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*Review*

# NAUSEA AND VOMITING ASSOCIATED WITH CHEMOTHERAPY AND PRINCIPLES OF MANAGEMENT IN THEIR PREVENTION

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**ABSTRACT**

Nowadays, there are many effective cancer treatments that use different combinations of chemotherapeutics agents to destroy cancer cells, often in advanced stages when radical surgery methods are no longer possible. Unfortunately, the toxicity of treatment can cause many side effects. One of them is nausea and vomiting, which significantly affects the quality of life and is a challenge for cancer patients. Nausea and vomiting affect 40-80% of patients receiving chemotherapy and/or radiotherapy. The likelihood of their occurrence depends on the treatment regimen, dose and route of administration. Of course, patient-related factors also play a role. The use of combination antiemetics, including setrons in combination with a neurokinin-1 (NK-1) receptor antagonist and glucocorticosteroids, can effectively prevent nausea and vomiting - in the early type in about 80-90% of patients and in the late type in about 60-80%. Nausea and vomiting can significantly reduce the quality of life of patents undergoing cancer treatment. However, adherence to an appropriate treatment regimen ensures that patients have an optimal quality of life during treatment. This article discusses current strategies for the prevention and treatment of nausea and vomiting using antiemetic drugs.

**KEYWORDS:** vomiting; nausea; chemotherapy; guidelines; glucocorticosteroids



## 1. Introduction

According to the report of the National Institute of Public Health - National Research Institute, malignant tumors statistically constitute the second cause of death in Poland [1]. According to data received by the National Cancer Registry, in 2020, almost 146,200 patients were diagnosed with cancer, of whom 99,900 died from it [2]. In advanced stages, most patients experience metastasis, which requires combined treatment. Treatment methods include local approaches as surgery and radiotherapy, as well as systemic methods such as chemotherapy, hormone therapy, immunotherapy, and targeted therapy [3]. Chemotherapy is often used in combination with other methods and can be a stand-alone treatment for some specific cancers [4].

However, it is associated with various early and late side effects, with common complications including:

- hematologic complications, including neutropenia, thrombocytopenia, and anemia;
- nausea and vomiting;
- inflammation of the gastrointestinal mucosa;
- diarrhea;
- thrombotic complications;
- reactions after drug infusion;
- organ damage, including neurological disorders;
- skin manifestations;
- hair loss [5].

Therefore, it is very important to prevent troublesome side effects. Nausea and vomiting affect about 80% of patients without prophylactic antiemetic treatment. They can lead to electrolyte disordes, weakness, loss of appetite, deterioration of the patient's physical and mental condition, negatively affecting the quality of life and reducing motivation for further treatment, and sometimes, even leading to treatment abandonment [6].

**2. Factors predisposing to nausea and vomiting during chemotherapy**

Factors predisposing to nausea and vomiting during chemotherapy include:

1. Age - more likely in patients <50 years.
2. Gender - nausea and vomiting are more common in women.
3. Cancer types - gastrointestinal and hematologic cancers [7,8].

The emetogenic potential of anticancer drugs determines the frequency of nausea and vomiting during chemotherapy.There are four risk levels:

- High (frequency of nausea and vomiting >90%),
- Medium (frequency of nausea and vomiting 30%-90%),
- Low (frequency of nausea and vomiting 10%-30%),
- Minimal (frequency of nausea and vomiting <10%) [7].

Chemotherapeutics agents with high emetogenic potential include: chlormethine, cisplatin, cyclophosphamide ≥ 1500 mg/m$^2$, dacarbazine, doxorubicin ≥ 60 mg/m$^2$, epirubicin > 90 mg/m$^2$, ifosfamide ≥ 10 g/m$^2$, carmustine > 250 mg/m$^2$, procarbazine, streptozotocin, and all regimens consisting of an anthracycline and cyclophosphamide (e.g. AC, FAC, TAC) [10].

**3. Pathophysiology of nausea and vomiting**

Nausea is defined as a subjective, unpleasant feeling of the need to vomit. In addition, it is often accompanied by symptoms from the autonomic nervous system, such as - pale skin, cold sweats, salivation or tachycardia. Vomiting is a sudden, violent expulsion of food content from the stomach through the mouth. If the volume of vomiting is significant, expulsion of content through the nose also often occurs. Vomiting is a complex proces, which involves the gastrointestinal tract, diaphragm and abdominal muscles [11]. Elements of the central and peripheral nervous system, receptors and neurotransmitters (serotonin, dopamine, norepinephrine, histamine), which participate in the development of symptoms, play a significant role in the pathopysiology.

Nausea and vomiting are complaints that more often affect women - the exact cause is unknown, probably related to greater sensitivity to opioid analgesics, cytostatics and other drugs and the type of cancer [12].

The pathophysiology of nausea and vomiting is not fully understood. It is certain that they perform the body's defense functions by preventing toxic substances from entering the bloodstream from the digestive tract [15].

**4. Vomiting prevention**

The main drugs with anti-emetic effects are 5-HT3 receptor antagonists, NK-1 receptor inhibitors and corticosteroids.

Nausea and vomiting occurring with chemotherapy treatment is divided into two types: early type, i.e. occurring on day 1 of chemotherapy, and late type, i.e. occurring on day 2 and subsequent days of treatment [13,16]. Drugs with antagonistic effects against the 5-HT3 receptor, namely setrones: ondansetron, granisetron, dolasetron, palonosetron, tropisetron, are gaining prevalence in the treatment of nausea and vomiting of the early type. They are used for chemotherapy with high or medium emetogenic potential. However, when it comes to nausea and vomiting of the late type, palonosetron, due to its prolonged action on the 5-HT3 receptor, and drugs with antagonistic action against the NK-1 receptor, are applicable with chemotherapy with high emetogenic potential. The efficacy of NK-1 rec. inhibitors is greater if used together with 5-HT3 inhibitors and corticosteroids on day 1 of anti-emetogenic therapy. Of the NK-1 rec. antagonists, aprepitant and netupitant are the most commonly recommended. It is worth remembering that aprepitant reduces the effectiveness of oral hormonal contraception, so during its intake and 28 days after the end of treatment, contraceptive methods should be modified. The third group of drugs used in anti-emetic therapy are corticosteroids, of which dexamethasone is the most commonly used, methylprednisolone less often. When added to other antiemetic drugs, they increase their effectiveness [9].

As with all drugs, anti-emetic drugs can cause side effects, but they are relatively rare. The most common side effects of setrones include headache and dizziness, sudden flushing of the skin and feeling of heat, hiccups, fatigue, constipation, transient and slight elevation of liver enzymes [5,17]. There may also be minimal changes in electrograms (except for palonosetron). Aprepitant, on the other hand, may cause hiccups, weakness, increased aminotransferases, anorexia, constipation or diarrhea, pain and dizziness [18]. In the case of corticosteroids, side

effects are of limited significance due to the short duration of use [6,17,16].

According to current data, with the appropriate use of a three-drug regimen (NK-1 receptor antagonist, 5-HT3 antagonist and dexamethasone), control of nausea and vomiting of the early type can be achieved in 80-90% of patients, and of the late type in about 60-80% of patients [13].

Complementary drugs can be included to increase the effectiveness of therapy: drugs with antagonistic effects against the D2 receptor, butyrophenone derivatives, phenothiazine derivatives, antihistamines and thienobenzodiazepines.

Of the drugs with antagonistic effects against the D2 rec, the main one is metoclopramide, which also shows low affinity for the 5-HT3 rec. Metoclopramide shows similar effectiveness to setrones in the treatment of late-type NV (nausea and vomitibg) with chemotherapy with low emetogenic potential. In contrast, it is less important in the treatment of early-type NV. Side effects include dystonic reactions, muscle tremors, lethargy and diarrhea. Phenothiazine derivatives have limited use due to their low activity. Antihistamines are used in premedication for chemotherapy that can cause sensitization reactions and for NV of the anticipatory type. Olanzapine, which belongs to the thienobenzodiazepine group, has found use in the treatment of NV in combination with setron and dexamethasone, using chemotherapy with high and intermediate emetogenic potential. However, it is important to remember not to combine olanzapine with metoclopramide due to extrapyramidal reactions [6,9].

In addition to pharmacological solutions, there are also natural ways to deal with nausea and vomiting. These include ginger eaten raw or added to tea, lemon juice, which when mixed with warm water, helps with nausea, aids digestion and to some extent, eliminates flatulence. Also, chili peppers containing capsaicin, which inhibits the vomiting center in the medulla oblongata by releasing special neurotransmitters. Capsaicin restores appetite and is a natural analgesic and anti-inflammatory. In addition, peppermint and garden mint rubbed on the gums or added to food reduces nausea. Inhaling the scent of mint can also be helpful. Coconut milk, sesame milk and flaxseed can also be used to relieve gastrointestinal discomfort. In addition, it's important to remember to properly hydrate the body and replenish electrolyte balance [19].

**5. General principles of management in the prevention of nausea and vomiting**

1. Assessment of the degree of emetogenicity of the planned chemotherapy.

2. Individual characteristics of the patient.

3. Selection of antiemetic drugs based on the collected information.

4. Use of combined therapy (taking into account the lowest effective doses of drugs).

5. Selection of the route of administration of antiemetic drugs (preferred intravenous route).

6. Implementation of antiemetic prophylaxis at an early stage of oncological treatment.

7. Evaluation of the effectiveness of the applied therapy (lack of the expected effect - taking into account other causes of nausea and vomiting for which drugs from the group of 5-HT3 and NK-1 receptor antagonists are ineffective, such as gastrointestinal obstruction, cerebral edema, electrolyte disorders).

8. Emergency treatment when first-line therapy is ineffective [6,16].

**6. Detailed rules of conduct**

In cases of high risk of nausea and vomiting (possible vomiting in more than 90% of patients), i.e. when using high-dose chemotherapy, combination regimens, regimens containing cisplatin or carboplatin (dose above 4 mg/mL), triple-drug prophylaxis is recommended: anti-5-HT3, anti-NK1 and corticosteroid. When using chemotherapy with high emetogenic potential, the risk of nausea and vomiting of the early type as well as both the late type is high. In the case of nausea and vomiting of the early type, better control is achieved. Adequate early and effective prophylaxis of early-type complaints avoids late-type complaints. It is important to remember that gradually increasing the dose of drugs or prolonging the use of anti-emetic prophylaxis is not justified [20].

At intermediate risk of nausea and vomiting (vomiting possible in 30-90% of patients), the risk of late-type complaints is much lower than the early type. For this reason, dual-drug therapy based on anti-NK1 and a corticosteroid is recommended. In addition, a benzodiazepine or chlorpromazine may be included [20].

Management of chemotherapy with low emetogenic potential (vomiting possible in 10-30% of patients) includes the use of only a corticosteroid on the day of chemotherapy administration.

In the situation of chemotherapy with minimal risk of nausea and vomiting (vomiting possible in <10%patients), it is recommended to use prophylaxis only in the situation of discomfort.

At the same time, supportive management should be kept in mind, such as proper hydration of the patient, equalization of electrolyte disturbances, sometimes the use of sedatives and psychotherapy. Proper nutrition should also be kept in mind, i.e. eating easily digestible meals at room temperature, in small portions [21].

**7. Rescue treatment**

If treatment for preventing nausea and vomiting fails, rescue treatment with a different mechanism of action or treatment with a higher antiemetic potential is implemented. In these patients, other causes of these symptoms should be excluded at the beginning, and treatment should also include adequate hydration, correction of electrolyte disorders and an appropriately selected diet. Benzodiazepines, metoclopramide or chlorpromazine can be used in rescue treatment. In situations where CTH (chemotherapy) with a low emetogenic potential is administered, the use of 5-HT3

receptor inhibitors is recommended, while in the case of CTH with an intermediate emetogenic potential, it is appropriate to include an NK1 antagonist in the treatment. However, it should be noted that in the case of 5-HT3 receptor inhibitors and NK1 antagonists, both increasing the dose and extending the duration of treatment do not improve the control of these symptoms [14]. Current studies indicate the efficacy of oral olanzapine in the treatment of transient nausea and vomiting [15]. For palliative chemotherapy, CTH with less emetogenic potential should be considered.

**8. Radiotherapy**

Radiotherapy is a common cause of nausea and vomiting in cancer patients, and studies indicate that these symptoms occur to varying degrees in 80% of patients undergoing this method of therapy [22]. The emetogenic potential depends on the strategy and area irradiated. The Radiation Therapy Antiemetic Research Group analyzed the prevalence of these symptoms in patients who received various types of radiotherapy [23]. The occurrence of nausea, vomiting or both was declared by 28% of patients. In contrast, treatment was administered to 17% of patients, of whom 12% received prophylactic treatment and 5% received ad hoc treatment. Symptoms caused by radiotherapy significantly impair patients' quality of life, and research shows that appropriate treatment or prevention is not used often enough [24].

Studies to date have proven the superiority of serotonin antagonists over other drugs in preventive treatment [25-28]. However, ondansetron and dolasetron have shown superiority over placebo or metoclopramide. Compared to placebo, fewer patients experienced residual vomiting when treated with ondansetron or dolasentron (40% vs. 57%), and fewer patients required rescue treatment (6.5% vs. 36%) [29]. However, nausea control appears to be more difficult with this treatment, and most patients experienced nausea despite treatment (70% vs. 83% in the placebo group) [30]. It should be noted that studies indicate that NIV is more likely to be controlled with 5-hydroxytryptamine-3 (5-HT3) receptor antagonists than metoclopramide, phenothiazine or placebo in patients undergoing upper abdominal irradiation [25-28]. In randomized studies comparing different 5-HT3 receptor antagonists did not obtain clear results, and the optimal timing of prophylaxis and treatment before, during and after the administration of radiotherapy should be determined [31]. Corticosteroids seem to be a good alternative for antiemetic treatment due to their widespread availability and low cost. A randomized trial conducted with dexamethasone showed its high efficacy in patients receiving radiotherapy to the epigastric area [32]. NK-1 receptor antagonists have an important role in the treatment of nausea and vomiting in patients undergoing chemotherapy, while there are no clear results of their effects in patients undergoing radiotherapy. Studies have shown limited effectiveness in preventing or treating nausea and vomiting in radiation therapy with drugs such as prochlorperazine, metoclopramide and cannabinoids, although they can be used to treat patients with milder symptoms and as rescue agents [33].

**9. Nausea and vomiting during chemotherapy in pregnant women**

Nausea and vomiting during chemotherapy in pregnant women is a very common problem – it affects up to 80% of women. Unfortunately, there are no specific treatment guidelines. The safest and most effective drug seems to be ondansetron (FDA category B) [34]. In the case of drugs from the 5-HT3 receptor antagonist group and for aprepitant, there are insufficient studies on the safety of use during pregnancy and breastfeeding [20]. As for metoclopramide (FDA category B, similar to ondansetron), there are reports of teratogenic effects on animal embryos, and the drug is not recommended for use in the first trimester of pregnancy. As reported in a large cohort study conducted in Denmark, ondansetron used for emantogenic prophylaxis during chemotherapy in pregnancy does not increase the frequency of miscarriages, premature births and congenital malformations, nor does it adversely affect the birth weight of newborns [35].

**10. Effectiveness of antiemetic treatment**

Up to half of people receiving antiemetic prophylaxis do not receive it correctly. Failure to bring ongoing prophylaxis in line with current recommendations is common, and the reasons for this are complex. Knowledge of the guidelines is insufficient and downplaying of symptoms by patients is quite common.

**11. Summary**

In summary, prevention and appropriate treatment of nausea and vomiting is a key element of patient care during cancer treatment. The aim is to improve the quality of life and comfort of patients. A review of studies and literature shows the benefit of using multi-drug regimens (5-HT3 anatagonists, NK1 antagonists, corticosteroids) instead of monotherapy, especially in the case of chemotherapy with a high emetogenic potential. In addition, patient education and continuous monitoring and adjustment of therapy are important. Such a combined approach allows for effective treatment of nausea and vomiting during chemotherapy.

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