treatment.

The FLIE questionnaire is one of the only published validated nausea- and vomiting-specific instrument currently available to assess the impact of CINV on a patient's ability to maintain daily life, and has been used in clinical trials of marketed antiemetics such as ondansetron [5, 6, 8, 16]. Although the Functional Assessment of Cancer Therapy—General (FACT-G) [4] and the European Organization for Research and Treatment Center Quality of Life Questionnaire (EORTC QLQ-C30) [1] include items that assess the amount of vomiting or nausea, they do not assess the impact of CINV on patient functioning.

The FLIE questionnaire, previously validated by Lindley et al., was shown to be a sensitive and acceptable measure for use within 3 days following chemotherapy initiation [13]. While the FLIE was developed to specifically assess the impact of nausea and vomiting on patient daily function, comparisons with other more general measures such as the Functional Living Index—Cancer support the content validity of the FLIE as a patient-reported outcome measure [15].

The internal consistency, construct and convergent validity of the modified version with 5-day recall as reported here are satisfactory for both the domains and the questionnaire as a whole. The results of convergent validity and internal consistency for this 5-day version are consistent with those previously reported for the original 3-day version [13]. Additionally, the 5-day version of the questionnaire was able to discriminate among patients with varying disease severity. By modifying the recall period to 5 days after receiving chemotherapy, we were able to quantify the impact of CINV on patients' daily lives throughout both the acute and delayed phases.

A valid instrument is essential for understanding results and drawing conclusions about test medications within a clinical trial setting. Likewise, an instrument such as the FLIE may be useful in clinical practice to better understand the effect of treatment on patients' everyday lives. The results from this analysis indicated the 5-day recall version of the FLIE was an appropriate instrument for assessing the impact of CINV on patients' daily lives during both the acute and delayed phases following highly emetogenic chemotherapy including cisplatin. Furthermore, the modified instrument was able to quantify the difference in impact of CINV between patients with and without controlled CINV. The FLIE data clearly indicated that uncontrolled CINV among patients receiving highly emetogenic chemotherapy had a significant negative impact on patients' daily lives compared to those whose side effects were controlled.

Due to fluctuations in severity and frequency of CINV, reproducibility was not assessed. An assessment of change in FLIE scores over time was not appropriate since this was a prevention trial among chemotherapy-naive patients during their first cycle of chemotherapy. Comparisons with other more general patient-reported outcomes were not made for two reasons: (1) the modification of the recall period was not expected to affect the content validity of the questionnaire, and (2) the patient burden associated with self-completed questionnaires was too great to justify the inclusion of another questionnaire. Future studies using the 5-day recall version of the FLIE should include assessment of the instrument's responsiveness to changes in symptom severity over multiple chemotherapy cycles. Further study of the questionnaire among patients receiving non-cisplatin-based chemotherapies is also warranted.

The 5-day recall version of the FLIE was shown to be an acceptable and reliable patient-reported outcome instrument suitable for use in cancer clinical trials to assess the impact of CINV on patients' daily lives over the acute and delayed phases. The FLIE may also be useful in everyday clinical practice to better understand patient outcomes and the impact of current antiemetic regimens following highly emetogenic chemotherapy.

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References

1. Aaronson NK, Ahmedzai S, Bergman B, et al (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376
2. Bernhard J, Maibach R, Thurlimann B, Sessa C, Aapro MS (2002) Patients' estimation of overall treatment burden: why not ask the obvious? J Clin Oncol 20:65–72
3. Borjeson S, Hursti TJ, Tishelman C, et al (2002) Treatment of nausea and emesis during cancer chemotherapy. Discrepancies between antiemetic effect and well-being. Pain Symptom Manage 24:345–358
4. Cella DF, Tulsky DS, Gray G, et al (1993) The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 11:570–579
5. Clavel M, Soukop M, Greenstreet YLA (1993) Improved control of emesis and quality of life with ondansetron in breast cancer. Oncology 50:180–185
6. Clavel M, Bonneterre J, d'Allens H, Paillarse JM, and the French Ondansetron Study Group (1995) Oral ondansetron in the prevention of chemotherapy-induced emesis in breast cancer patients. Eur J Cancer 31A:15–19
7. Cronbach LJ (1951) Coefficient alpha and the internal structure of tests. Psychometrika 16:297–334
8. Crucitt MA, Hyman W, Grote T, et al (1996) Efficacy and tolerability of oral ondansetron versus prochlorperazine in the prevention of emesis associated with cyclophosphamide-based chemotherapy and maintenance of health-related quality of life. Clin Ther 18:508–518
9. de Boer-Dennert M, de Wit R, Schmitz PI, et al (1997) Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer 76:1055–1061
10. Gralla RJ, Rittenberg C, Peralta M, et al (1996) 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 53 [Suppl 1]:86–91
11. Gralla RJ, Osoba D, Kris MG, et al (1999) Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. J Clin Oncol 17:2971–2994
12. Griffin AM, Butow PN, Coates AS, et al (1996) On the receiving end. V: Patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 7:189–195
13. Lindley CM, Hirsch JD, O'Neill CV, et al (1992) Quality of life consequences of chemotherapy-induced emesis. Qual Life Res 1:331–340
14. Multinational Association of Supportive Care in Cancer (1998) Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia Consensus Conference. Antiemetic Subcommittee of the MASCC. Ann Oncol 9:811–819
15. Shipper H, Clinch J, McMurray A, et al (1984) Measuring the quality of life of cancer patients: the Functional Living Index—Cancer) development and validation. J Clin Oncol 2:472–483
16. Stewart A, McQuade B, Cronje JDE, et al (1995) Ondansetron compared with granisetron in the prophylaxis of cyclophosphamide-induced emesis in out-patients: a multicentre, double-blind, double-dummy, randomized, parallel-group study. Oncology 52:202–210
17. Streiner DL (1993) A checklist for evaluating the usefulness of rating scales. Can J Psychiatry 38:140–148