Chemotherapy-induced nausea and vomiting in acute leukemia and stem cell transplant patients: results of a multicenter, observational study

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Background and Objectives. The aim of this study was to evaluate the incidence and severity of chemotherapy-induced nausea and vomiting (CINV) in oncohematology in routine clinical practice, its impact on quality of life, and caregivers' perception of the extent of the problem.

Design and Methods. This was a multicenter, prospective, observational follow-up study including: (i) acute myeloid leukemia patients treated with moderately to highly emetogenic chemotherapy and (ii) hematopoietic stem cell transplant recipients, without reduced intensity conditioning. No exclusion criteria were applied. All patients received at least one 5-HT$_3$ antagonist for emesis prophylaxis. Patients recorded emetic episodes and rated nausea daily. Quality of life was assessed through a validated functional living Index-Emesis questionnaire. A survey of caregivers' predictions of CINV was made and the predictions then compared with the observed CINV.

Results. One hundred consecutive transplant and 77 acute myeloid leukemia patients were studied. Transplant conditioning was the most important risk factor for CINV: complete response occurred in only 20% of transplant patients (vs. 47% for leukemia patients). Among patients with emesis, the mean percentage of days with emesis and the mean (±SD) total number of emetic episodes were 61% and 9.4±8.9 (transplant recipients), and 53.6% and 6.2±7.3 (leukemia patients), respectively. CINV control was lower in the delayed than in the acute phase. Antiemetic rescue therapy was ineffective. CINV had a deleterious effect on quality of life, especially among transplant recipients. Caregivers underestimated the incidence of delayed nausea and emesis in the transplant setting.

Interpretation and Conclusions. Despite 5-HT$_3$ antagonist prophylaxis, CINV remains a significant problem in oncohematology, especially in the delayed phase and in transplant recipients.

Key words: emesis, chemotherapy, nausea, vomiting, transplant, leukemia.

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The advent of 5-HT$_3$ receptor antagonists more than a decade ago led to the perception of a dramatic improvement in the prevention of chemotherapy-induced nausea and vomiting (CINV). Data from clinical trials show a major control of emesis in 71-97% of leukemia and hematopoietic stem cell transplant patients during the first hours after starting chemotherapy,[1,2] although there is a sharp decline to 10-30% in the following days.[3] However, the real magnitude of emesis control in daily practice for leukemia and transplant patients remains unknown. Firstly, most of these data came from clinical trials involving small numbers of patients with intrinsic biases in their recruitment (such as exclusion of patients with anticipatory emesis, which may affect 18-57% of patients).[4,5] Secondly, larger published observational studies have excluded leukemia and transplant patients.[6] We, therefore, conducted an observational study to assess the incidence and severity of CINV in routine clinical practice in acute myeloid leukemia patients and stem cell transplant recipients receiving multiple-day, moderately to highly emetogenic chemotherapy. The incidence of nausea and vomiting, the need for rescue medication, the impact of CINV on the quality of life of the patients and the perception of the extent of the problem by caregivers were evaluated in the acute (first 24 hours) and the delayed phases (24-120 hours) after starting chemotherapy/conditioning.

Design and Methods

This was a multicenter, prospective, observational follow-up study conducted in six Spanish university teaching tertiary care hospitals. The protocol was reviewed by Hospital Ramón y Cajal Ethics and Clinical Research Committee (Madrid). All patients gave written informed consent to their par-

ticipation in the study.

All in-patients, more than 18 years-old, receiving multiple-day chemo/radiotherapy for acute myeloid leukemia or transplant conditioning were eligible for enrollment. The chemotherapy had to be considered as moderately to highly emetogenic (Hesketh grade 3 to 5).[7]

Patients were included consecutively and had acute myeloid leukemia, at diagnosis or first relapse, treated with the schemes detailed in Table 1, or (ii) had been admitted for a stem cell transplant (bone marrow or peripheral stem cell) with a non-reduced-intensity conditioning regimen. Reduced-intensity transplants were excluded since fludarabine – used in most of these transplants - has a low emetogenic potential. Accepted conditioning regimens included: BEAM (BCNU [carmustine], VP-16 [etoposide], AraC [cytarabine] and melphalan), CBV (cyclophosphamide, BCNU and VP-16), CYTBI (total body irradiation followed by cyclophosphamide) and busulphan-based regimens (high dose busulphan and cyclophosphamide followed or not by other alkylating agents or VP-16).

Assessments

Patients' CINV diary

For 5 days (0-120 hours) after starting chemo/radiotherapy, the patients recorded emetic episodes and rated nausea daily on a validated 100-mm visual analog scale (VAS). In the 2 hours prior to starting chemotherapy, patients recorded whether or not they had suffered from vomiting and the rate of nausea in the previous 24 hours; 0 mm was labeled *no nausea* and 100 mm was labeled *nausea as bad as it could be*. The investigators reviewed the diary with the patient in order to ensure the completeness of the data. Rescue therapy (defined as any medication taken to treat established nausea or emesis) was recorded after reviewing the medical and nursing charts.

Functional Living Index for Emesis (FLIE)

In the 6 hours prior to starting chemo/radiotherapy, and again on day 6, the patients completed a validated FLIE questionnaire to assess the effect of nausea and emesis on quality of life during the 5-day study period.

Estimation of the incidence of nausea and emesis by caregivers

Hematologists (n=38) and nurses (n=46) who agreed to participate were asked to complete a questionnaire regarding their perceptions of the incidence of nausea and vomiting in myeloblastic leukemia chemotherapy and transplant patients. Their predictions, which were not weighted for patient accrual at the individual sites, were compared with the observed CINV in the study.

Efficacy measurements

A vomiting episode was defined as one or more episodes of emesis or retching (an attempt to vomit). Distinct vomiting episodes were, by definition, separated by at least one minute. No nausea was defined as a VAS score of <5 mm on the 100 mm scale. A patient was considered to have had significant nausea if the VAS score was >25 mm. The primary end-point for the efficacy analysis was the proportion of patients with a complete response, defined as no emetic episodes and no rescue therapy. Several studies have shown that this criterion is a highly accurate and reliable measure that correlates well with the patients' satisfaction with their emetic control.[8] The control of nausea is subjective and information provided by this measure is of less value.[9]

Other end-points included: no emesis, time to first emesis, no use of rescue therapy, no nausea, no significant nausea, complete protection (no emesis, no rescue therapy and no significant nausea), total control (no emesis, no rescue therapy and nausea with a VAS score of <5 mm) and the impact of CINV on daily life (a total FLIE score of >108 means *no or minimal impact of CINV*

Table 1. Baseline characteristics by treatment group.

	Leukemia group (n=77)	*Transplant group (n=100)*
Gender: female	51.9%	44.0%
Mean (±SD) age (years)	49.3±1.8	45.8±1.1
Other emetogenic treatment	11.7%	17.0%
Hesketh score		
3	54.5%	–
4	7.8%	–
5	37.7%	100%
Type of chemotherapy		
Standard dose AraC + anthracycline ± VP16*	59.7%	–
Intermediate dose AraC + anthracycline +VP16**	3.9%	–
High dose AraC ± others#	36.8%	–
CBV	–	19.0%
BEAM	–	26.0%
CYTBI	–	26.0%
BUCY	–	29.0%
Patients not having received previous chemotherapy	48.1%	8.1%
History of CINV	26%	59%
Type of transplant: autologous/allogeneic	–	56%/44%
Type of disease: Number of cases (% of autologous transplants in transplant column)		
Acute myeloid leukemia	77	28 (35.7%)
Acute lymphocytic leukemia	–	11 (0%)
Hodgkin's disease	–	13 (92%)
Non-Hodgkin's disease	–	26 (92.3%)
Multiple myeloma	–	8 (100%)
Chronic myeloid leukemia	–	6 (0%)
Other	–	8 (25%)
Number of prophylactic anti-emetics:		
1	72.7%	72%
2	23.4%	9%
3	3.9%	11%
4	–	6%
5	–	2%

**Standard dose AraC: <200 mg/m²/day (37 patients with idarubicin; 5 with daunoblastin; 4 with idarubicin and VP-16); **Intermediate dose AraC: 500 mg/m²/day (1 with idarubicin and 2 with mitoxantrone; all with VP-16); #high dose AraC: >1000 mg/m²/day (alone: 1; plus mitoxantrone : 10; plus idarubicin: 8; plus VP-16: 1; plus topotecan: 2; plus fludarabin and idarubicin:6). AraC: cytarabine; VP-16: etoposide; CBV: cyclophosphamide, BCNU (carmustine) + VP-16; BEAM: BCNU, VP-16, AraC + melphalan; CYTBI: total body irradiation followed by cyclophosphamide; BUCY: busulphan + cyclophosphamide.*

Table 2. Influence of CINV risk factors on study end-points during the 5-day follow-up (univariate analysis, all patients).

Risk factor	*Significant nausea*	*Vomiting*	*Rescue therapy*	*Complete response*	*Complete protection*
Female/male	51.2/38.7 (0.09)	72.1/64.5 (0.26)	22.6/20.4 (0.85)	27.4/34.4 (0.3)	26.2/34.4 (0.3)
<40/>40 years	56.1/37.6 (0.01)	81.8/60.6 (0.004)	27.3/18.3 (0.18)	16.1/39.4 (0.002)	16.7/38.5 (0.002)
Previous CINV: yes/no	60.3/31.6 (0.0002)	82.1/57.1 (0.0005)	28.2/16.3 (0.06)	16.7/42.9 (0.0002)	16.7/41.8 (0.0003)
Hesketh's score:5/<5	51.2/27.1 (0.006)	73.6/54.2 (0.01)	25.6/10.4 (0.03)	25.6/45.8 (0.01)	25.6/43.8 (0.02)
Number of anti-emetics: 1/>1	42.2/51.0 (0.31)	68.8/67.3 (0.85)	23.4/16.3 (0.41)	30.5/32.7 (0.85)	29.7/32.7 (0.71)
Transplant/ chemotherapy	60.0/24.7 (0.00000)	80.0/53.2 (0.00018)	30.0/10.0 (0.001)	19.0/46.8 (0.0001)	19.0/45.5 (0.0002)

values given as % (p value).

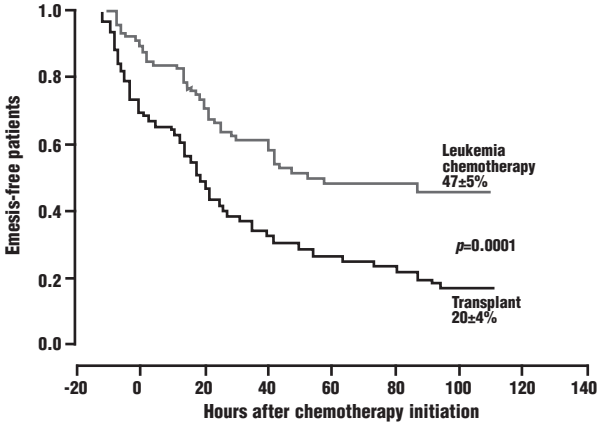


Figure 1. Actuarial probability of remaining emesis-free in transplant recipients and acute myeloid leukemia patients

on daily activities).[10] These criteria were assessed over the following periods: overall (0-120 hours following initiation of chemo/radiotherapy); acute (0-24 hours); and delayed (24-120 hours).

Statistical analysis

Descriptive statistics were used to summarize patients' demographic data. The χ^2 test or exact Fisher's exact test was used to test the association between qualitative variables. Student's t-test, ANOVA and non-parametric statistics, where appropriate, were used to analyze quantitative variables for every independent variable. Logistic regression models were adjusted to study which variables were associated with a better complete response; the variables were selected according to clinical relevance and statistical significance ($p<0.10$) in univariate analyses. Kaplan-Meier curves were plotted to determine the probability of patients fulfilling predefined response criteria following the initiation of chemotherapy. Comparisons were made using Breslow's test. Mean estimated incidence rates, with 95% confidence intervals (CI), of nausea and emesis predicted by caregivers were compared with mean observed incidence rates (95% CI) of nausea and emesis. The κ concordance index between prediction and real data (obtained from the patients) was calculated.

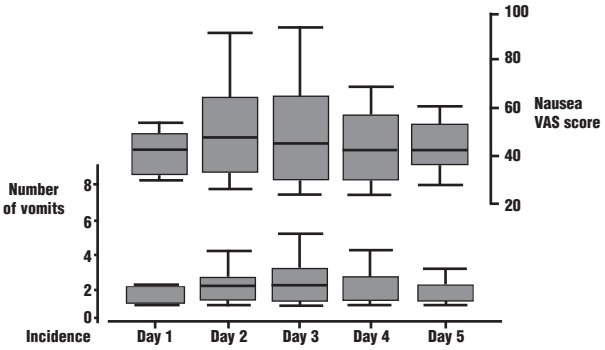
Results

Data were collected on 188 consecutive chemo/radiotherapy cycles received by 154 patients in the period from 15 June 2003 to 30 April 2004. Twenty-four patients received two or more cycles during the study (seven of whom were treated with both chemotherapy and transplantation). Only 11 diaries were not evaluable (difficulty in understanding the diary process [n=6]/Spanish language [n=3] were the main reasons for invalidation), suggesting the lack of bias in data recording. The quality of the FLIE questionnaires was considered non-optimal in 22 cases (mainly due to defects in their completion) and these were excluded from the data analysis. When FLIE analysis was performed *as is* (that is, including these cases to avoid any bias) no meaningful differences from the results presented here were obtained. In summary, a total of 177 complete cycles were analyzed (100 cycles involving conditioning for stem cell transplantation and 77 chemotherapy for acute myeloid leukemia). The patients' baseline characteristics are shown in Table 1.

Risk factors for CINV

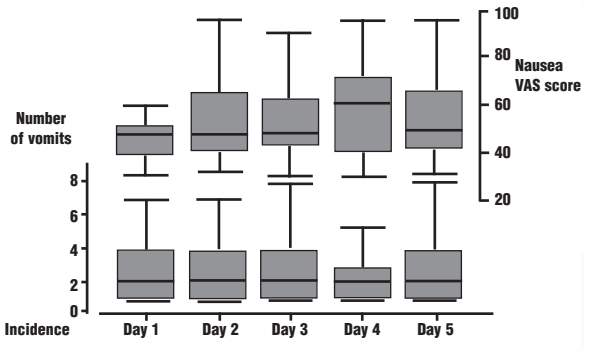
Table 2 shows the univariate analysis of risk factors for CINV. Younger age, a history of previous CINV, higher Hesketh´s scores and being a recipient of a transplant were associated with higher incidences of CINV and, consequently, lower protection rates in univariate analysis. There was also a non-significant trend towards a lower response rate in females. The influence of these variables was observed in the acute, as well as in the delayed, period (*data not shown*). In the multivariate model for the primary end-point of the study i.e. *overall complete response* (no emesis and no rescue therapy for the whole observation period), being a recipient of a hematopoietic transplant, age less than 40 years and a history of CINV were the variables that maintained significance (odds ratios of 2.7, 2.4 and 2.2 and p values of 0.06, 0.02 and 0.03, respectively).

The Kaplan-Meier curves for time to emesis also showed striking differences between the leukemia and the transplant groups: while 47% of patients treated with chemotherapy for myeloblastic leukemia remained emesis-free at the fifth day, only 20% of transplant patients did so (p=0.0001) (Figure 1). No differences were found when autologous and allogeneic recipients conditioned with the same schemes were compared (the percentages of autologous and allogeneic recipients emesis-free for 5 days were, respectively,



Vomiting	17%	35%	39%	25%	26%
Significant nausea	10%	15%	15%	13%	8%
Any nausea	23%	46%	34%	33%	29%

Figure 2. Acute myeloid leukemia group: the severity of significant nausea in patients with VAS score>25 (upper boxes) and number of emetic episodes in patients with vomiting (lower boxes). Boxes represent the median and inter-quartile range with outer bars showing the 95% confidence intervals. The percentages of patients with nausea, significant nausea and vomiting are shown below the graph.



Vomiting	31%	51%	51%	54%	57%
Significant nausea	26%	35%	38%	32%	31%
Any nausea	52%	63%	62%	65%	55%

Figure 3. Stem cell transplant group: the severity of significant nausea in patients with VAS score>25 (upper boxes) and number of emetic episodes in patients with vomiting (lower boxes). Boxes represent the median and inter-quartile range with outer bars showing the 95% confidence intervals. The percentages of patients with nausea, significant nausea and vomiting are shown below the graph.

28% and 20%, with busulphan conditioning, and 0 and 10% with total body irradiation).

CINV prophylaxis

All patients received 5-HT$_3$ receptor antagonists as CINV prophylaxis (ondansetron in 95.8% of cases). Other anti-emetic drugs, mainly anti-dopaminergics, were added to the 5-HT$_3$ receptor antagonist in 27.3% of chemotherapy patients and 28% of transplant recipients. Corticosteroids were not used. The mean (±SD) number of anti-emetics used in leukemia and transplant patients was 1.30±0.54 and 1.54±1.04, respectively.

Emesis

Anticipatory emesis was observed in 7.8% of patients with myeloid leukemia and 8% of transplant recipients. The incidence and intensity of emesis during the study are presented in Figures 2 (acute myeloid leukemia) and 3 (stem cell transplant). Transplant patients suffered more from CINV than did leukemia patients treated with chemotherapy: the 5-day actuarial probability of suffering from emesis was 80% vs 53% (Figure 1; p=0.0001); the mean percentage of days with vomiting among patients with emesis was 61% vs 53.6% (p<0.02) and the number of emetic episodes during the whole period was 9.46±8.95 vs 6.27±7.38 (p=0.02). Other data concerning the main end-points of the study for leukemia and transplant patients are summarized in Tables 3 and 4, respectively.

Nausea

Baseline nausea or significant nausea was observed in 10% and 4% of patients, respectively, without differences between leukemia and transplant patients. The evolution of these parameters during the study is shown in Figures 2 and 3. The incidence of nausea and significant nausea was higher on day 5 than at baseline in the leukemia and transplant groups (p=0.002 and p=0.001, respectively). Again, transplant recipients had a significantly higher incidence of nausea and significant nausea when compared with leukemia patients (p<0.002 and p<0.01 from days 1 to 5 for nausea and significant nausea, respectively) (Figures 2 and 3 and Tables 3 and 4).

Anti-emetic rescue medications

Rescue medication was required by 31% of transplant recipients and 10.3% of leukemia patients to control nausea/emesis, mainly in the delayed phase. Rescue anti-emetics varied among centers, but dopamine antagonists were the drugs most often prescribed in this setting (leukemia patients: 62% antidopaminergics alone, 38% combined with anti-5HT$_3$; stem cell transplant: 85.8% antidopaminergics, combined with antihistaminergics in 47.7% of cases, anti-5HT$_3$ in 10.2% and steroids in 3.8%). Only 10% of transplant recipients treated with rescue medication, and none in the leukemia group, experienced no new emetic episodes after receiving CINV rescue therapy.

Emetogenicity of chemotherapy schemes and emesis during subsequent cycles

Significant differences between the various conditioning regimens were observed, even though all patients received antineoplastic treatment graded as Hesketh score 5 (p=0.0015) (Figure 4). The BEAM scheme was the least emetogenic regimen in transplant recipients, although it was more emetogenic than Hesketh grade 5 chemotherapy for myeloblastic leukemia (Figure 4). In leukemia patients, no significant differences were found among the chemotherapy schemes, either comparing high vs intermediate vs low cytarabine dose (51%, 67% and 49% of patients with emesis, respectively; p=0.34), or comparing the schemes according to Hesketh´s score (54%, 67% and 50%, of patients with emesis for scores 5, 4 and 3, respectively).

Table 3. Main study end-points in acute myeloid leukemia patients.

Event: % (95% CI)	*Period Acute (0-24 h)*	*Delayed (24-120 h)*	*Overall (0-120 h)*
Nausea			
Significant (>25 mm)*	10.5 (5.4-19.2)	24.7 (16.4-35.4)	24.7 (16.4-35.4)
Any (>5 mm)*	23.7 (15.3-34.0)	55.8 (44.7-66.4)	57.1 (46.0-67.6)
Vomiting	17.1 (10.1-26.8)	51.9 (40.9-62.7)	53.2 (42.2-64.0)
Any nausea/vomiting /rescue therapy	27.3 (18.6-38.1)	62.3 (51.2-72.3)	62.3 (51.2-72.3)
Complete response (no vomiting, no rescue therapy)*	81.8 (71.8-88.9)	48.1 (37.3-59.0)	46.8 (36.0-57.8)
Complete protection (no vomiting, no rescue therapy and nausea <25 mm)*	80.5 (70.3-87.8)	46.8 (36.0-57.8)	45.5 (34.8-56.5)
Total control (no vomiting, no rescue therapy and nausea <5 mm)*	72.2 (61.9-81.4)	37.7 (27.7-48.8)	37.7 (26.7-48.8)

**On visual analog scale.*

Table 4. Main study end-points in stem cell transplant recipients.

Event: % (95% CI)	*Period Acute (0-24 h)*	*Delayed (24-120 h)*	*Overall (0-120 h)*
Nausea			
Significant (>25 mm)*	26.3 (18.4-35.4)	59.0 (49.2-68.1)	60.0 (50.2-69.1)
Any (>5 mm)*	51.5 (42.3-61.5)	87.0 (79.0-92.2)	87.0 (79.0-92.2)
Vomiting	31.0 (22.8-40.6)	78.0 (68.9-85.0)	80.0 (71.1-86.7)
Any nausea/vomiting/ rescue therapy	52.0 (42.3-61.5)	88.0 (80.2-93.0)	89.0 (81.4-93.7)
Complete response (no vomiting, no rescue therapy)	69.0 (59.4-77.2)	21.0 (14.2-30.0)	19.0 (12.5-27.8)
Complete protection (no vomiting, no rescue therapy and nausea <25 mm)*	60.0 (50.2-69.1)	20.0 (13.3-28.9)	19.0 (12.5-27.8)
Total control (no vomiting, no rescue therapy and nausea <5 mm)*	48.0 (38.5-57.7)	12.0 (7.0-19.8)	11.1 (6.3-18.6)

**On visual analog scale.*

Sixteen patients received the same chemotherapy scheme twice (mainly standard dose cytarabine and an anthracycline). Overall, the complete response rate was higher in the first cycle than in the second (50% vs. 31.3%), although the difference did not achieve statistical significance (p=0.09), probably because of the small number of patients in whom this analysis could be performed.

The impact of CINV on quality of life

The impact of CINV on quality of life was assessed through the validated FLIE questionnaire. A significant number of patients reported that CINV had an impact

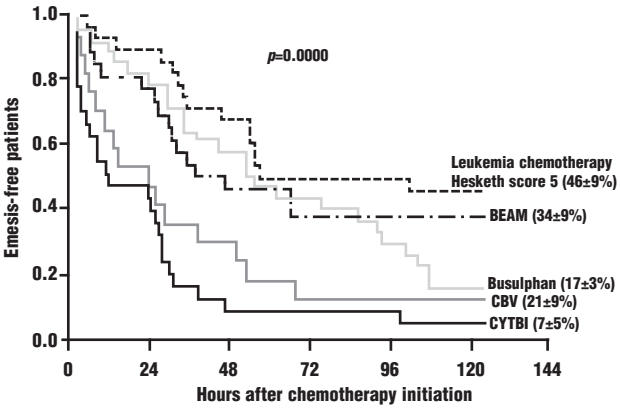


Figure 4. Actuarial probability of remaining emesis-free in transplant patients and leukemia patients receiving Hesketh level 5 chemotherapy. BEAM: BCNU (carmustine), VP-16 (etoposide), AraC (cytarabine) + melphalan; CBV: cyclophosphamide, BCNU + VP-16; CYTBI: total body irradiation followed by cyclophosphamide.

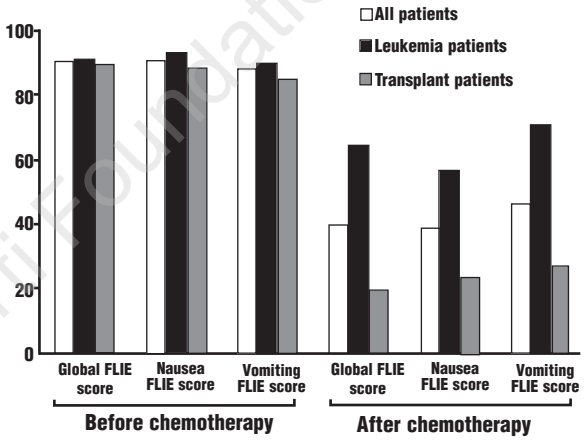


Figure 5. Impact of quality of life determined by the *Functional Living Index-Emesis* (FLIE) questionnaire in leukemia patients and stem cell transplant recipients. Columns represent the proportion of patients in whom CINV had no impact on daily life (FLIE score >108 for global scores and >54 for separated nausea/vomiting scores).

on their daily life (Figure 5) (p=0.000 for all comparisons between pre- and post-therapy); this effect was more marked for transplant patients. Consonantly, when only patients who showed a complete response (no vomiting, no rescue therapy) were analyzed, the FLIE vomiting score was not affected (92% of patients reporting a minimal impact of CINV pre-therapy vs. 90.2% post-therapy; p=n.s.).

Prediction of acute and delayed CINV by caregivers

Physicians and nurses underestimated the incidence of delayed nausea and emesis in the transplant setting: The predicted incidence of delayed nausea and emesis was 65% and 44%, respectively, compared with an observed incidence of 87% and 78% (p=0.02 for both comparisons). In leukemia patients, caregivers slightly, but non-significant, overestimated acute nausea (*data not shown*).

Discussion

Our study, in which every effort was made to reflect the reality of clinical practice, shows that the problem of controlling CINV in hematologic patients receiving chemotherapy over several days, especially stem cell transplant recipients, is far from solved. Despite receiving 5-HT$_3$ antagonist therapy, 53% and 80% of leukemia and transplant patients, respectively, vomited during their chemotherapy/conditioning regimen. Among this large majority of patients who experienced vomiting, emesis intensity was high: at least one vomiting episode was observed on approximately 60% of days and the mean number of emetic episodes was 6 and 9 for leukemia and transplant patients, respectively, during the whole 5-day observation period. The problem was most evident in the delayed phase (24 hours after starting chemotherapy/conditioning) and in transplant recipients. In consonance with these data, emesis and nausea had a severe impact on quality of life, as determined by the FLIE score. These figures would be considered high enough to ensure anti-emetic intervention in the solid tumor setting.[11]

We identified the same risk factors for poor emesis control in hematologic patients as those previously reported in patients with solid tumors.[12] However, being a recipient of a transplant was the most important risk factor in the multivariate model developed for the whole duration of the study (odds ratio: 2.7; p=0.006).

Emesis

All our patients received 5-HT$_3$ antagonists as emesis prophylaxis; some also received other anti-emetic drugs. Emesis was controlled in 81.8% and 69% of leukemia and transplant patients, respectively, during the first 24 hours. However, the control declined sharply in the following days to 48% and 21%, as others had already reported.[13–16] Our global results in acute myeloid leukemia patients receiving chemotherapy are similar to the 50% complete responses observed in another study that used ondansetron[17] and are better than those with standard *classical* anti-emetic prophylaxis reported in most, but not all, studies.[18] For transplant recipients, our results are inferior to those published in the literature. This may be explained by: (i) not having excluded patients with anticipatory nausea/vomiting, who comprise 5-12% of patients in this and some other studies;[16,19] (ii) the inclusion of patients with central nervous system pathology and those in whom potential emetogenic procedures such as lumbar punctures were performed; and (iii) the widespread use of total body irradiation (26% of patients), which is more emetogenic than other schemes.[19,20]

The intensity of emesis in our study was high, especially among transplant recipients. These results are similar to other published data, although children and recipients of non-total body irradiation regimens experience a more benign course,[16,21] and not very different from those reported in some studies in the pre-5HT$_3$-antagonist era,[22,23] even though peaks of 8-10 emetic episodes/day were not rare at that time. Not surprisingly, no difference in emesis incidence was found between autologous and allogeneic recipients conditioned with the same scheme since the drugs used in the first days of conditioning are similar in these two types of transplants. It should be stressed that not all conditioning schemes have the same emetogenic potential, even those graded with the same Hesketh´s score. Emesis was more common among transplant recipients than leukemia patients treated with schemes with the same Hesketh score of *5*, while in contrast, chemotherapy schemes with different Hesketh scores did not show differences in emetogenicity in leukemia patients. Among transplant recipients, we found that total body irradiation had a very high emetogenic potential (similar to that of high-dose busulphan), which contrasts with previous reports[19,24,25] but is in agreement with some current guidelines.[4] BEAM was the best tolerated scheme. It should be noted, however, that although widely used, the Hesketh score was designed only to predict the risk of acute emesis.[7] The trend observed in our study towards poorer emesis control during subsequent cycles is in agreement with experience in patients with solid tumors,[26] but contrasts with previous published reports on hematologic patients.[13,17,27]

Nausea

Nausea was raised to the most distressing side effect in oncological patients after the advent of 5-HT$_3$ receptor antagonists.[28] Bearing in mind that there is a high level of subjectivity in the perception of nausea, and that the use of the VAS scale is of somewhat limited value (although the scale used here has often been employed in recent anti-emetic studies), our results show that significant nausea was observed, almost every day, in about one quarter of leukemia and two-thirds of transplant patients. This is concordant with the results of studies by Kalycio and Barbounis, who used 5HT$_3$-antagonists with or without steroids,[15,19,29] and in marked contrast to those of Belkacemi *et al.*, who reported that 78% of patients who received total body irradiation were free of nausea and vomiting. The relatively gross gradation scale used in Belkacemi's study may explain this difference.[30] Climent *et al.* reported intermediate values for nausea (around 40% in the delayed phase versus 0% on the first day of conditioning) using an aggressive four-drug (granisetron, dexamethasone, haloperidol and lorazepam) regimen against CINV.[31] In two published studies that used the same scale for evaluation of nausea as we did, the mean nausea score also increased steeply during the days of conditioning despite the use of 5-HT$_3$ antagonists and steroids.[19,21] The importance of nausea should not be minimized. In our study, when patients without emesis were studied, even mild nausea was associated with a deterioration of quality of life in 24.9% of patients.

Impact of CINV on quality of life

The impact of CINV on quality of life has been addressed in only a few studies, predominantly in the transplant setting. Abbot *et al.*,[32] using a simple non-validated and limited questionnaire, reported that conditioning regimens result in 4% of patients being bedridden because of nausea/vomiting. Another 31% of the transplant patients found some difficulty in eating despite granisetron and steroid anti-emetic prophylaxis. We used a broader, validated questionnaire to assess the consequences of CINV on quality of life. Our results show that CINV has a tremendous impact on daily activities, with 28% and 70% of leukemia and transplant patients, respectively, having a worsened quality of life, as determined by changes in the global FLIE score (for nausea and vomiting). Not unexpectedly, patients who neither vomited nor received anti-emetic rescue medications showed no emesis-related impact on daily life activities.

Future directions

Since treatment strategies for patients who fail anti-emetic prophylaxis are lacking,[4,25] most effort should be directed towards the design of an effective anti-emetic prophylactic regimen. There appear to be no differences in efficacy among the various 5HT$_3$-antagonists[25] and, as shown in our study, combinations of these drugs do not improve the results. Corticosteroids remain the cornerstone of prophylaxis against delayed emesis.[33] However, no large study has directly addressed their benefits in oncohematologic patients and review of the various non-comparative studies in the transplant field does not show a clear benefit.[22,29,34,35] Moreover, there is some reluctance to use corticosteroids for anti-emetic purposes in oncohematologic patients because of the additional immunosuppression they can cause[36] and a possible increase in chronic graft-versus-host disease.[37]

A new class of anti-emetic drug, the neurokinin (NK)-1 receptor antagonists, which modulate biological activities of substance P, seems promising in the prevention of CINV. One of these drugs, aprepitant, has reduced acute and delayed emesis (and also nausea, although more modestly) in patients receiving highly[38,39] and moderately[40] emetogenic chemotherapy, showing an additive effect in 5HT$_3$-antagonist and corticosteroid combinations. Aprepitant also maintained its efficacy during several chemotherapy cycles.[41] However, although promising, aprepitant has not been assessed either in patients with hematologic neoplasias or in the setting of multiple-day chemotherapy.

In summary, although CINV control during the first 24 hours of intensive chemotherapy/conditioning is good, our results highlight the sub-optimal control of delayed emesis and nausea in leukemia and transplant populations. CINV still has an important deleterious effect on quality of life. More emphasis should be placed on gaining a better understanding of the underlying pathogenesis of CINV as this will eventually lead to an improved control of these distressing chemotherapy-related symptoms.

JL-J and GF were responsible for the study design. JL-J co-ordinated the study, analyzed and interpreted the data (with CF) and drafted the paper. EM-B, AS, CU, IL, RC, MA and DG-B contributed to changes in CRF and design of the study, were responsible for the clinical management of patients and collection of data and critically reviewed the final version of the paper. The order of authorship is based on the number of patients included per center. The authors report no potential conflicts of interest except for GF, who is an employee of Merck Sharp & Dohme, Spain. This study was supported by a Medical School Grant from Merck Sharp & Dohme, Madrid, Spain.

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