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# Chemotherapy-induced nausea and vomiting in Italian cancer centers: results of CINVDAY, a prospective, multicenter study

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ABSTRACT

**Purpose.** Guideline consistency in the prevention of chemotherapy-induced nausea and vomiting (CINV) remains low (29% in the Pan European Emesis Registry study) and very low (11%) in regimens with a high emetogenic risk. The aim of this study was to evaluate the guideline consistency of CINV prophylaxis for acute emesis in daily clinical practice in Italy.

**Methods.** This was a prospective, observational, multicenter study. Patients scheduled to receive antitumor treatment on a single prespecified day were included. Data on patient characteristics (demographic and clinical), type of anticancer therapy, and type of antiemetic therapy prescribed for acute emesis were collected on electronic data capture forms. Chemotherapy regimens and antiemetic prophylaxis were categorized according to the MASCC 2011 guidelines. The study was approved by the local ethics committees.

**Results.** From July 2013 to February 2014, a total of 502 patients were enrolled at 26 study sites. Median age was 62 years (range 27-87 years). Colorectal cancer and breast cancer were the most common malignancies. The emetogenic potential of the chemotherapy regimens used was high (HEC) (23.7%), moderate (MEC) (40.6%), low (31.3%) or minimal (4.4%). Overall, guideline consistency was 19.3%. Consistency reached 45% when the various 5HT3 receptor antagonists were considered equivalent and interchangeable in MEC regimens. Adherence to guidelines was lowest for HEC and MEC risk groups. [AUTHORS: This is at odds with the Results section and Figure 1, which show that adherence was lowest in the MEC and MINIMAL groups] Ten percent of patients in HEC and MEC regimens did not receive any 5HT3 receptor antagonists. NK1 receptor antagonists were used in 8% of all regimens.

**Conclusions.** Our study indicates that antiemetic guideline inconsistency remains an issue in daily clinical oncology practice in Italy.

***Key words***: CINV, guidelines adherence, emesis, antiemetic therapy.

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*Conflict of interest:* All authors have declared not financial relationship with the organization that sponsored the research. They have also declared that they have full control of all primary data and that they agree to allow the journal to review their data if requested.

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## Introduction

In the last 3 decades important progress has been made in the prophylaxis and treatment of chemotherapy-induced nausea and vomiting (CINV)[1]. Today, new insights into the pathophysiology of CINV, better knowledge of risk factors, and new available antiemetic agents have contributed to improve CINV control, but the problem is still significant in clinical practice and it is experienced by patients as one of the most feared side effects of anticancer therapies[2]. Additionally, symptoms of CINV can negatively affect patients' quality of life and adherence to scheduled chemotherapy, causing delays or discontinuation of potentially effective treatments[3]. It has been documented that in up to 30% of patients CINV is so distressing as to encourage treatment interruption[4]. So, despite an overall improvement, CINV is still reported in a considerable percentage of patients treated with either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC)[5,6].

Over the years many evidence-based guidelines have been published to assist healthcare providers with the management of CINV[7-10]. However, several studies have shown that adherence to treatment recommendations is less than optimal[11]. A large European study (the Pan European Emesis Registry [PEER] study) showed that of 991 patients only 29% received prophylactic antiemetic therapy adhering to international guidelines[12], and among patients receiving HEC regimens adherence was only 11%. In the same study, the authors showed that in cases where adherence to guidelines was higher, control of CINV symptoms was greater than in cases of non-adherence (59.9% *vs* 50.7%, respectively; $P = 0.008$). The aim of the present study was to evaluate the guideline consistency of antiemetic therapy for CINV in the daily practice of Italian cancer centers.

## Patients and methods

This was a prospective, observational, multicenter study, named CINVDAY, performed in Italian cancer centers. All patients scheduled to receive antitumor treatment in the form of chemotherapy or biological therapy on a prespecified day were eligible for inclusion in the study. The following data were recorded: patient's age and gender, educational level, site of primary tumor, stage of disease, risk factors for emesis (use of opioids, high alcohol intake, central nervous system metastases, kinetosis), type of antitumor therapy including setting (primary, adjuvant, metastatic), dose schedule, line of therapy, and number of previous cycles administered. The type of antiemetic therapy prescribed for acute emesis, including drug name and the use of corticosteroids, was also recorded, along with data on prophylaxis for delayed emesis (DE). All the data were uploaded into an *ad hoc* generated electronic data capture form on a Web platform. Chemotherapy regimens and antiemetic prophylaxis were categorized according to the 2011 antiemetic guidelines of the Multinational Association of Supportive Care in Cancer (MASCC) (http://www.mascc.org/antiemetic-guidelines). The definition of guideline-consistent CINV prophylaxis was as follows: triplet for HEC regimens (corticosteroid + 5HT3 receptor antagonists [RAs] + NK1 RAs, considering all 5HT3 RAs equivalent and interchangeable), doublet for MEC regimens (corticosteroid + palonosetron), single agent for chemotherapy with low emetogenic potential (LOW) (corticosteroid or 5HT3 RA or metoclopramide) and no prophylaxis for chemotherapy with minimal emetogenic potential (MINIMAL). Anthracycline-based chemotherapy regimens were included among the HEC regimens. No specific statistical design was planned, nor was minimum sample size calculated. A multiple correspondence analysis (MCA) was used to analyze possible relationships among all variables and identify specific profiles[13]. In the MCA, associations between variables are displayed graphically as maps, and their position in the graphic is exclusively informative. No CINV outcomes about the efficacy of the prescribed antiemetics were measured. The study was approved by the local ethics committee at each clinical site; all patients gave their written informed consent.

## Results

From July 2013 to February 2014, a total of 502 patients were enrolled at 26 cancer centers in 12 Italian regions. The long accrual period (6 months) was necessary to obtain approval by local ethics committees. The median age of the enrolled patients was 62 years (range 27-87 years). Most patients were female (58.6%), had disease stage IV (73.3%) and were in first-line therapy (42%). Table 1 summarizes the demographic and clinical characteristics of the patients. Colorectal cancer (n = 146) and breast cancer (n = 126) were the most common malignancies (Table 2). The emetogenic potential of the chemotherapy regimens used was as follows: HEC (23.7%), MEC (40.6%), LOW (31.3%) and MINIMAL (4.4%). The chemotherapeutic regimens used are listed in Table 3. Prophylactic therapy (of any type) for acute emesis was prescribed to 87.1% of patients. Approximately one-half of them (48%) had no prescription for DE. Corticosteroid therapy (of any type) was prescribed to 97% of patients.

Overall, adherence to the MASCC 2011 guidelines was observed in 97/502 (19.3%) patients. Consistency was higher (45%) when the different 5-HT3 RAs employed were considered equivalent and interchangeable in MEC regimens, because 157 of these 186 patients [AUTHORS: Change OK?] received a first-generation 5-HT3 RA instead of palonosetron. The poor overall consisten-

**Table 1 - Patient characteristics (n = 502)**

| Characteristics | n (%) | Characteristics | n (%) |
|---|---|---|---|
| Age (years) | | Educational level | |
| Median (range) | 62 (27-87) | Primary | 176 (34.9) |
| | | Secondary | 114 (22.7) |
| Gender | | Pre-university | 148 (29.5) |
| Female | 294 (58.6) | Graduate | 64 (12.9) |
| Male | 208 (41.4) | | |
| Cancer stage | | Setting | |
| Stage I | 28 (5.7) | Primary | 22 (4.2) |
| Stage II | 32 (6.2) | Adjuvant | 113 (22.5) |
| Stage III | 75 (14.8) | Metastatic | 367 (73.3) |
| Stage IV | 367 (73.3) | | |
| Line of chemotherapy | | | |
| Primary & adjuvant | 135 (26.7) | | |
| 1st line | 201 (40.1) | | |
| 2nd line | 89 (17.8) | | |
| 3rd line | 43 (8.6) | | |
| 4th line | 23 (4.6) | | |
| 5th line | 11 (2.2) | | |

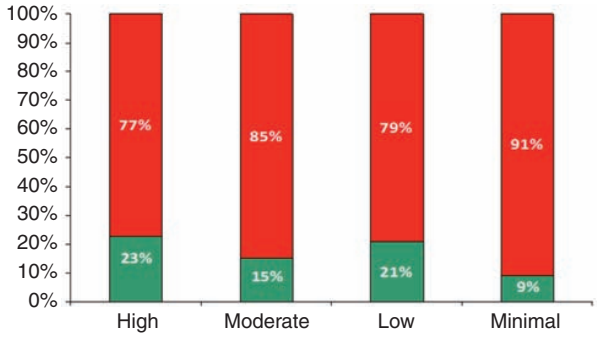
**Table 2 - Type of malignancy**

| Primary tumor | n (%) |
|---|---|
| Colorectal | 146 (29.1) |
| Breast | 126 (25.1) |
| Lung | 59 (11.7) |
| Ovarian | 32 (6.4) |
| Pancreatic | 29 (5.8) |
| Gastric | 20 (4.0) |
| Uterine | 12 (2.4) |
| Prostatic | 12 (2.4) |
| Bladder | 8 (1.6) |
| Biliary | 5 (1.0) |
| Melanoma | 5 (1.0) |
| Testis | 5 (1.0) |
| CNS | 4 (0.7) |
| Other | 39 (7.8) |

**Table 3 - Chemotherapy regimens**

| Chemotherapy regimens | n (%) |
|---|---|
| Platinum based | 79 (15.7) |
| Anthracycline based | 41 (8.1) |
| Taxane monotherapy | 89 (17.7) |
| FOLFIRI/FOLFOX | 123 (24.5) |
| Mono-chemotherapy | 148 (29.6) |
| Biological monotherapy | 22 (4.4) |

cy was similar in all emetogenic risk groups: 23% in HEC, 15% in MEC, 21% in LOW and 9% in MINIMAL (Figure 1). In HEC and MEC regimens, 10% of the patients did not receive any 5HT3 RAs, whereas NK1 RAs were used in 8% of regimens overall and in only 2% of HEC regimens. Three percent of patients in HEC regimens did not receive any antiemetic prophylaxis. Adherence to therapy clusters was observed in the northern regions of Italy and in patients treated with opioids,whereas there was no adherence to clusters in patients with central nervous system metastases and in those affected by kinetosis (Figure 2).




Green = consistent. Red = inconsistent.

Figure 1 - Consistency with guidelines in different emetogenic risk groups (%).

## Discussion

Since the 1960s, antiemetic therapy in oncology has been a large field of medical research, but CINV is still a major clinical issue. Significant progress in the understanding of the pathophysiology of CINV has led to the development of several antiemetic agents, ranging from antidopaminergics, corticosteroids, 5-HT3 RAs, NK1 RAs up to new antipsychotic agents such as olanzapine. This rich drug armamentarium has led to the institution of several international guidelines for the prevention and treatment of CINV, but current patient reports indi-

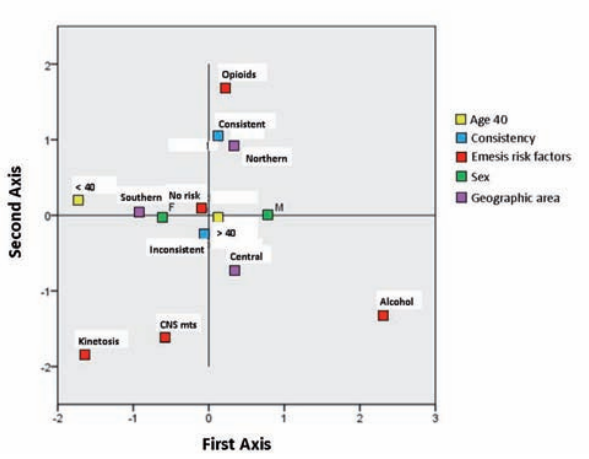



Figure 2 - Multiple correspondence analysis (MCA).

cate that the use of these drugs is still suboptimal. The PEER study[12] showed that patients whose treatment was consistent with guideline indications were more likely to achieve complete control of CINV symptoms, but the same study showed poor guideline consistency, especially for HEC regimens.

The present study indicates that antiemetic guideline inconsistency remains an issue also in daily oncology practice in Italy. In fact, complete adherence to the MASCC guidelines was found in only 19.3% of patients. Consistency was poor regardless of the emetogenic risk class of the drugs, and seems to be lower for regimens with a low emetogenic risk (9% in MINIMAL *versus* 23% in HEC). Moreover, about 10% of patients treated with HEC received no therapy for acute emesis. No difference between platinum-based chemotherapy and anthracycline-based regimens was observed. Adherence to guidelines improved (from 19.3% to 42%) [AUTHORS: In the Abstract and the Results section you mention 45%. Please check] when first-generation 5HT3 RAs were considered equivalent to palonosetron in MEC regimens. However, drug characteristics and literature recommendations do not justify this substitution. The leading cause of guideline inconsistency seems to be the lack of antiemetic prescription (especially NK1 inhibitors) in HEC regimens and excessive prescription in LOW regimens (where no antiemetic drugs should be prescribed).

Our consistency assessment referred only to the prophylaxis of acute CINV, but data analysis also showed that 48% of patients received no prescription for DE. Even if DE was no endpoint of our study and this finding was not included in our guideline consistency analysis, it is relevant to emphasize that 64.3% of patients were treated with HEC and MEC regimens, all of which associated with a high incidence of DE.

The patients enrolled in the present study represent different geographic areas (northern, central and southern regions of Italy) and different sizes and types of cancer treatment facilities (national cancer centers, medium-sized institutions as well as small peripheral day hospitals). Therefore, the poor adherence to guidelines we observed is likely to reflect the actual practice of the country.

An extensive discussion took place among the investigators involved in the study, which highlighted several aspects that could explain the observed low adherence to guidelines: (i) poor knowledge of guidelines; (ii) low (or critical) acceptance of guideline indications; (iii) poor attention to CINV symptoms; (iv) administrative and/or prescribing obstacles. Even if Ballatori *et al.*[14] showed that optimal CINV control could reduce the budgetary impact of CINV, the economic burden of CINV prophylaxis has also been considered a potential barrier to optimal care, especially in the case of MEC regimens[15]. Instead, the present study shows that even in patients treated with chemotherapy having minimal emetogenic risk, where no prophylaxis is needed, some kind of antiemetic therapy was nevertheless used, and this actually amounts to useless and expensive overtreatment. Interestingly, similar results emerged from previous studies performed in Italy about 10 years ago, when some therapeutic options, like NK1 RAs, were not yet available[16,17]. Probably all the above-mentioned reasons can influence the oncologist's choice, but in order to improve treatment compliance and patient quality of life, any effort should be made to overcome them. Recently, the American Society of Clinical Oncology (ASCO) strongly advised oncologists to use prophylactic antiemetic therapy in accordance with evidence-based guidelines, to avoid more expensive or ineffective treatments[18]. In conclusion, improved adherence to guidelines for antiemetic treatment of CINV is urgently needed in daily clinical practice in Italy.

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