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ORIGINAL ARTICLE

Chemotherapy-induced nausea and vomiting (CINV) in patients with advanced lung cancer during the first-line treatment: assessment by physicians, nurses, and patients from an Italian multicenter survey

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Abstract

Purpose Chemotherapy-induced nausea and vomiting (CINV) still represents a common side-effect of chemotherapy, and often, its perception differs between patients and healthcare professionals. The aim of this study was to evaluate the agreement on the perception of CINV and other items among clinicians, patients, and nurses.

Methods This observational prospective study was part of an evaluation program promoted by the Women Against Lung Cancer in Europe (WALCE) Onlus. From August 2015 to February 2016, a survey was administered in 11 oncologic institutions to 188 stage IV lung cancer patients and to their oncologists and nurses during first-line chemotherapy. Our survey investigated 11 aspects: anxiety, mood, weakness, appetite, nausea, vomiting, pain, drowsiness, breath, general condition, and trust in treatments. These items were assessed through Numerical Rating Scale at four consecutive evaluations: at T0 (immediately prior to the first cycle), at T1 (immediately prior to the second cycle), at T2 (immediately prior to the third cycle), and at T3 (immediately prior to the fourth cycle). Clinician versus patient (CvP), nurse versus patient (NvP), and clinician versus nurse (CvN) agreements were estimated applying Weighted Cohen's kappa. A multivariate logistic model and generalized equation estimates were applied to evaluate factors possibly influencing CINV development.

Results The incidence of patients reporting CINV varied from 40% at T0 to 71% at T3. Both CvP and NvP agreement on the investigated items were mainly moderate, slightly increasing over time, and becoming substantial for some items, in particular for NvP. Pre-chemotherapy anxiety in its mild, moderate, and severe manifestations, as well as mild, moderate, and severe anxiety experienced after chemotherapy start, exposed patients to a higher risk of anticipatory and acute/delayed CINV, respectively.

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Conclusions Despite clinical staff awareness of patients' status and perceptions, CINV still represents a clinical problem. This study confirms that particular attention should be paid to anxiety due to its key role in CINV development.

Keywords Chemotherapy-induced nausea and vomiting · Lung cancer · First-line treatment · Anxiety

Background

Nausea is defined as the unpleasant feeling causing the desire to vomit and can be accompanied by symptoms such as tachycardia, dizziness, and weakness. Vomiting is defined as the contraction of the muscles of the abdomen and diaphragm that triggers the expulsion of stomach contents. Chemotherapy-induced nausea and vomiting (CINV) is a particularly distressing event for oncology patients, both from a physical and psychological perspective [1].

Despite significant progresses in its prevention and control, CINV is still representing an unmet need in the oncology field. A study conducted in 14 centers and six countries showed that around 35 and 60% of patients experienced acute and delayed CINV, respectively [2].

CINV perception often differs between patients and healthcare professionals. In fact, it has been estimated that 75% of the healthcare professionals underestimate CINV incidence and severity [3], with these differences representing a perceptual gap between patients and physicians/nurses who care for them. Even if not life-threatening, CINV can influence patients' willingness to continue chemotherapy, thus impacting survival outcomes and quality of life (QoL) [1]. A systematic review by Sommariva et al. showed that CINV has a negative influence on health-related QoL also among patients receiving moderately emetogenic chemotherapy (MEC). The worsening of QoL in oncological adult patients due to emesis has been measured by several studies emphasizing the importance of early prevention and good management of CINV [1].

The 2016 update of Antiemetic Guidelines developed by the Multinational Association for Supportive Care in Cancer (MASCC) and the European Society of Medical Oncology (ESMO) recommends the administration of a 5-HT3 receptor antagonist in combination with dexamethasone and a NK1 receptor antagonist for the prevention of acute CINV in patients treated with highly emetogenic chemotherapy (HEC). For patients receiving a moderately emetogenic chemotherapy (MEC), a combination of a 5-HT3 receptor antagonist and dexamethasone is recommended, except for subjects treated with carboplatin-based chemotherapy, that should be administered with the same combination adopted for HEC. Guidelines also state that the best approach for the prevention of anticipatory CINV is the best possible control of acute and delayed CINV [4].

Despite these recommendations, adherence to the prophylaxis of emesis in Europe is very low and this significantly correlates with the lack of CINV control [5].

Together with chemotherapy's emetogenicity, a number of variables have been implicated in the development of CINV, including female gender, younger age, history of nausea/vomiting, and anxiety [6]. The aim of this study was to evaluate the degree of agreement among clinicians, patients, and nurses on the perception of CINV and other relevant items and to understand whether anxiety and other demographic and treatment-related factors could play a role in CINV development.

Patients and methods

This observational prospective study was part of an evaluation program promoted by the Women Against Lung Cancer in Europe (WALCE) Onlus. WALCE Onlus is a European advocacy group devoted to lung cancer patients and their families. Questionnaires were developed in agreement with a psychologist and advocates (please see Appendixes 1, 2, and 3 for further details). Eleven Italian oncologic institutions with strong expertise on lung cancer's treatment and collaborating with WALCE in awareness and patient support programs were the participating centers. For each center, a dedicated physician and a dedicated nurse were identified as representatives. The first inclusion criterion was the application of international guidelines for antiemetics in oncology [7]. From August 2015 to February 2016, stage IV non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) patients referring to these centers and their oncologists and nurses took part to the survey. Three different questionnaires were administered to patients, oncologists, and nurses at four consecutive evaluations (T0, T1, T2, and T3) during first-line chemotherapy, immediately before chemotherapy administration. Patients included had to be 18 years older, chemotherapy-naïve, and eligible for MEC or HEC. Questionnaires investigated 11 chemotherapy-related aspects (anxiety, mood, weakness, appetite, nausea, vomiting, pain, drowsiness, breath, general condition, and trust in treatments) as perceived by patients, oncologists, and nurses, by means of a Numerical Rating Scale (NRS) ranging from 0 to 10. Oncologist's questionnaire also collected information on patients' demographic characteristics, clinical features, and antiemetic therapy.

Statistical analysis

Descriptive statistics were used to provide an overview on patients' demographic and clinical characteristics and on treatments. Clinician versus patient (CvP), nurse versus patient (NvP), and clinician versus nurse (CvN) agreements were estimated in relation with the investigated items applying Weighted Cohen's kappa and the grid of Landis and Koch. Weighted kappa coefficients were considered as poor, slight, fair, moderate, substantial, and almost perfect according to Landis and Koch [8].

CINV occurrence was defined as a rating greater than zero assigned to the item nausea and/or a rating greater than 0 assigned to the item vomiting. Presence of anxiety was defined as a rating greater than zero assigned to the respective item, with anxiety level defined as mild when the rating was included in the range 1–3, moderate when ranging from 4 to 7, and severe when comprised in the range from 8 to 10.

A multivariate logistic model was performed to evaluate factors possibly influencing anticipatory CINV as perceived by patients: the response variable was the occurrence of anticipatory CINV before the first chemotherapy cycle (T0) based on patients' ratings; the covariates included were age, gender, and anxiety level. Generalized equation estimates (GEE) for repeated measures were used to evaluate factors possibly influencing CINV development overall once first cycle of chemotherapy had been already administered. Response variable was the presence/absence of CINV as perceived by patients at T1, T2, and T3, with GEE for repeated measures accounting for intra-subject correlation. The covariates considered were age, sex, anxiety level at each cycle subsequent to the first one, anxiety level before the first chemotherapy cycle, the chemotherapy scheme, and presence/absence of anticipatory CINV. Odds ratios (ORs) and weighted Kappa coefficients were reported together with their 95% confidence intervals (95% CIs).

Results

One hundred eighty-eight patients completed the questionnaire at T0, 164 at T1, 138 at T2, and 101 at T3. Duly compiled questionnaires accounted for 99%. Patients' mean age was around 65 years and men accounted for more than 70% of the patients. Adenocarcinoma was the most represented histological form, followed by squamous cell carcinoma and small cell carcinoma. Cisplatin was administered to 99 (53%) patients and carboplatin to 86 (46%). Among patients undergoing cisplatin-based chemotherapy, those prescribed with both 5-HT3 and NK1 antagonist and those prescribed with 5-HT3 antagonist only accounted for about 83 and 13% at T0, respectively. Among patients undergoing carboplatin-based chemotherapy, those prescribed with both 5-HT3 and NK1 antagonist and those prescribed with 5-HT3 antagonist accounted for about 13 and 86%, respectively (Table 1). When considering the following cycles, the proportion of patients treated with both 5-HT3 and NK1 antagonist and with 5-HT3 antagonists only among those undergoing cisplatin-based chemotherapy did not vary; differently, when focusing on carboplatin-based chemotherapy patients, proportions of those treated with the combination increased over time (data not shown). All CINV prevention regimens were assumed to include steroids as by MASCC/ESMO guidelines [4].

The use of concomitant drugs was evaluated at each assessment. The drugs most frequently used were strong and weak opioids, antidepressants, neuroleptics, and antipsychotics. In particular, 37, 39, 32, and 32% of the patients assumed weak opioids at T0, T1, T2, and T3, respectively; strong opioids were used by 34, 27, 30, and 27% of the patients at T0, T1, T2, and T3, respectively. No correlation was observed between the use of opioids and the occurrence of CINV.

Patients who reported anticipatory nausea, anticipatory vomiting, and anticipatory CINV accounted for 39, 21, and 40%, respectively. Proportions of patients experiencing anticipatory CINV were higher among women and patients 50 years younger. At T1 (first cycle), 68% of the patients experienced nausea, 38% vomiting, and 68% CINV, with

Table 1 Patients' characteristics at T0

Total number of patients, 188			
Gender	*N* (%)		
Male	134 (71)		
Female	54 (29)		
Age (mean 64.6; SD 8.4; min 41.0; max 83.0)	*N* (%)		
40–50	13 (7)		
50–60	32 (17)		
60–70	92 (49)		
> 70	51 (27)		
Histological form	*N* (%)		
Adenocarcinoma	114 (61)		
Squamous carcinoma	36 (19)		
Small cells carcinoma	30 (16)		
Poorly differentiated carcinoma	7 (4)		
Other	1 (0)		
Antiemetic class			
Chemotherapy	5-HT3 antagonists + NK1 antagonists *N* (%)	5-HT3 antagonists only *N* (%)	Other *N* (%)
Carboplatin-based	11 (13)	74 (86)	1 (1)
Cisplatin-based	82 (83)	13 (13)	4 (4)
Other	0	2 (67)	1 (33)

these proportions being quite similar at the following cycles. Likewise for anticipatory CINV, CINV occurrence over time was more frequently reported by women and younger patients (Table 2).

Pre-chemotherapy anxiety was reported by 167 (89%) patients (mild 27%; moderate 43%; severe 19%) and was more common in those experiencing also anticipatory CINV. Proportions of patients perceiving anxiety increased to 93%

Table 2 Proportions of patients experiencing anticipatory CINV and acute/delayed CINV

T0			
	Anticipatory nausea *N* (%)	Anticipatory vomiting *N* (%)	Anticipatory CINV *N* (%)
Overall (*N* = 188)	74 (39)	40 (21)	75 (40)
Gender			
Male (*N* = 134)	50 (37)	27 (20)	51 (38)
Female (*N* = 54)	24 (44)	13 (24)	24 (44)
Age classes			
40–50 (*N* = 13)	8 (62)	3 (23)	8 (62)
50–60 (*N* = 32)	13 (41)	5 (16)	13 (41)
60–70 (*N* = 92)	33 (36)	20 (22)	34 (37)
> 70 (*N* = 51)	20 (39)	12 (24)	20 (39)
T1			
	Acute/delayed nausea *N* (%)	Acute/delayed vomiting *N* (%)	Acute/delayed CINV *N* (%)
Overall (*N* = 164)	109 (66)	62 (38)	112 (68)
Gender			
Male (*N* = 117)	74 (63)	44 (38)	77 (66)
Female (*N* = 47)	35 (74)	18 (38)	35 (74)
Age classes			
40–50 (*N* = 12)	10 (83)	5 (42)	10 (83)
50–60 (*N* = 30)	22 (73)	15 (50)	23 (77)
60–70 (*N* = 81)	54 (67)	30 (37)	54 (67)
> 70 (*N* = 41)	23 (56)	12 (29)	25 (61)
T2			
	Acute/delayed nausea *N* (%)	Acute/delayed vomiting *N* (%)	Acute/delayed CINV *N* (%)
Overall (*N* = 138)	98 (71)	45 (33)	98 (71)
Gender			
Male (*N* = 98)	65 (66)	26 (27)	65 (66)
Female (*N* = 40)	33 (83)	19 (48)	33 (83)
Age classes			
40–50 (*N* = 10)	9 (90)	4 (40)	9 (90)
50–60 (*N* = 27)	19 (70)	8 (30)	19 (70)
60–70 (*N* = 68)	47 (69)	23 (34)	47 (69)
> 70 (*N* = 33)	23 (70)	10 (30)	23 (70)
T3			
	Acute/delayed nausea *N* (%)	Acute/delayed vomiting *N* (%)	Acute/delayed CINV *N* (%)
Overall (*N* = 101)	72 (71)	37 (37)	72 (71)
Gender			
Male (*N* = 71)	47 (66)	23 (32)	47 (66)
Female (*N* = 30)	25 (83)	14 (47)	25 (83)
Age classes			
40–50 (*N* = 6)	5 (83)	3 (50)	5 (83)
50–60 (*N* = 18)	17 (94)	9 (50)	17 (94)
60–70 (*N* = 55)	33 (60)	19 (35)	33 (60)
> 70 (*N* = 22)	17 (77)	6 (27)	17 (77)

at T1 (mild 41%; moderate 39%; severe 13%), 90% at T2 (mild 43%; moderate 38%; severe 9%), and 92% at T3 (mild 38%; moderate 46%; severe 8%), thus quite stable also when compared with pre-chemotherapy anxiety. In addition, proportions of anxious patients were higher among those experiencing CINV at all the time points underlying a potential association between the two phenomena (Fig. 1).

Results about the degree of agreement between CvP, NvP, and CvN are shown in Table 3. Overall, CvP, NvP, and CvN agreements resulted to be moderate for the majority of the items considered.

The multivariate logistic model investigating the potential predictors of anticipatory CINV showed a statistically significant association between anticipatory CINV occurrence and anxiety experienced by patients before the first cycle of chemotherapy in all its mild, moderate, and severe manifestations. No association was detected for gender and age classes. Results from the GEE for repeated measures revealed that overall anxiety could effectively play a role in CINV development: a raising trend corresponding to increasing levels of anxiety was observed. Statistically significant association between CINV occurrence after chemotherapy start and anticipatory CINV was also detected. No association was found with gender, age classes, chemotherapy scheme, and anticipatory anxiety; however, despite missing the significance, the trend of the estimated ORs suggested an increased risk of developing CINV for women and patients undergoing cisplatin-based chemotherapy and a decreased risk for older patients (Table 4).

Discussion

Four major findings emerge from this survey: (1) the importance of symptom questionnaires during routine chemotherapy in lung cancer patients; (2) despite antiemetic prophylaxis, the proportion of patients experiencing both anticipatory and acute/delayed CINV is quite high; (3) CvP, NvP, and CvN agreements are moderate for the majority of the considered items; and (4) anxiety represents a strong predictor of nausea and vomiting.

Drawing comparisons with results from the literature is difficult due to the variability in study designs. However, a study by Cohen et al. reported that during cycle 1 of chemotherapy, only 33% of the patients had neither acute nor delayed CINV [9], which means patients experiencing acute and/or delayed CINV were about 67%, thus in line with the results from the present study (68%).

The agreement between patients and healthcare professionals was good for almost all the investigated items; this finding is in contrast with available data that often underline the gap between patients' and healthcare professionals' perceptions [10]. This difference could be explained as a positive response to Grunberg et al.'s trial data that revealed how medical staff underestimates the risk of CINV (particularly the delayed type) and concluded that educational program should be developed [5]. A study by Vidall et al. suggested that nausea severity and impact experienced by the patients were greater than perceived by physicians and oncology nurses; they also showed that healthcare professionals failed to distinguish between acute and delayed CINV [11]. Moreover, it is worth noting that for two items investigating aspects that are not objectively measurable (anxiety and mood), the agreement grade was almost always moderate, suggesting that a dialog between patients and healthcare professionals does exist. A good relationship with patients should be an important starting point to improve CINV-related outcomes and patients' QoL perception, with these aspects being highly correlated. Pre-chemotherapy anxiety showed to play a key role in the development of anticipatory CINV, and being anxious at the subsequent cycles increased the risk of acute/delayed CINV. Oncologists' and nurses' awareness about this issue could facilitate their intervention in relieving patients, with healthcare professionals not being just prescribers, but becoming caregivers in a more comprehensive way. The influence of anxiety on CINV development was observed in previous studies [9, 12], with the present survey further reinforcing evidences. In light of this, it is worth mentioning the emerging role of olanzapine. Primarily marketed as an antipsychotic,

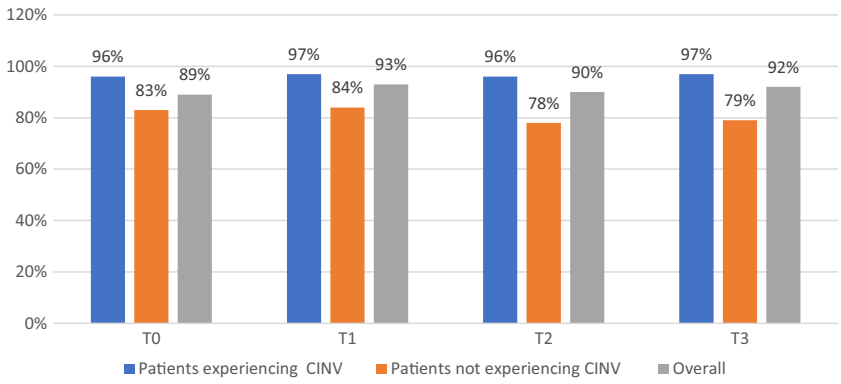

Fig. 1 Patients experiencing anxiety stratified by CINV occurrence at T0, T1, T2, and T3

Table 3 CvP and NvP agreement grade about the considered items at T0, T1, T2, and T3

	Agreement grade		Agreement grade	
	CvP Kappa [95% CI]; grade	NvP Kappa [95% CI]	CvP Kappa [95% CI]; grade	NvP Kappa [95% CI]; grade
	Anxiety		Pain	
T0	0.51 [0.43–0.59]; moderate	0.50 [0.43–0.58]; moderate	0.51 [0.44–0.59]; moderate	0.57 [0.49–0.65]; moderate
T1	0.51 [0.42–0.60]; moderate	0.48 [0.39–0.57]; moderate	0.64 [0.57–0.71]; substantial	0.62 [0.54–0.70]; substantial
T2	0.36 [0.26–0.46]; fair	0.49 [0.40–0.59]; moderate	0.60 [0.51–0.69]; moderate	0.58 [0.49–0.67]; moderate
T3	0.52 [0.42–0.62]; moderate	0.65 [0.56–0.73]; substantial	0.60 [0.50–0.70]; moderate	0.72 [0.64–0.80]; substantial
	Mood		Drowsiness	
T0	0.45 [0.37–0.54]; moderate	0.51 [0.44–0.58]; moderate	0.38 [0.29–0.47]; fair	0.52 [0.44–0.60]; moderate
T1	0.49 [0.41–0.58]; moderate	0.47 [0.38–0.56]; moderate	0.52 [0.43–0.60]; fair	0.56 [0.47–0.64]; moderate
T2	0.38 [0.27–0.49]; fair	0.54 [0.44–0.64]; moderate	0.55 [0.46–0.65]; moderate	0.62 [0.53–0.72]; substantial
T3	0.55 [0.46–0.65]; moderate	0.60 [0.50–0.70]; moderate	0.47 [0.36–0.59]; moderate	0.67 [0.58–0.75]; substantial
	Weakness		Breath	
T0	0.38 [0.29–0.46]; fair	0.46 [0.39–0.54]; moderate	0.49 [0.41–0.58]; moderate	0.54 [0.46–0.61]; moderate
T1	0.44 [0.36–0.52]; moderate	0.49 [0.41–0.58]; moderate	0.60 [0.52–0.67]; moderate	0.56 [0.47–0.65]; moderate
T2	0.47 [0.37–0.56]; moderate	0.53 [0.44–0.61]; moderate	0.59 [0.50–0.68]; moderate	0.51 [0.40–0.61]; moderate
T3	0.58 [0.49–0.67]; moderate	0.57 [0.47–0.67]; moderate	0.57 [0.47–0.68]; moderate	0.68 [0.58–0.77]; moderate
	Appetite		General condition	
T0	0.38 [0.29–0.47]; fair	0.45 [0.36–0.54]; moderate	0.28 [0.19–0.38]; fair	0.34 [0.25–0.44]; fair
T1	0.50 [0.41–0.59]; moderate	0.56 [0.48–0.63]; moderate	0.28 [0.19–0.38]; fair	0.29 [0.19–0.39]; fair
T2	0.55 [0.46–0.64]; moderate	0.53 [0.43–0.64]; moderate	0.38 [0.28–0.48]; fair	0.44 [0.34–0.54]; moderate
T3	0.50 [0.39–0.61]; moderate	0.61 [0.50–0.72]; substantial	0.34 [0.23–0.45]; fair	0.38 [0.26–0.49]; fair
	Nausea		Trust in treatments	
T0	0.32 [0.19–0.44]; fair	0.41 [0.30–0.53]; moderate	0.30 [0.21–0.39]; fair	0.43 [0.34–0.53]; moderate
T1	0.51 [0.42–0.61]; moderate	0.60 [0.51–0.69]; moderate	0.28 [0.18–0.39]; fair	0.50 [0.41–0.60]; moderate
T2	0.34 [0.25–0.44]; fair	0.55 [0.45–0.66]; moderate	0.45 [0.35–0.55]; moderate	0.60 [0.51–0.68]; moderate
T3	0.56 [0.45–0.68]; moderate	0.68 [0.57–0.80]; substantial	0.43 [0.33–0.53]; moderate	0.60 [0.49–0.71]; moderate
	Vomiting			
T0	0.31 [0.14–0.47]; fair	0.43 [0.25–0.60]; moderate		
T1	0.51 [0.39–0.62]; moderate	0.61 [0.51–0.72]; substantial		
T2	0.60 [0.48–0.72]; moderate	0.57 [0.42–0.71]; moderate		
T3	0.52 [0.38–0.67]; moderate	0.60 [0.44–0.76]; moderate		

olanzapine showed to improve QoL by allowing a better management of CINV when administered as an add-on therapy [13] also in platinum-based chemotherapy-naïve patients [14].

Likewise anxiety, also anticipatory CINV occurrence was a strong predictor of CINV, with this result in agreement with that from the study by Kim et al. where CINV in prior cycles was a strong predictor of CINV in subsequent cycles [15].

Contrary to what was expected, treatment with cisplatin-based chemotherapy was not significantly associated with a higher risk of developing CINV. The majority of patients receiving a cisplatin-based chemotherapy were treated with a 5-HT3 and NK1 antagonist combination, while the proportion of patients administered with a carboplatin-based chemotherapy who received a 5-HT3 and NK1 antagonist combination was quite low, particularly at the first cycle. This result is probably linked to the fact that carboplatin is still being considered as a "less heavy" drug in the context of CINV by several oncologists. Recently, an update of MASSC and ESMO guidelines has recommended the administration of a 5-HT3 receptor antagonist in combination with dexamethasone and a NK1 receptor antagonist for the prevention of acute CINV also in patients receiving a carboplatin-based MEC [7]. A study by Kitazaki et al. concluded that triple therapy with aprepitant, palonosetron, and dexamethasone can be recommended for supporting both carboplatin-based and cisplatin-based chemotherapy [16]. In this study, the lack of a significant association between chemotherapy scheme and CINV occurrence could suggest that a correct management of patients receiving HEC could allow a control of CINV symptomatology in patients at higher risk of CINV that is even

Table 4 Results from Multivariate Logistic Regression Model and GEE estimates for repeated measures

Covariates	Multivariate Logistic Regression Model at T0		
	Odds ratio	[95% CI]	*p* value
Gender			
Female versus male	1.0	[0.5–1.9]	0.88
Age classes			
50–60 versus 40–50	0.6	[0.2–2.2]	0.42
60–70 versus 40–50	0.4	[0.1–1.3]	0.13
70+ versus 40–50	0.5	[0.1–1.9]	0.31
Anxiety at T0			
Mild versus absence	5.0[1]	[1.3–19.8]	0.02
Moderate versus absence	4.9[1]	[1.3–18.5]	0.02
Severe versus absence	4.7[1]	[1.1–20.0]	0.04
GEE estimates for repeated measures			
Covariates	Odds ratio	[95% CI]	*p* value
Gender			
Female versus male	1.6	[0.8–3.2]	0.2
Age classes			
50–60 versus 40–50	0.6	[0.2–2.2]	0.45
60–70 versus 40–50	0.5	[0.1–1.5]	0.20
70+ versus 40–50	0.6	[0.2–2.4]	0.48
Anxiety at T0			
Mild versus absence	1.0	[0.4–2.5]	0.94
Moderate versus absence	1.1	[0.4–2.7]	0.90
Severe versus absence	0.9	[0.3–2.7]	0.81
Overall anxiety[2]			
Mild versus absence	10.0[1]	[3.3–30.6]	<0.001
Moderate versus absence	11.2[1]	[3.5–35.7]	<0.001
Severe versus absence	12.9[1]	[2.8–58.5]	<0.001
Anticipatory CINV			
Presence versus absence	2.3[1]	[1.2–4.3]	0.01
Chemotherapy scheme			
Cisplatin-based versus carboplatin-based	1.8	[1.0–3.2]	0.07

GEE generalized equation estimates, CINV chemotherapy-induced nausea and vomiting

[1] Statistically significant based on 95% confidence intervals and *p* values

[2] Anxiety level based on the mean of ratings assigned to the item anxiety at T1, T2, and T3

better than that achieved in patients at lower risk but not receiving a combination of 5-HT3 and NK1 receptor antagonists. Under this perspective, adherence to updated guidelines, the necessity for healthcare professionals to be always aware of improvement in pharmacology treatments is fundamental.

Finally, according to recent literature data, this study highlighted the decisive role of questionnaires assessing symptoms during treatment of advanced cancers to identify early adverse events and to improve symptom management [17, 18]. The use of patient-reported outcomes (PROs) in clinical practice to improve QoL and manage toxicity should be encouraged particularly considering results from the recent study by Basch. In fact, Basch and colleagues reported an increase of overall survival in association with the adoption of electronic patient-reported symptom monitoring [19]. Furthermore, Basch suggested that patient-reported data could be used in several areas (as to improve the management of post-chemotherapy nausea or to identify unexpected symptoms associated with a particular drug) to turn the rhetoric regarding "patient-centered care" into a reality [20].

Our study represents a further confirmation about the importance of collecting PROs, with "patients' voices" having allowed us to detect the strong link between anxiety and CINV. This result can stimulate the conduction of new trials to refine the management of this symptom and, indirectly, of CINV.

A strength of the present study was the homogeneity of the sample in terms of type of neoplasia, stage, chemotherapy line, treatment, and adherence to guidelines. Similarly, the simultaneous assessment of physicians', nurses', and patients' perception and their comparison constituted a strength.

Furthermore, the proportion of duly compiled questionnaire was very high, probably reflecting the interest in the investigated issue and ensuring accuracy of data collected. The number of patients taking part to the survey was not very high, although, the implementation of GEE for repeated measures allowed handling of missing data without excluding patients lost to follow-up [21].

The most relevant result emerging in this study is therefore the key role of anxiety and its link with CINV development. It follows that a better assessment and management of anxiety could improve CINV control through close cooperation among healthcare professionals and advocacy patients.

Conclusion

Even if clinical staff was aware and sensitive about patients' status and perceptions, CINV is still representing a problem among patients undergoing chemotherapy. This study further confirms that physicians and nurses should pay particular attention to anxiety due to its key role in CINV development.

Compliance with ethical standards

Conflict of interest SN has been a speaker bureau for Eli Lilly, Roche, Merck Sharp & Dohme, Bristol Myers Squibb, Boehringer Ingelheim, and Astra Zeneca. VP and NC are Quintiles IMS employees. All remaining authors have declared no conflicts of interest.

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