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# Prevention of chemotherapy-induced nausea and vomiting — standards versus clinical practice

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## ABSTRACT

In patients' perception, chemotherapy-induced nausea and vomiting (CINV) are the main treatment-related adverse events of anti-cancer treatment. The probability of CINV incidence depends on the treatment regimen, dose, administration route, and patient-dependent factors. According to the current guidelines, a combination of setrons, neurokinin-1 receptor antagonists, and glucocorticoids results in control of acute emesis in 80–90% of patients and delayed emesis in 60–80%. Despite the availability of recommendations for prophylaxis CINV, the level of adherence to the guidelines in clinical practice is lower than observed in trials. Only half of the patients with highly and moderately emetogenic chemotherapy receive prophylaxis consistent with recommendations. Overuse of 5-hydroxytryptamine-3 receptor antagonists, incorrect dosing of corticosteroids, and overuse of metoclopramide in prophylaxis of delayed emesis are the main issues of non-adherence. Possible reasons for non-adherence are: insufficient knowledge of the guidelines, inappropriate CINV risk assessment, underestimation of symptoms reported by the patients, and difficulties in communication between a patient, medical personnel, and physician. To improve adequate control of CINV and adherence to the guidelines repetitive educational, administrative, and scientific actions need to be taken.

**Key words:** nausea, vomiting, chemotherapy, guidelines

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## Introduction

Chemotherapy-induced nausea and vomiting (CINV) are among the most frequent side effects of anticancer therapy. Patients consider CINV as the main complication of planned chemotherapy. CINV have a negative impact on the quality of life (QoL) during the treatment and remain the main cause of stress, discomfort, and limited social, professional, and personal activity. The estimated rate of CINV in chemotherapy patients amounts to 70% [1]. Persisting CINV may cause hydroelectrolytic imbalance, modify the primary treatment schedule, reduce the optimal doses of the drugs, and consequently decrease the efficacy of the anticancer therapy. The probability of the occurrence of CINV depends on the treatment scheme, the drug dose and administration route, and on patient-related factors.

Despite the easy accessibility of the antiemetic prophylaxis recommendations during chemotherapy,

the rates of CINV control and of adherence to supportive care standards remains unsatisfactory in clinical practice. This article reviews the process of introducing the antiemetic standards and analyses the difficulties in the use of the CINV prophylaxis recommendations in clinical practice.

## The standards of the antiemetic treatment — presentation

Drugs used in the prophylaxis of chemotherapy-induced nausea and vomiting (CINV)

Until the mid 1990s, pronounced CINV were one of the reasons to terminate chemotherapy. The introduction of the antagonists of the serotonin (5-hydroxytryptamine) binding to its type 3 receptors (5-HT<sub>3</sub>, 5-hydroxytryptamine receptor type-3) to the routine use

with chemotherapy with a high or moderate emetogenic potential, significantly limited the incidence of acute vomiting (occurring on the first day of the chemotherapy).

Until recently, delayed (usually starting on the second or third day of/post chemotherapy) vomiting remained an unresolved issue. The mechanism of delayed vomiting is independent of the serotonin pathways, so the efficacy of the serotonin antagonists 5-HT<sub>3</sub> is very low. The other cytokines (e.g. substance-P or noradrenaline) are mediators of delayed CINV. The use of the neurokinine-1 inhibitor (NK-1) receptor antagonist, mediated by substance-P, reduced the prevalence of delayed vomiting associated with highly or moderately emetogenic chemotherapy and improved patients' tolerance of the therapy.

According to the current recommendations, adequate use of both groups of drugs combined with corticosteroids leads to control of acute vomiting in 80–90% of patients, and of delayed vomiting in 60–80% of cases [2–7].

Another important issue is the presence of nausea, which at any intensity may impair the patient's quality of life (QoL). In studies evaluating the efficacy of antiemetic therapy, the occurrence of a grade 3 nausea influenced the overall CINV control rate. Irrespective of the intensity grade, the estimated rate of patients reporting acute nausea, despite the use of the antiemetic drugs and satisfying vomiting control, reaches 30%, and of delayed nausea may even exceed 50% [8]. Following recent data, olanzapine use at 10 mg per day over the first four days of therapy improves the control of highly and moderately emetogenic chemotherapy-induced nausea [9].

The results of the observation studies show that the CINV control rate is significantly lower in clinical practice compared to the indices reported in registration clinical trials [2, 10–12]. Based on the data from an observatory study of 200 patients receiving highly emetogenic chemotherapy, control of acute CINV was reached in 46%, and of delayed CINV in 61%, of patients [13]. In the analysis made in 2013, this percentage was significantly lower and totalled 30% and 40%, respectively [12]. The improvement of the CINV control was a result of the higher frequency of antiemetic prophylaxis use, according to the standards of the three-drug protocol (NK-1 receptor antagonist, 5-HT<sub>3</sub> antagonist, and dexamethasone). The better public reimbursement of the drugs included in the recommendation probably influenced the results.

Adherence to the recommendations of antiemetic prophylaxis

Multidrug antiemetic prophylaxis is a standard of care in patients receiving highly and moderately em-

etogenic chemotherapy schedules. Based on scientific data, a number of organisations, such as the Multinational Association of Supportive Care in Cancer (MASCC), the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN), established and regularly update the recommendations concerning the antiemetic prophylaxis [4, 14, 15]. Despite some differences, all recommendations are coherent in the key issues. The clinical value of each recommendation depends on its popularity, accessibility, and acceptance by the medical professional and primarily on the patients' and physicians' level of compliance.

It was observed that not respecting the guidelines results in a 30% increase of the CINV risk compared to the adequate prophylaxis [2, 6]. The current recommendations for antiemetic prophylaxis issued by the Polish Society of Clinical Oncology are almost concordant with the MASCC and ESMO recommendations [16].

During the ESMO congress in 2014, the results of the survey study, which analysed the current medical practice concerning aetiological and supportive treatment (including antiemetic therapy) were presented. The survey was made in five European countries. The analysis included data concerning the treatment of almost 60 thousand patients. In the group of chemotherapy patients 52.4% received an antiemetic therapy. In the study the highest rate of highly and moderately emetogenic chemotherapy programmes was seen in patients with non-Hodgkin lymphomas, colon cancer, and breast cancer. Despite the high percentage of antiemetic prophylaxis during highly and moderately emetogenic chemotherapy (including anthracyclines and cyclophosphamide-containing regimen, AC) in the analysed groups approximately 30% of patients did not receive the appropriate antiemetic prophylaxis. Only 12% of patients undergoing highly emetogenic chemotherapy, 14% receiving AC regimen, and 47% of patients treated with other, moderately emetogenic programmes received the antiemetic therapy as recommended in MASCC or ESMO guidelines.

In March 2015 a similar study was performed to evaluate the use of antiemetic prophylaxis in seven mid-European countries (including Poland). In total 356 oncologists participated in this study. Patients with a diagnosis of a breast, lung, colon, and ovary cancer were included. In Poland only 1% of patients receiving highly emetogenic chemotherapy and 4% on moderately emetogenic treatment did not receive any antiemetic agents. Based on the observations from this study, it was established that the patients had received antiemetic therapies not in line with the standards. Only half of the patients receiving chemotherapy with high and moderate emetogenic potential were treated following the MASCC or ESMO recommendations. In most coun-

Table 1. Drugs used in the consecutive days post highly emetogenic chemotherapy [13]

| Drug   | Day after chemotherapy (percentage of patients) |     |     |     |     |
|--------|---|-----|-----|-----|-----|
|        | n = 200 (100%)                                  |     |     |     |     |
|        | 1.  | 2.  | 3.  | 4.  | 5.  |
| aNK1   | 48%   | 46% | 43% | –   | –   |
| a5-HT3 | 94%   | 48% | 35% | 28% | 22% |
| dex    | 87%   | 60% | 51% | 34% | 11% |
| Other  | 16%   | 9%  | 8%  | 10% | 12% |
| None   | 1%  | 24% | 27% | 43% | 62% |

aNK1 — NK1 receptor antagonist; a5-HT3 — 5-HT3 receptor antagonist; dex — dexamethasone

tries the patients had received a suboptimal treatment. Defining the violation of the recommendations as an administration of the inappropriate drug combination and a modification of drug dose or frequency, in the Polish study amongst patients receiving chemotherapy with high risk of CINV (containing cisplatin, a dose over 70 mg/m<sup>2</sup>), only 25% obtained an antiemetic recommended prophylaxis (Tab. 1) [13].

An equally low percentage of American physicians used the CINV prophylaxis recommended by NCCN (29% in patients on highly emetogenic chemotherapy and 73% on a schedule of moderate emetogenic potential) [17].

Similar data were reported from European studies. The most frequent violations of the recommendations concerned the use of 5-HT3 receptor inhibitors were: higher dose than recommended, and the administration of this group of agents in the following days as a delayed CINV prophylaxis. Another common practice was the inadequate dosing of corticosteroids in both acute and delayed CINV prophylaxis, and the overuse of metoclopramide instead of corticosteroids in a delayed emesis prophylaxis. Compliance to the recommendations was high for the chemotherapy with a high emetogenic potential, whereas for the regimens with moderate or low CINV risk an excessive or unnecessary prevention was observed [18].

#### Reasons for noncompliance with the guidelines

The reasons for use of the CINV prophylaxis not in line with the current international and national guidelines are complex. Probably physicians do not know the recommendations well enough even if they declare the opposite. Another problem seems to be that the medical professionals ignore and underestimate the symptoms reported by patients. CINV are important problems for cancer patients. It was observed that — compared to the other side effects — even mild CINV are subjectively less well tolerated than memory loss or disorders, ototoxicity, febrile, and many other complications of

anticancer therapy [19]. On the other hand, patients often do not report CINV occurring after the final cycle of chemotherapy. This is probably caused by the opinion that vomiting ‘must’ accompany the systemic treatment.

Di Maio et al. compared the reporting of different side effects by patients and by physicians in a group of over 1000 patients enrolled into three clinical trials. In all three studies a 40% underestimation of the CINV by the physicians was shown [20], which concerned both the frequency and intensity of the side effects.

A direct comparison of symptoms reported by a patient and by a physician in a group of 467 patients during more than 4000 visits in the memorial Sloan-Kettering Cancer Centre in New York showed that patients reported symptoms significantly earlier and more often than the clinicians. Both analysed groups — patients and physicians — recorded the symptoms following the ‘Common Terminology Criteria for Adverse Events’ (CTCAE), defining the intensity (grade) of the side effects, set by the National Cancer Patients Institute. The highest difference (30%) between reporting CINV and their real incidence concerned delayed vomiting [8].

Communication difficulties between patient and physician are one of the mentioned causes of noncompliance with the guidelines, especially in the moderately emetogenic group. Lack of communication may convince a physician that preventive therapy is unnecessary. In a document by the New England Health Institute it was stated that 70% of cardiologists and 25% of orthopaedists follow the guidelines. The paper did not analyse the adherence to recommendations by oncologists [21].

A question directly addressing the adherence to recommendations is the appropriate evaluation of the risk of CINV. The tables describing the emetogenic risk of each cytotoxic agent are commonly known. However, in the total risk evaluations we do not include patient-related factors. It is suggested that new factors be included, analogously to the febrile neutropaenia risk scales, into the emetogenic risk evaluation system (sex, age, history of alcohol abuse, anxiety, chemotherapy-associated nausea and vomiting in the past, motion sickness, morning

sickness, and vomiting due to pregnancy). It mostly concerns patients undergoing chemotherapy with moderate emetogenic potential, which includes a broad range of CINV risks (30–90%). In clinical practice it is observed that after inclusion of the individual risk factors, a modification of the prophylaxis schedule may be necessary.

Special clinical situations, which may demand the modification of the recommended antiemetic prevention schedule, remain an unresolved issue. Corticosteroids are one of the basic drugs used in CINV prevention, both in monotherapy and in drug combinations. In some patients the use of corticosteroids is contraindicated due to co-morbidities (diabetes mellitus, chronic gastric or duodenal ulcer disease, and thromboembolic disease) or poor tolerance. In those cases there are no clear recommendations concerning the modification of the prophylaxis schedule. One could consider modifying the modification of the corticosteroid dose or using a drug from another group of antiemetics (e.g. benzodiazepine, thiethylperazine, olanzapine, dopamine antagonists).

The efficacy, in general control of CINV, of the antiemetic prophylaxis schedules, containing a single dose of corticosteroids combined with palonosetron, in patients treated with AC chemotherapy regimen, is comparable to the standard prevention schedules. However, the number of patients reporting nausea on the third day was higher in the arm receiving a single dose of dexamethasone [22]. The patients who received corticosteroids together with the premedication prior to chemotherapy (e.g. toxoids, pemetrexed) form another group. In these patients, it seems reasonable to reduce the single corticoid dose in antiemetic prophylaxis on the days when premedication is administered. Analysis of the efficacy of antiemetic prophylaxis reported no significant impact of the administration route of the corticosteroids. It is necessary to include the above-mentioned clinical situations into future recommendations. Lower efficacy of the antiemetic prophylaxis, despite adhering to the recommendation, may in some cases result from the changes in the pharmacokinetics of the substance. Drugs belonging to group of NK-1 receptor inhibitors are metabolised through the same enzymatic system — cytochrome P-450 — as many other drugs, which may promote the reciprocal drug interactions. Another cause of the insufficient control of the chemotherapy-associated CINV is disrespecting the late phase recommendations by the patients. In the following days after chemotherapy, antiemetic drugs are taken by patients on their own at home. The studies evaluating patients' compliance to the recommendations have a difficult methodology and are fraught with a high risk of error. However, their results and clinical observations suggest that the necessity of taking supplementary drugs becomes a problem when facing the polypragmasia in cancer patients. Making the schemes

simple and limiting the number of prescribed drugs may improve the discipline and the efficacy of the antiemetic prophylaxis.

A promising composed agent is a combination of netupitant (NK-1 inhibitor) with palonosetron. Used in a single dose on the first day of a cycle and combined with corticoid, it allows the administration of the antiemetic drugs to be skipped in the following days [23]. The effective control of CINV in the first five days post chemotherapy decreases the risk of anticipating vomiting prior to the next treatment cycle. The mechanism of the anticipating vomiting is not fully clear and has a psychogenic background [24]. European pharmaco-economic analyses suggest that there are benefits of proper CINV control. Chemotherapy-induced CINV of high intensity increase the general cost of the treatment. The difference results from the additional cost of the antiemetic drugs, supporting drugs, of rehydrating a patient, and in some cases of an unscheduled admission to the outpatient unit or to the hospital ward [25]. The indirect costs related to sick leave or to worse quality of life were not included in the analysis. There are numerous observational studies reporting that the recommendations are frequently ignored by physicians. Still, there are few data suggesting the efficacy of any activity aiming to convince the physicians that the recommendations, and routine use of the optimal antiemetic prophylaxis are very important.

The educational initiatives (interactive workshops, expert lectures) but also administrative activities (audits, interventions of pharmacists) need to be repeated to become effective in practice. It is crucial to improve the communication between the medical staff and the patient. One of the practiced methods is introducing validated, simplified dairies of CINV observations into clinical practice. An exemplary diary proposed by MASCC is filled by a patient twice — after the first and on the fifth day of a chemotherapy cycle [26]. The correlation of a simplified version of a diary with questionnaires filled in daily is high and exceeds 70%. Another method that can potentially improve the use of the recommended antiemetic prophylaxis is to modify the computer programmes commonly used in hospitals to generate an electronic chemotherapy prescription.

Introducing adequate prophylaxis added to a chemotherapy regimen, depending on its emetogenic potential, may help physicians to prescribe the optimal CINV prevention schedule.

## Summary

Supportive treatment is an inseparable part of anticancer therapy. Preventing the side effects of anticancer treatment often influences the effectiveness of the therapy. Even though the chemotherapy-induced CINV

prophylaxis recommendations are commonly accessible, they are not highly strictly followed. As a consequence, the CINV control ratio is lower in clinical practice than observed in clinical studies of new antiemetic drugs. Only a comprehensive approach to the compliance to the recommendations could improve the CINV control and decrease the costs of treatment [27, 28].

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