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Role of Psychosocial Variables on Chemotherapy-Induced Nausea and Vomiting and Health-Related Quality of Life among Cancer Patients: A European Study

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Key Words

Chemotherapy-induced nausea and vomiting · Coping · Hopelessness · Emotional distress

Abstract

Background: Chemotherapy-induced nausea and vomiting (CINV) continue to be a distressing problem still reported by cancer patients, with negative consequences on quality of life (QoL). ***Aims:*** To prospectively explore the association of psychosocial variables, including emotional distress, maladaptive coping styles and the doctor-patient relationship, with CINV and QoL among cancer outpatients. ***Methods:*** A prospective study was conducted on 302 consecutive cancer patients (response rate 80.9%) in Austria, Italy and Spain. The Distress Thermometer (DT), the Mini-Mental Adjustment to Cancer (Mini-MAC), and the Patient Satisfaction with Doctor Questionnaire (PSQ) were used to assess psychosocial variables before chemotherapy. In the 5 days after chemotherapy, CINV was examined by using a daily diary, and the Functional Living Index for Emesis (FLIE) was used to assess QoL. ***Results:*** More than half of the patients reported nausea (54%), and a small percentage reported vomiting (14%). CINV had a negative impact on QoL (FLIE caseness, $p < 0.01$). Maladaptive coping (i.e. hopelessness-helplessness and anxious preoccupation) and emotional distress were associated with CINV ($p < 0.05$) and poorer QoL ($p < 0.05$). In logistic regression analysis, nausea was predicted by Mini-MAC/H (OR = 1.1, $p = 0.03$) and younger age (OR = 0.97, $p = 0.04$); negative impact on QoL was predicted by grade of chemotherapy emetogenesis (OR = 1.7, $p < 0.01$) and Mini-MAC/H (OR = 1.2, $p = 0.04$). ***Conclusions:*** Screening and assessment of psychological variables, especially coping, could help in identifying cancer patients at risk for chemotherapy-induced nausea, in spite of the use of antiemetic treatment.

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Introduction

In spite of a significant improvement of antiemetic treatment and the use of antiemetic prophylaxis in the last 20 years [1–3], chemotherapy-induced nausea and vomiting (CINV) remain one of the most significant problems reported by cancer patients, with approximately 45–65% of patients experiencing significant nausea (mainly delayed) and 15–25% vomiting (mainly delayed) [4, 5]. Nausea is, from the patients' own perspective, even more negative than vomiting, while, in contrast, medical providers tend to consider their patients' vomiting worse than nausea, with the risk to underestimate the latter [6, 7]. CINV has extremely negative consequences by reducing daily functioning and quality of life (QoL) [8–12].

Some retrospective studies have been conducted on the role of psychological variables in CINV, with some data suggesting that emotional distress, anxiety and patients' expectations may play a role on patients' perception, frequency, intensity and severity of nausea and other chemotherapy-induced side effects [13–15]. In a small prospective study of 56 cancer patients [16], a significant relationship was found between pretreatment distress and the severity of the patients' subsequent delayed nausea, but not acute nausea. Trait anxiety and fatigue [17], pretreatment cancer distress, moderate to severe depression and neuroticism [18], fear of dying and inability to relax were also identified as potential CINV predictors [19]. Contradictory results emerged in other studies [20, 21], with psychological variables associated with anticipatory nausea, but not with CINV. However, the way in which patients cope with cancer in terms of cognitive and behavioral responses, which have been shown to influence several aspects of cancer experience (e.g. QoL, psychological distress, physical symptoms and pain) [22, 23], has not been studied, with respect to CINV.

Emotional support from interpersonal ties has also been indicated as a variable reducing CINV and its negative effects of cancer patients [24, 25]. Regarding the doctor-patient relationship as an area of possible support for the patient, limited data is available with regard to CINV. Only a few studies have examined the role of the doctor-patient communication in terms of the management of CINV, with possible positive effects on the patients' QoL and psychosocial well-being [26–29].

With this as a background, this study aimed to prospectively examine the association of both psychological factors, namely emotional distress and coping styles, and relational variables, namely patients' perception of the support received in the relationship with their doctor, as measured before chemotherapy, with CINV and QoL after chemotherapy.

Subjects and Method

This longitudinal study was conducted in the departments of oncology in European cancer centers in Italy (S. Anna University Hospital, Ferrara; Cancer Institute of Romagna, Forlì, and linked regional area; Cà Foncello Hospital, Treviso), Spain (Hospital de la Santa Creu i Sant Pau, Barcelona; University Hospital Sant Joan de Reus, Reus) and Austria (Clinical Department of Oncology, Medical University, Graz). Patients were consecutively recruited at cancer outpatient clinics and day hospitals, meeting the following criteria: an age between 18 and 65 years; a cancer diagnosis at any site; intravenously administered chemotherapy regimen (at least one chemotherapy undertaken); no cognitive deficit due to disease or treatment during clinical evaluation; a score >60 on the Karnofsky Performance Status Scale; life expectancy >6 months. For each center it was ascertained that the standard protocols and guidelines for antiemetic treatment were followed. Ethical review committees of the participating centers approved the study, and all patients provided written informed consent.

A series of psychological questionnaires were individually administered in the clinics by a research assistant trained in psycho-oncology the day before the chemotherapy course. The patients were followed on a daily basis by completing questionnaires investigating the possible onset of nausea and vomiting and their impact on QoL (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000431256).

Psychological and Relational Variables

Before chemotherapy, each patient completed the following instruments:

(i) The Distress Thermometer (DT) in its validated form was used to assess emotional distress on a 0–10 visual analog scale (0 = no distress; 10 = extreme distress), developed by the National Comprehensive Cancer Network panel [30], with a cutoff ≥4 identifying clinical distress [31, 32].

(ii) The Mini-Mental Adjustment to Cancer (Mini-MAC) scale [33, 34], in its validated version, was used to assess the patients' cognitive and behavioral attitudes towards cancer. Only two subscales were used in this study, specifically hopelessness-helplessness (H) and anxious preoccupation (AP), being key maladaptive coping strategies [34]. Mini-MAC/H and Mini-MAC/AP both consist of 8 items (1–4 Likert scale: 1 = it definitely does not apply to me; 4 = it definitely applies to me) measuring the tendency to adopt a pessimistic and despairing attitude about the illness, and the tendency to feel worried and preoccupied about cancer, respectively. Both subscales showed a good internal consistency (Cronbach's α: H = 0.84; AP = 0.82).

(iii) The Patient Satisfaction with Doctor Questionnaire (PSQ) [35, 36] was used to measure the patients' satisfaction with the interaction with the physician responsible for their care. The PSQ is a 24-item scale including 2 factors: (i) medical disengagement (PSQ-MD, 13 items), measuring the extent to which patients appraise their physicians as interested only in the medical aspects of

their problems; (ii) perceived support (PSQ-PS, 11 items), measuring the extent to which patients perceive their physicians as supportive and aligned with the patient's best interests. Exploratory factor analysis confirmed the PSQ 2-factor structure and good reliability (Cronbach's α: PSQ-MD = 0.91; PSQ-PS = 0.82).

CINV and QoL

After their cycle of chemotherapy, each patient completed the following instruments:

(i) CINV diary: in order to study CINV, the administration of chemotherapy was followed by 5 days of recording of nausea and vomiting. To examine that, in agreement with the methodology of Ballatori et al. [8], patients were provided with a daily diary and asked to record at home, for each day during the week after their course of chemotherapy, the number of nausea and vomiting episodes, and the intensity of nausea on a 4-point Likert scale for nausea (0 = no nausea; 1 = mild nausea, i.e. presence of nausea but able to do all daily activities; 2 = moderate nausea, i.e. unable to do all daily activities; 3 = severe nausea, i.e. bedridden because of nausea). To ensure accurate completion of the diary, each patient was contacted by telephone or in person on day 2, to remind him/her to fill in the diary, and on day 6. As elsewhere [8], CINV was considered acute if it was experienced within the first 24 h, and delayed thereafter. As also described by Ballatori et al. [8], duration of CINV was defined as the number of days, during the 5-day period, in which either nausea or vomiting was experienced (≤2/5 days = short duration; ≥3/5 days = long duration); the intensity of vomiting was considered to be severe or less severe if the number of emetic episodes was ≥3 or ≤2, respectively, during the 5-day period; the intensity of nausea was defined as nonsevere (if mild) and severer (if moderate or severe) during days 1–5.

(ii) The Functional Living Index for Emesis (FLIE) questionnaire [37, 38] in its validated versions was used to assess the impact of nausea and vomiting on the patient's daily life in the last 5 days. The FLIE includes 18 items (9 for nausea and 9 vomiting), each of them rated on a 100-mm (1–7 points) visual analog scale with anchors corresponding to 'none/not at all' and 'a great deal'. Each domain score ranges from 9 (maximum impact) to 63 (no impact), with higher scores reflecting less impact on QoL that was considered separately for nausea and for vomiting (FLIE-N and FLIE-V). According to the FLIE scoring [39], the cutoff for 'no impact of nausea (or vomiting) on daily life' versus impact of nausea (or vomiting) on daily life was defined by the score of >6 on a 7-point scale (i.e. domain score of >54).

Data concerning medical variables and clinical status were taken from the patients' charts. According to the literature [40], and a more recently proposed modification [41, 42], classification of emetogenicity of antineoplastic agents was based on the degree of emetogenicity (risk of incidence) in 4 categories: highly emetogenic (high risk, incidence >90%; e.g. cisplatin, mechlorethamine, carmustine), moderately emetogenic (moderate risk, 31–90%; e.g. oxaliplatin, daunorubicin, doxorubicin, carboplatin), slightly emetogenic (low risk, 10–30%; e.g. paclitaxel, docetaxel, mitoxantrone) and minimally emetogenic (minimal risk, <10%; e.g. bevacizumab, bleomycin, busulfan). Accordingly, antiemetic therapy (e.g. 5-HT_3 receptor antagonists, corticosteroids), including prophylaxis for delayed CINV, consistent with the guidelines in force at the time and place of the study, was used, with all the centers indicating that these guidelines were routinely applied in clinical practice.

Statistical Analysis

Statistical analysis was performed with the SPSS version 20 package. Student's t test, ANOVA, Pearsons' correlation and χ^2 test were used when appropriate to examine differences and correlations between groups. In agreement with other authors [14, 20, 21], logistic regression was used to ascertain the effects of sociodemographic, medical and psychosocial variables on the likelihood that participants were to develop delayed nausea and had a CINV-determined reduction in their QoL (FLIE caseness). Caseness on FLIE (0 = noncase, 1 = case) and incidence of delayed nausea (0 = no nausea; 1 = delayed nausea) were the dependent variables, with sociodemographic (age and sex), clinical (stage of cancer and emetogenic grade of chemotherapy) and psychosocial (DT, Mini-MAC/H and AP, PSQ) factors entered as independent variables. Statistical significance was set at the 0.05 level.

Results

A total of 373 patients meeting the inclusion criteria were approached over the study period. Of these, 21 declined participation, 18 were unavailable for the prospective part of the study, and 32 had missing measures for different reasons (too ill or forgot to complete all the diaries), leaving 302 patients (response rate = 80.9%) as the complete sample (Italy, n = 143, 47.3%; Spain, n = 89, 29.5%; Austria, n = 70, 23.2%). There was no difference on any sociodemographic and clinical variable between participants and nonparticipants. The characteristics of the sample, divided by country, are reported in table 1. Most patients were females (n = 180, 59.6%) and married (n = 223, 74%). Primary tumor sites included mainly gastrointestinal (n = 109, 36%) and breast locations (n = 94, 31%). A slight majority was in a metastatic phase (n = 152, 51%), and most had undergone surgery (n = 220, 74%). All patients were submitted to chemotherapy alone or in combination with hormone or radiotherapy or both. No major differences were reported between centers, apart from a larger representation of gastrointestinal cancer in the Austrian sample.

General Data on CINV and Impact on QoL

Overall, a low percentage of patients (13.9%) reported vomiting, while a higher percentage (54.6%) reported nausea, with one third (52/164) delayed only and two thirds (105/164) both acute and delayed. The duration of vomiting was shorter (74% ≤2 days) than nausea (73% ≥3 days), with 52% of the patients with vomiting reporting it as severe versus 36% of those with nausea (table 2). The FLIE data indicated that 64% of the patients with vomiting and 52% of those with nausea reported a reduced QoL (FLIE 'cases'). In the latter group, FLIE-N caseness was significantly higher among patients with

Table 1. Sociodemographic and clinical data of the patients

	Italy (n = 143; 47)	Spain (n = 89; 30)	Austria (n = 70; 23)
Sex			
Male	53 (37.1)	33 (37.1)	36 (51.4)
Female	90 (62.9)	56 (62.9)	34 (49.6)
Education, years	54±9	51±11	54±9
Marital status			
Never-married	14 (10)	9 (10)	9 (13)
Separated/divorced	12 (8)	12 (14)	13 (19)
Married	112 (78)	64 (72)	47 (67)
Widowed	4 (3)	3 (3)	1 (1)
Unknown	1 (1)	1 (1)	0 (0)
Occupation			
Employed	74 (52)	44 (49)	35 (50)
Unemployed	3 (2)	6 (7)	0 (0)
Housewives	18 (13)	4 (4)	2 (3)
Retired	48 (33)	28 (32)	28 (40)
Students	0 (0)	3 (3)	0 (0)
Other	0 (0)	3 (3)	5 (7)
Unknown	0 (0)	1 (1)	0 (0)
Cancer site*			
Gastrointestinal	44 (30)	26 (29)	47 (67)
Breast	53 (37)	25 (28)	16 (23)
Genitourinary	11 (8)	13 (14)	5 (7)
Respiratory	22 (15)	8 (9)	1 (1)
Blood	7 (5)	17 (19)	1 (1)
Other	6 (4)	0 (0)	0 (0)
Stage			
Local and locoregional	79 (55.6)	39 (53.8)	37 (54.3)
Metastatic	63 (44.4)	50 (56.2)	39 (55.7)
Surgery			
Yes	110 (77)	59 (66)	50 (71)
No	33 (23)	30 (34)	20 (29)
Emetogenicity			
Minimal	9 (6)	4 (5)	5 (8)
Low	10 (7)	7 (8)	7 (10)
Moderate	49 (34)	18 (20)	28 (40)
High	75 (53)	60 (67)	30 (42)

Percentages are given in parentheses. * $p < 0.05$.

Table 2. Rate and intensity of CINV and impact on QoL

	CINV	
	vomiting	nausea
Type		
Acute (day 1) but not delayed	8/302 (2.6)	7/302 (2.5)
Delayed (days 2–5) but not acute	17/302 (5.6)	52/302 (17.2)
Both acute and delayed	17/302 (5.6)	105/302 (34.7)
Total CINV (days 1–5)	42/302 (13.9)	164/302 (54.3)
Duration		
≤2 days	31/42 (73.9)	46/164 (28.1)
≥3 days	11/42 (26.2)	119/164 (72.5)
Intensity		
Not severe (mild)	20/42 (48)	105/164 (64)
Severe (moderate/severe)	22/42 (52)	59/164 (35.9)
	Caseness on FLIE	
	among patients who suffered from vomiting	among patients who suffered from nausea
Type		
Acute (day 1) but not delayed	2/8 (28)	0/7 (0)
Delayed (days 2–5) but not acute	13/17 (76)	20/52 (38)
Both acute and delayed	12/17 (70)	66/105 (63)*
Total CINV (days 1–5)	27/42 (64)	86/164 (52)
Duration		
≤2 days	20/31 (64.5)	5/46 (11)
≥3 days	7/11 (70)	81/119 (69)*
Intensity		
Not severe (mild)	13/20 (65)	37/105 (36)
Severe (moderate/severe)	14/22 (63)	49/59 (83)*

Data are given as number found/total number with percentages in parentheses. * $p < 0.01$.

both acute and delayed ($\chi^2 = 32.7$, $p = 0.001$), longer (≤2 days 11% vs. ≥3 days 68%; $\chi^2 = 41.2$, $p = 0.001$) and severer nausea (not severe 36% vs. severe 83%; $\chi^2 = 32.7$, $p = 0.001$). No difference was shown with respect to age, sex and between countries with respect to characteristics of CINV and impact on QoL.

Association of Psychosocial Factors with CINV and QoL (FLIE)

Table 3 shows the mean and standard deviation on the psychosocial measures of subjects not experiencing CINV (n = 138) and patients with CINV (vomiting n = 42; nausea n = 164): The group of patients who had experienced nausea was also separated according to the characteristics of CINV (type, duration and intensity). All the analyses performed showed that patients not experiencing CINV had lower scores on the Mini-MAC/H and Mini-MAC/AP subscales and DT with respect to (i) presence of CINV (both vomiting and nausea, Mini-MAC/H and Mini-MAC/AP, $p < 0.01$; DT $p < 0.05$); (ii) type of nausea (delayed or acute + delayed vs. no CINV: Mini-MAC/H and Mini-MAC/AP, $p < 0.01$; DT $p < 0.05$); (iii) duration of

Table 3. Comparison between patients without CINV and patients with CINV on the psychosocial variables

	Mini-MAC/H	Mini-MAC/AP	DT	PSQ-MD	PSQ-PS
Patients without CINV (n = 138)	11.5±3.8	17.2±4.8	3.9±2.6	20.6±6.5	36.3±5.2
Patients with CINV					
Vomiting (n = 42)	13.8±5.1**	19.3±5.1**	4.6±2.2*	21.1±5.6	35.5±4.4
Nausea (n = 164)	13.1±4.1**	19.2±5.4**	4.6±2.6*	21.6±6.1	35.4±3.9
Type of nausea					
Delayed (n = 52)	13.3±4.1**	19.3±5.2**	4.6±2.6*	21.6±6.1	35.4±4.8
Acute + delayed (n = 157)	13.1±4.1**	19.5±5.2**	4.6±2.6*	21.6±6.1	35.4±4.9
Duration of nausea					
≤2 days (n = 46)	13.1±4.2**	18.8±4.8*	4.6±2.7*	23.5±6.3	34.5±5.3
≥3 days (n = 119)	12.9±3.9**	19.1±5.3**	4.9±2.6**	21.9±5.9	35.7±4.6
Intensity of nausea					
Not severe (n = 105)	13.1±4.2**	18.9±5.1**	4.6±2.6*	21.8±5.9	35.6±4.9
Severe (n = 59)	13.4±4.4**	19.4±5.3**	4.6±2.8*	21.2±6.4	34.9±4.8

** $p < 0.01$ and * $p < 0.05$ when comparing patients without CINV vs. (i) patients with CINV (both vomiting and nausea) and (ii) patients with nausea according to the characteristics of nausea (type, duration and intensity). Student t test values not shown (available from the authors on request).

nausea (nausea for at least 2 days and ≥3 vs. no CINV: Mini-MAC/H and Mini-MAC/AP, $p < 0.01$; DT $p < 0.05$), and (iv) intensity of nausea (moderate or severe nausea vs. no CINV: Mini-MAC/H and Mini-MAC/AP, $p < 0.01$; DT $p < 0.05$; table 3). Pearson r correlation analysis indicated that both duration and intensity of nausea were significantly associated with Mini-MAC/H ($r = 0.28$, $p < 0.01$; $r = 0.27$, $p < 0.01$, respectively) and Mini-MAC/AP ($r = 0.24$, $p < 0.01$; $r = 0.21$, $p < 0.01$, respectively). The DT score was marginally associated with intensity of nausea ($r = 0.19$, $p < 0.05$). Regarding vomiting, subjects not reporting CINV had lower scores on Mini-MAC/H with respect to subjects experiencing delayed and acute/delayed vomiting (ANOVA $F = 5.62$; $p < 0.01$), and a trend to higher scores on Mini-MAC/H as far as intensity of vomiting was concerned (ANOVA $F = 2.6$; $p = 0.06$).

With respect to QoL, as measured by the FLIE, significant correlations were found between FLIE-N and Mini-MAC/H and Mini-MAC/AP ($r = -0.27$, $p = 0.01$; $r = -0.23$, $p = 0.01$, respectively) and, to a smaller extent, between FLIE-V and the same Mini-MAC factors (Mini-MAC/H, $r = -0.18$, $p < 0.01$; Mini-MAC/AP, $r = -0.12$, $p < 0.05$).

In comparison with subjects with nausea who were cases on FLIE-N (n = 86), patients without CINV (n = 138) had lower scores on Mini-MAC/H ($t = 4.9$, $p < 0.01$), Mini-MAC/AP ($t = 3.4$, $p < 0.01$) and DT ($t = 2.8$, $p < 0.01$). When the scores on the psychosocial measures were compared within the group of patients with CINV (nausea), FLIE-N cases (n = 86) had higher scores on Mini-MAC/H in comparison with those that, even if reporting nausea, were noncases on FLIE-N (n = 78; $t = 3.04$, $p = 0.05$; online suppl. table 1). The same analysis on FLIE-V was not carried out, given the small number of patients with vomiting who were FLIE-V cases (n = 15).

Logistic regression analysis showed that the emetogenic grade of chemotherapy and Mini-MAC/H were predictors of FLIE caseness ($\chi^2 = 37.01$, $p < 0.001$; Nagelkerke $R^2 = 0.17$), while Mini-MAC/H and younger age were the only predictors of incidence of delayed nausea ($\chi^2 = 26.83$, $p < 0.001$; Nagelkerke $R^2 = 0.12$; online suppl. table 2).

Discussion

This study investigated the association of psychosocial factors with CINV and QoL among cancer patients in three European countries.

The results of the study confirmed that CINV, especially delayed nausea, remains a significant problem in cancer patients, in spite of advances in antiemetic therapy [2–6]. More than half of the population reported acute and/or delayed nausea in the week after chemotherapy, while only 14% of the patients reported vomiting. For two thirds of the patients, the duration of nausea was >3 days, and one third reported it as severe. As expected, and in line with the existing literature [8–12], CINV was related

to an impairment of QoL, as measured by the FLIE. Besides vomiting, nausea had also a significant impact on QoL, with half of the patients with nausea experiencing a negative impact on their daily activities. This was particularly evident for those suffering from delayed nausea. These aspects confirm that, although health care professionals tend to pay more attention to vomiting than nausea, the latter is also extremely negative for patients who undergo chemotherapy [6, 7].

As a specific result of the study, psychological variables had also a role in the development of postinfusional CINV and reduction of QoL. More particularly, patients who developed nausea after chemotherapy had higher despairing and preoccupied attitudes about their disease (hopelessness-helplessness and anxious preoccupation in the Mini-MAC), as well as a higher level of emotional distress, as measured before chemotherapy. These data were also confirmed by analyzing the type of CINV (acute and delayed), the intensity and the duration of nausea, which were found to be associated with maladaptive coping styles (i.e. anxious preoccupation and hopelessness-helplessness) and, to a lesser extent, to emotional distress. Similar results were obtained with respect to vomiting, although only hopelessness-helplessness was more marked among patients who developed acute and/or delayed vomiting, while no main effect was found on the intensity of vomiting. These differences regarding a lesser role of psychological variables on vomiting in comparison with nausea might be related to the efficacy of antiemetic treatment, which is reported to improve more the vomiting symptoms (as an objective side effect) than nausea, and confirm that nausea is more related than vomiting to individual emotional factors.

In terms of QoL (daily life activities), as measured by the FLIE, a relationship with psychosocial variables was also found. As expected, the patients who had an impact of nausea on their own daily life had higher scores on both maladaptive coping (hopelessness-helplessness and anxious preoccupation) and emotional distress, as measured before chemotherapy, in comparison with those who did not develop CINV. These results confirm other studies indicating that lower levels of anxiety and positive emotions are associated with better CINV-related QoL [43], but also underscore the role of maladaptive coping, specifically hopelessness-helplessness, as a specific area that needs to be monitored in cancer settings. In fact, a more marked helpless attitude before chemotherapy differentiated, in our study, the patients who subsequently developed nausea and reported an impact on their QoL (FLIE-N cases) in comparison with those who, even if they developed nausea, did not report any impact on their QoL (FLIE-N noncases). Logistic regression analysis confirmed, although the explained variance was not high, that among sociodemographic, clinical and psychosocial variables we examined, the likelihood to develop delayed nausea was associated with a decreasing age and increasing hopelessness-helplessness; the emetogenic grade of chemotherapeutic agents and hopelessness-helplessness were associated with an increased likelihood of having a negative impact on QoL after chemotherapy.

The interpretation of these results is not easy. It is possible that a hopeless-helpless style, which is a more constant attitude, may not only favor the increase in a state condition of emotional distress before chemotherapy, but also make the patient more vulnerable to the subjective perception of somatic symptoms, such as nausea. A few data related to this hypothesis have been provided by Koller et al. [44] and Badger et al. [45], who found that negative affect and depression influence cancer patients' reporting of somatic symptoms. Since hopelessness and helplessness have also been related to higher levels of depression in previous studies [22, 46], a negative perception of somatic symptoms and a reduction of QoL [47], a further explanation is that a concomitant depressive condition may have contributed to increase the subjective perception of postinfusional CINV. Since we did not measure depression in our study, more research is needed with respect to this. Also, data have been reported regarding the role of expectations about CINV and onset of CINV [48], with a possibility that the expectations among patients with maladaptive coping can be more negative. Again, this area needs to be explored further. Regarding the role of emotional distress in increasing the impact of nausea on patient's QoL, Higgins et al. [16], who also found a significant effect of pretreatment distress on the severity of patients' subsequent CINV in a study of 56 breast cancer patients, theorized that distress may modify the pharmacological effect of chemotherapy on the central nervous system both centrally, through a direct effect of distress on the central nervous system or perhaps through the enteric nervous system. A further hypothesis is that distress may just reduce the threshold of nausea, favoring the subjective perception of this symptom.

With respect to the doctor-patient relationship, from our study it appears that the side effects of chemotherapy were not dependent on the patient's perception of the attitudes of his/her physician. This is in part in contrast with other authors [20, 21] who found a role for social support in reducing the impact of CINV, although the attention of these studies was concentrated on family support rather

than on the support derived from the doctor-patient relationship. Further research is necessary with respect to this area by using a more specific analysis of the doctor-patient relationship and taking into a more specific consideration the information the patients have received from health care professionals and the possible support from other key figures, besides their own physicians.

There are several limitations in the present study. First, we did not examine possible between-center differences in care, and we did not explore possible differences in type and dose of antiemetic therapy, taking for granted the standards of care of the centers, and assuming that prophylaxis and treatment guidelines were followed. A second limitation is that the sample consisted only of patients with different types of cancer and recruited only in day hospital services and outpatient clinics. More data are necessary to examine the role of psychosocial variables on CINV in other cancer settings, including inpatient services. A further issue regards the fact that we did not analyze anticipatory nausea and vomiting, which is a variation of CINV appearing before chemotherapy and has also been particularly linked to psychological processes [49] and a negative impact on QoL [50, 51]. Related to this, more research is needed to understand the possible association between maladaptive coping mechanisms, as assessed in our study, and expectation about chemotherapy, that we did not measure in our study. In fact, since maladaptive coping, even if significant, explained only part of the variance of CINV and QoL reduction, a broader exploration of other factors (including previous psychosocial disorders, occurrence of life stress events in the past, personality traits, expectations, general beliefs and attitudes, demoralization, abnormal illness behavior) [52–55], would have given more information about the psychosocial correlates of CINV.

With all these limitations in mind, our findings confirm that the significant side effects of chemotherapy, particularly nausea, are still a problem in cancer settings and that these symptoms negatively affect the patients' QoL. Furthermore, attention to the psychological dimensions, especially maladaptive coping mechanisms, is important in clinical practice, since these variables have been shown to exert a possible role in influencing postchemotherapy symptoms (i.e. nausea) and QoL. As underscored by Higgins et al. [16], since the literature suggests that delayed nausea is more resistant to antiemetic drugs than acute nausea [56], optimal holistic care should include a better psychosocial assessment before chemotherapy in order to identify the patients with higher levels of distress or maladjustment to illness who might be responsive to psychological interventions before chemotherapy treatments.

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Disclosure Statement

The authors do not report any potential conflicts of interest relevant to this article.

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