Chemotherapy- and radiotherapy--induced nausea and vomiting

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Table of contents

According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. *The quality of scientific evidence*
   I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-randomized cohort studies)
   III — Scientific evidence obtained from retrospective observational studies or case-control studies
   IV — Scientific evidence obtained from clinical experiences and/or experts, opinions
2. *Category of recommendations*
   A — Indications confirmed unambiguously and absolutely useful in clinical practice
   B — Indications probable and potentially useful indications in clinical practice
   C — Indications determined individually

Introduction

Nausea and vomiting (N&V) constitute the side effects of anticancer therapy and are particularly frequent during chemotherapy (CTH) and radiotherapy (RT). Prevention and alleviation of the intensity of N&V is important due to the negative impact on quality of life (including decreased motivation to continue therapy and, in extreme cases, resignation from therapy) as well as a risk of development of fluid-electrolyte imbalance, loss of appetite, and worsening of the patient's performance status.

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Table 1. Intensity of nausea according to WHO criteria [4]

Grade I	Grade II	Grade III	Grade IV	Grade V
Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Disorders of oral intake of liquids and solid foods	No oral caloric intake, severe nausea, the symptoms are continuous	Death

Appropriate prevention of N&V is the most effective method of reducing the risk of developing the above-mentioned consequences of N&V.

Chemotherapy-induced nausea and vomiting

Depending on the administered CTH regimen and some other patient- and therapy-dependant factors, N&V may occur in 70–80% of patients who do not receive prophylactic antiemetic therapy. The classification, which is based on the length of the interval between the administration of CTH and the onset of N&V [1, 2] differentiates the following types of N&V:

— early (occurring in the first 24 hours, usually after several minutes to several hours after administration of CTH and achieving maximal intensity after 5–6 hours);
— late (occurring after 24 hours and usually achieving maximal intensity 48–72 hours after administration of CTH and persisting for 3–7 days);
— anticipatory (occurring before the administration of a consecutive dose of CTH, affecting 20–60% of patients and usually consisting of nausea without vomiting).

The occurrence of early N&V is a risk factor of delayed symptoms. However, in 25% of patients late N&V are seen without acute symptoms. Sometimes late N&V becomes persistent and continues for up to several days (so-called prolonged N&V) [1, 2].

The anticipatory N&V is usually related to some psychogenic factors and affects patients in whom the previous antiemetic management was not effective. Stimulation of the cortical centres is a key factor in this type of N&V, and the classical antiemetic drugs are ineffective (except for anxiolytics). In this situation, drugs with an unspecific mechanism of activity, directed towards the type 1 histamine receptors may be additionally used.

All types of N&V may be accompanied by general symptoms (anxiety sensation, excessive sweatening, increased saliva secretion, vertigo, loss of appetite or anorexia associated with anxiety about the occurrence of N&V, sensation of fullness in stomach even after small meals) [1, 2].

Pathogenesis and risk factors

The pathomechanism is complex and specific for a particular type of N&V. Generally, activation of the trigger centre in the area located in the fundus of the IV chamber and of the brain trunk (area postrema) results in N&V. The activation of the trigger zone in the central nervous centre (CNS) is a result of direct activation of the receptors by the factors delivered by blood or by the cerebrospinal fluid, or of the indirect activation through the vagus nerve of the receptors in the pharynx and in the gastrointestinal tract. The activation of the trigger centre may also occur during the stimulation of the vestibular apparatus (typical for the platinum derivatives) or through the stimulation of the cortical centres (psychogenic effect, olfactory and vision disturbances). The transduction of the signal of the emetic reaction, except for the type induced by stimulation of the cortical centres, is done by numerous neurotransmitters (serotonin, dopamine, acetylcholine, histamine, neurokinin, or noradrenaline) [2]. Preventive management is based on the mechanism of induction of N&V. The concept of this approach is to interrupt the reaction through the inhibition of the activity of the receptors of the individual neurotransmitters.

The most important neurotransmitters and receptors that cause early N&V include primarily serotonin [5-hydroxytryptamine (5-HT)] and serotonin receptor type 3 (5-HT3) as well as dopamine and dopamine receptor type 2 (D2). The introduction into clinical practice 5-HT3 antagonists agents that block the binding of 5-HT to 5-HT3 receptor) increased the efficacy of the prevention of early vomiting and — to a lesser extent — of nausea. The drugs that block the D2 receptor are less efficient (especially in the case of the CTH with high and moderate emetogenic potential), and in addition they induce some important side effects [1–3].

The pathomechanism of the late N&V is different, which is confirmed by weak efficacy of the 5-HT3 receptor antagonists. Substance P plays a major role in the transduction of the signal stimulating the emetogenic reaction. Substance P is a neuropeptide that binds to neurokinin receptor type 1 (NK-1), which through neurokinin may activate the trigger centre in the CNS. The

Table 2. Intensity of the vomiting according to the WHO criteria [4]

Grade I	Grade II	Grade III	Grade IV	Grade V
1 episode in 24 hours	2–5 episodes in 24 hours	> 6 episodes in 24 hours	> 10 episodes in 24 hours	Death

Table 3. The emetogenic potential (risk) of the anticancer drugs [3, 4]

Risk group	Frequency	Drug/dose
High	> 90%	Chlormethine, cisplatin, cyclophosphamide ≥ 1500 mg/m^2, dacarbazine, doxorubicin ≥ 60 mg/m^2, epirubicin > 90 mg/m^2, iphosphamide ≥ 10 g/m^2, carmustine > 250 mg/m^2, streptozotocin, procarbazine, and all schedules including anthracycline and cyclophosphamide (e.g. AC, FAC, TAC)
Moderate	30–90%	Aldesleukin > 12 mln IU/m^2, alemtuzumab, altretamine, amifostine > 300 mg/m^2, azacitidine, bendamustine, bosutinib, busulfan, ceritinib, cyclophosphamide < 1500 mg/m^2, cytarabine > 1000 mg/m^2, dactinomycin, daunorubicin, doxorubicin < 60 mg/m^2, epirubicin ≤ 90 mg/m^2, estramustine, hexamethylmelamine, idarubicin, imatinib, ifosfamide < 10 g/m^2, interferon alfa ≥ 10 mln IU/m^2, interleukin-2 > 12–15 mln IU/m^2, irinotecan, carboplatin, carmustine ≤ 250 mg/m^2, clofarabine, crizotinib, lomustine, melphalan, methotrexate ≥ 250 mg/m^2, mitotane, oxaliplatin, temozolomide, arsenictrioxide, trabectedin, trifluridine-tipiracil, vinorelbine (oral formulation)
Low	10–30%	Afatinib, aflibercept, axitinib, aldesleukin ≤ 12 mln IU/m^2, emetasinealdo-trastuzumab, amifostine < 300 mg/m^2, atezolizumab, bortezomib, brentuximab, cetuximab, cytarabine ≤ 1000 mg/m^2, dabrafenib, dasatinib, docetaxel, liposomal doxorubicin, eribulin, etoposide, everolimus, floxuridine, fludarabine, fluorouracil, gemcitabine, ibrutinib, ixabepilone, interferon alfa 5–10 mln IU/m^2, cabazitaxel, liposomal formulation of irinotecan, ipilimumab, capecitabine, carfilzomib, lapatinib, lenalidomide, methotrexate > 50 mg/m^2 as well as < 250 mg/m^2, mitomycin, mitoxantrone, nilotinib, olaparib, paclitaxel (conventional and liposomal formulation), pazopanib, pemetrexed, pentostatin, regorafenib, sunitinib, thiotepa, topotecan, vinflunine
Minimal	< 10%	Alectinib, alemtuzumab, asparaginase, bevacizumab, bleomycin, chlorambucil (orally), cytarabine < 100 mg/m^2, daratumumab, dasatinib, dexrazoxane, erlotinib, everolimus, fludarabine, gefitinib, hydroxyurea (oral formulation), interferon alfa < 5 mln IU/m^2, cabozantinib, cladribine, melphalan (oral formulation), lapatinib, lenalidomide, mercaptopurine, methotrexate < 50 mg/m^2, nelarabine, nilotinib, nivolumab, ofatumumab, osimertinib, palbociclib, panitumumab, pazopanib, pentostatin, pomalidomide, ramucirumab, rituximab, sorafenib, thalidomide, temsirolimus, tioguanine, trastuzumab, trametinib, vandetanib, vemurafenib, vinblastine, vindezine, vincristine, vinorelbine (intravenous formulation), vismodegib, vorinostat

Levels of evidence and grades of recommendations — I, A

inhibitors of the NK-1 receptor are effective in the prevention of late N&V, and their activity in the prevention of acute N&V indicates that substance P and receptor NK-1 influence the occurrence of acute symptoms. The pathogenesis of late N&V also depends — although to a lesser extent — on some other neurotransmitters (e.g. dopamine and noradrenaline) as well as on some additional mechanisms that directly stimulate the CNS (e.g. transitional oedema of the brain after administration of platinum derivatives) [1–4].

The intensity of N&V is classified according to the World Health Organisation (WHO) (Tab. 1 and 2) [1]. Assessment of the expected severity of N&V during the CTH is crucial in determining the appropriate management.

The intensity of N&V depends mostly on the risk of symptoms occurrence (so-called emetogenic potential) after the administration of each particular anticancer drug in patients who do not receive prophylactic management [3–5]. The drugs may have a high (> 90%), moderate (30–90%), low (10–30%), or minimal (< 10%) emetogenic risk (II, A) (Tab. 3). The aforementioned emetogenic risk groups are mainly related to early N&V. The combination of two or more drugs (e.g. anthracyclines and alkylating agents in an AC regimen) may result in a synergistic increase of the emetogenic risk. In multidrug schedules the expected emetogenic risk is determined by the drug with the highest emetogenic potential. The emetogenic potential of the individual drug is of no importance for high-dose

CTH, that represents a high emetogenic potential independently from the used schedule. Due to a different mechanism, the above-presented classification does not apply to anticipatory N&V. The classification of N&V risk is actualised in parallel with the introduction of new anticancer drugs.

Except for the emetogenic potential of the used drugs, the risk of the occurrence of N&V depends on the patient's characteristics. Young persons and females (especially females who have a history of severe vomiting during pregnancy), as well as persons with travel sickness and the presence of so-called spontaneous morning sickness, have a higher predisposition to develop N&V and lower efficacy of the preventive management. A lower tendency to develop intensive N&V is observed in patients with strong motivation to receive anticancer treatment and in good general condition as well as in patients who have a history of alcohol abuse (over 100 grams of ethanol per day). The tolerance of previously administered CTH is a good predictor of the intensity of N&V. A role in predicting N&V intensity has a tolerance of prior CTH; a risk is higher in case of previous symptoms, whereas good control of N&V during previous CTH may result in less intense symptoms (including — low risk of anticipatory N&V. All the above listed factors should constitute a basis to define the risk of N&V in an individual patient and to choose the appropriate management as well as to modify antiemetic therapy during chemotherapy [6].

Antiemetic drugs

Basic antiemetic therapies are 5-HT3 receptor antagonists, NK-1 receptor antagonists and corticosteroids (Tab. 4).

Serotonin 5-HT3 receptor antagonists

The individual drugs from the group of 5-HT3 receptor antagonists (setrons) have different chemical structure and pharmacokinetic parameters, but they are characterised by a similar activity and toxicity profile (palonosetron constitutes an exception due to higher affinity to the receptor and a longer half-life compared to ondansetron and other 5-HT3 antagonists). The higher efficacy of the 5-HT3 antagonists compared

Table 4. Antiemetic drugs from the 5-HT3 i NK-1 antagonists group and corticosteroids

Drug	Usualdosing	Administration schedule
5-HT3 antagonists		
Dolasetron	100 mg *p.o.*	1 hour prior to CTH — day 1
Granisetron	1 mg or 0.01 mg/kg *i.v.*	1 hour prior to CTH — day 1
	1–2 mg *p.o.*	1 hour prior to CTH — day 1
Ondansetron	8 mg or 0.15 mg/kg *i.v.*	1 hour prior to CTH — day 1
	8–16 mg *p.o.*	Every 12 hours — day 1
Tropisetron	5 mg *i.v.*	1 hour prior to CTH — day 1
	5 mg *p.o.*	1 hour prior to CTH — day 1
Palonosetron	0.25 mg *i.v.* 0,5 mg *p.o.*	1 hour prior to CTH — day 1
	0.5 mg *p.o.*(product containing palonosetron and netupitant)	1 hour prior to CTH — day 1
NK-1 antagonists		
Aprepitant	125 mg *p.o.* on day 1	1 hour prior to CTH — day 1
	80 mg *p.o.*	Day 2 and day 3
Netupitant	300 mg *p.o.* in combination with palonosetron 0.5 mg *p.o.* (the product containing both drugs) — day 1	1 hour prior to CTH — day 1
Corticosteroids		
Dexamethasone	8–12 mg *i.v.* or *p.o.*	0.5–1 hour prior to CTH — day 1
	8–16 mg *p.o.**	Days 2–4
Methylprednisolone	40–125 mg *i.v.*	1 hour prior to CTH

*In patients receiving the NK-1 antagonists, use of dexamethasone is recommended in a dose of 8–12 mg on day 1 and 8 mg on days 2–4; *p.o.*— orally; *i.v.* — intravenously; CTH — chemotherapy

to other drugs (e.g. D2 receptor antagonists) in the prevention of early N&V induced by CTH of high and moderate emetogenic risk (I, A) has also been proven. Their activity does not depend on the type of cytotoxic agent or on the route and mode of administration of the antiemetic drug — intravenous, oral (tablet, syrup), transrectal (suppository), or transdermal as well as on the dosing schedule (the efficacy of a single daily dose and of the multiple divided doses is comparable) [7, 8]. The advantage of the 5-HT3 inhibitors over other drugs in the prevention of the late N&V has not been demonstrated. The only exception is palonosetron, which, due to its prolonged activity against the 5-HT3 receptor prevents early N&V and reduce late symptoms (I, A), that has been demonstrated in several clinical studies and in a meta-analysis [9]. Drugs that are antagonists of 5-HT3 receptors show no activity in the case of the anticipatory N&V and emesis caused by factors other than anticancer therapy (except for the use of setrons in the therapy of postsurgical N&V; indication included in the SPC). The side effects of setrons are relatively rare and the most common include headaches, transitory and mild elevation of liver enzyme activity, and constipation.

The constipation induced by 5-HT3 antagonists may significantly influence the quality of life. In case of occurrence of this complication the demand for setrons should be evaluated and the dose reduction as well as addition of a drug with a different antiemetic mechanism (e.g. D2 antagonist or dexamethasone) considered. Due to the mechanism of setrons-induced constipation (paralytic mechanism), classic laxative drugs may be ineffective (e.g. lactulose). Provided that the opioids have an additive constipatory effect, a modification of the analgesic therapy may be considered [4].

After the use of ondansetron and of granisetron and dolasetron the electrocardiography (ECG) may show some disorders of the sub-form of PR and QT prolongation. These disorders usually do not cause any symptoms; however, they may sometimes result in heart arrhythmia (patients with coexisting cardiac arrhythmias and other heart diseases as well as with hypokalaemia or hypomagnesemia). Heart condition should be monitored in patients with the presence of the above-mentioned risk factors, who receive setrons [4, 5]. Cardiac disorders have not been observed during the administration of palonosetron.

NK-1 receptor antagonists

The mechanism of action of NK-1 receptor antagonists, explains their efficacy in the therapy of the early and late N&V induced by chemotherapy with a high or moderate emetogenic potential [4, 5]. These data are confirmed by the results of many randomised clinical trials, which have been summarised in a systemic review (I, A) [10]. Among the drugs belonging to the discussed group, aprepitant and netupitant (accessible as a formulation combined with palonosetron) are reimbursed in Poland.

The clinical trials demonstrated higher efficacy of the combination of NK-1 antagonist with 5-HT3 inhibitors and with corticosteroids on the first day of therapy (I, A) [2, 4, 5, 10, 11]. Aprepitant should be administered during three consecutive days (on day 2 and day 3 in combination with dexamethasone and without any 5-HT3 antagonist), while a formulation of the netupitant in combination with palonosetron should be used only on day 1 (consecutive days — dexamethasone only). Both agents are the CYP3A4 enzymes inhibitors that require a reduction of the dose of dexamethasone (day 1 — 8–12 mg, days 2–4 — 8 mg). For the same reasons, any other drugs should also be used with caution (e.g. warfarin). The choice of NK-1 receptor antagonist should depend on the convenience of administration and cost of therapy, as well as superiority of netupitant over aprepitant in terms of better control of N&V, which has been proven in head-to-head comparisons.

Corticosteroids

The exact mechanism of the antiemetic activity of corticosteroids is unknown. The anti-oedematous effect on the CNS matters. Clinical trials have shown that the addition of corticosteroids to the other antiemetic drugs increases their efficacy [8, 10]. The corticosteroids show also some activity in the prevention of late N&V. In clinical practice dexamethasone is the most frequently used corticosteroid (less frequently — methylprednisolone). The typical side effects of corticosteroids are not clinically significant in the prevention of N&V due to the short period of their administration.

Adjuvant drugs

An adjuvant effect (lower antiemetic activity) is seen in receptor D2 antagonists, phenothiazine derivatives, butyrophenone derivatives, antihistaminic drugs, and benzodiazepines (Tab. 5) [4, 5].

Receptor D2 antagonists

Metoclopramide is used in clinical practice. The main mechanism of metoclopramide activity is inhibition of the activity of the D2 receptor; however, this drug also has some (significantly lower than setrons) affinity to the 5-HT3 receptor. The efficacy of metoclopramide in the prevention of early N&V induced by chemotherapy with a high or moderate emetogenic potential is significantly lower than that of setrons. Metoclopramide and setrons show similar efficacy in late N&V and complaints induced by chemotherapy with low emetogenic potential. Some reversible side effects (dystonic reactions, muscle

Table 5. Antiemeticdrugs — adjuvants

Drug	Usualdosing	Administration route
Metoclopramide	1–2 mg/kg *i.v.*	Before CTH and after 2 hours
Prochlorperazine	10–30 mg *i.v.*	Every 6–8 hours during the CTH
	10–20 mg *p.o.*	Every 6–8 hours during the CTH
Chlorpromazine	12.5–50 mg *i.v.*	Every 6–8 hours during the CTH
	10–25 mg *p.o.*	Every 6–8 hours during the CTH
Clonazepam	0.5–2 mg *i.v.*	Every 4–6 hours during the CTH
	0.5–1 mg *p.o.*	In the evening and in the morning before CTH — anticipatory N&V
Droperidol	1 mg *i.v.*	15 minutes before CTH and then if necessary every 6 hours
Olanzapine	5–10 mg *p.o.*	1 × daily on the day of CTH and for 3 days after the completion of chemotherapy (prevention) 1 × daily for 3 days (therapy)
Thiethylperazine	6.5 mg *p.o.* or *p.r.*	Every 4–6 hours during the CTH and after the completion of therapy
	6.5 mg *i.v.*	Every 8–24 hours — severe N&V

p.o. — orally; *i.v.* — intravenously; *p.r.* — per rectum; CTH — chemotherapy; N&V — nausea and vomiting

tremor, and sleepiness) may occur during therapy with metoclopramide, especially in young persons. In contrast to setrons, metoclopramide does not cause constipation (on the contrary, due to the pro-kinetic effect onto the gastrointestinal tract it may sometimes induce diarrhoea). The metoclopramide is contraindicated in patients with the risk of sub-ileocolitis.

Phenothiazine derivatives

The use of drugs from the group of phenothiazine derivatives is limited due to their low antiemetic activity.

Butyrophenone derivatives

The antiemetic activity of butyrophenone consists of the inhibition of the D2 receptor; however, the activity is lower than that of metoclopramide.

Antihistaminic drugs

They have limited individual activity, but they are used in premedication of anticipatory N&V. They are also indicated in premedication in case of chemotherapy that might induce allergic reactions (toxoids, oxaliplatin).

Thienobenzodiazepine

Olanzapine (an antipsychotic drug) has shown in phase III studies efficacy in the prevention of the N&V that occurs despite optimal prophylaxis, which results from the antagonistic effect of the drug against 5-HT3 and the D2 as well as against other receptors that participate in the development of N&V (e.g. histaminic or muscarinic) [12]. The drug should be used in combination with setron and dexamethasone [4, 12]. Olanzapine may induce sleep disturbances and tiredness (precaution is recommended in elderly persons), and it favours the occurrence of the QT-interval prolongation on ECG. The drug should not be used in combination with metoclopramide (risk of extrapyramidal reactions).

The objective efficacy of other benzodiazepines in the prevention of N&V is minimal. The sedative activity of benzodiazepines is much more important. It may be used in the prophylaxis of anticipatory and prolonged N&V as well as in complaints induced by CTH with a low emetogenic potential.

Preventive management

General rules of management

The general rules of management are generally accepted. They include the necessity to:

— evaluate the emetogenic potential of the planned CTH (necessity to define the risk extent determined by the drug with the highest emetogenic potential; the superadditive effect of combinations of some cytostatic drugs should also be considered);
— define the individual characteristic of the patient in the aspect of the risk of developing N&V;
— select the antiemetic drugs based on the evaluation of the emetogenic potential of the CTH regimen and on the individual patient characteristics, as well as on the potential side effects of the antiemetic drugs (in the case of CTH scheduled for several days, the evaluation of the N&V risk on each day of the therapy and an appropriate choice of antiemetic therapy);
— use a combined antiemetic therapy with consideration of the lowest efficient doses of the drugs;
— use preferably drugs that are administered orally;
— avoid using or to decrease the dose of corticosteroids in the case of their concomitant use in the CTH

Table 6. A prophylactic antiemetic management depending on the emetogenic potential of the chemotherapy (CTH)

The risk of nausea and vomiting	Management
High	5-HT3 antagonist on day 1 + Dexamethasone 12 mg on day 1 and 8 mg on days 2–4 + NK-1 antagonist — netupitant on day 1 (a drug in a combined formulation with palonosetron)* or aprepitant on days 1–3 The recent ASCO guideline [5] indicates that use of the 4-drug regimen (5-HT3 antagonist, dexamethasone, NK-1 antagonist and olanzapine) may be associated with greater benefits
Moderate	5-HT3 antagonist on day 1 + Dexamethasone 8 mg on days 1–3
Low	Dexamethasone 4–8 mg on day 1
Minimal	Only when the symptoms are present

*In the case of netupitant, it is not necessary to use the 5-HT3 antagonist (netupitant in a combined formulation with palonosetron)

regimen or to use an NK-1 receptor antagonist in the antiemetic management;
- evaluate the efficacy of the antiemetic therapy after each cycle of CTH;
- consider other causes of N&V in the differential diagnostics (e.g. gastrointestinal tract obstruction, liver impairment, metastases to the CNS or to the liver, oedema of the brain, neoplastic involvement of meninges, hypercalcaemia or any other electrolyte imbalances, uraemia, use of opioids or of some other drugs);
- use rescue therapy in case of a documented inefficacy of the first-line preventive therapy.

It is very important to follow the rules of the cost-effectiveness of the therapy. The ineffective escalation of the 5-HT3 and NK-1 inhibitors should be avoided and the time of the therapy with these drugs should not be prolonged (the use of 5-HT3 inhibitor on day 2 and on consecutive days after the completion of CTH is illegitimate). We should remember that the 5-HT3 and NK-1 inhibitors are not effective in the therapy of N&V induced by factors other than the antineoplastic therapy (except for setrons in postoperative N&V).

The schedule of preventive management depending on the emetogenic potential of the CTH is presented in Table 6.

The detailed principles of antiemetic management

In the case of CTH with high emetogenic potential, combined use of 5-HT3 inhibitor, anti-NK-1, and a corticosteroid is recommended [4, 5]. Preventive management should be used in every clinical situation. The validity of the administration of NK-1 antagonists in case of CTH containing cisplatin at a dose exceeding 50 mg/m^2 and in regimens with anthracyclines and cyclophosphamide is based on clinical proof with the highest level of evidence (I, A).

The administration of the NK-1 antagonist in combination with anti-5HT3 and dexamethasone may be considered in patients who receive carboplatin-containing CTH (carboplatin dose higher than 4 AUC) (I, B), because higher response rate (no N&V) of combination of anti-NK-1 and anti-5-HT3 drugs has been demonstrated in randomised trials. However, the differences have not always been significant [4].

The results of the randomised clinical trials do not justify the concomitant use of 5-HT3 and NK-1 antagonists and dexamethasone in patients who receive oxaliplatin in the chemotherapeutic schedule [4, 5].

Patients who receive CTH with high emetogenic potential usually develop intensive early and late N&V. The early N&V may be completely controlled. Effective control of early N&V is important because it conditions the absence of the delayed symptoms in about 75% of patients. The efficacy of the prevention of late N&V is lower. We should remember that the escalation of the dose and the prolongation of the duration of the antiemetic therapy beyond the recommended time does not improve its efficacy. The repeated administration of the 5-HT3 antagonist on consecutive days is justified only for dose fractionationation of the drug with high emetogenic potential (antiemetic drugs should be used sufficiently for the emetogenic potential of the CTH administered on a particular day and, if necessary, during the two days after the completion of this type of CTH) [4, 5].

The management of N&V induced by CTH with moderate emetogenic potential is differentiated. The N&V prophylaxis is obligatory in all patients at the

beginning of the CTH (I, A). The majority of the CTH regimens are characterised by a relatively high risk of early N&V while the probability of late symptoms is considerably lower. For this reason, the prophylactic use of the 5-HT3 receptor antagonist (only on the day of CTH administration; many medical societies recommend palonosetron) and of the corticosteroid as well addition of benzodiazepine or chlorpernazine is recommended (I, A). The exceptions are regimens containing doxorubicin or epirubicin and cyclophosphamide (a high risk of early and late N&V — the antiemetic therapy in this case is the same as the one used in the CTH with high emetogenic potential) [4, 5].

In case of CTH with low emetogenic potential it is advisable to use N&V prophylaxis in form of monotherapy with corticosteroids. Administration of more active drugs or prolongation of the prophylactic management is indicated only in the case of inefficiency of the standard procedures (I, A) [4, 5].

The chemotherapy with minimal emetogenic potential does not initially require any pharmacological prevention of N&V.

The principles of management in case of anticipatory N&V are completely different. Due to the psychogenic background and a different pathomechanism, classical drugs are useless. Sedative drugs or psychotherapy may alleviate the symptoms, but the most effective prophylaxis is good control of early and late symptoms.

Supportive therapy constitutes and important part of the management. In case of severe N&V, patients should receive appropriate hydration and correction of the electrolyte imbalance. The use of H2 receptor blockers may be effective (e.g. ranitidine, which alleviates the symptoms of the biliary reflux to the stomach during vomiting).

Rescue management

The principle of rescue management in case of failure of the preventive therapy is the administration of drugs with a different mechanism of action (II, C). In patients who receive CTH with low emetogenic potential, 5-HT3 receptor inhibitors are mostly recommended, while during chemotherapy with moderate emetogenic risk the use of NK-1 antagonist is recommended (if not initially used). The use of chloropenazine, benzodiazepine, or metoclopramide may also be considered. Lack control of the N&V during CTH with high emetogenic potential constitutes an especially difficult clinical situation, particularly when the most active antiemetic drugs have already been used initially. The escalation of the doses of 5-HT3 and NK-1 receptor inhibitors and the prolongation of the time of administration of these drugs does not improve the control of N&V. There is no defined standard of management; the use of setron with different pharmacological proprieties (e.g. palonosetron), the addition of supportive drugs, or the use of fractionated CTH (mostly cisplatin) may be considered. If CTH is administered with palliative intention and the N&V is not controlled and significantly decreases the quality of the patient's life, then the use of a CTH regimen with lower emetogenic risk may be a good solution [4, 5].

Table 7. The emetogenic potential of radiotherapy (RT) depending on the irradiated field [13]

Grade of hazard	Irradiated field
High	TBI
Moderate	HBI
	RT of the upper abdomen and of the pelvis
	RT — a lower field
	RT CNS
Low	RT chest
	Radiosurgery CNS
Minimal	Othertypes of RT

TBI (total-body irradiation) — RT of the total body; HBI (hemi-body irradiation) — RT of half of the body

Radiotherapy-related nausea and vomiting

Pathomechanism and risk factors

The mechanism of the development of N&V during radiotherapy is not completely clear. During the irradiation of the abdominal cavity the major mechanisms are the stimulation of the mucosal receptors and a consecutive transduction of the signal through the neurotransmitters (mostly serotonin and dopamine) to the CNS. On the other hand, brain irradiation my result in direct interaction with the trigger centre receptors [13]. The emetogenic potential of RT — depending on the strategy and the irradiation field — is presented in Table 7 (II, A).

Management

The prophylactic use of the antiemetic drugs — antagonists of the 5-HT3 receptor and of the corticosteroids — is indicated only in the case of the RT with high emetogenic risk (in clinical practice in TBI). In patients undergoing a TBI it is recommended that a single dose of a 5-HT3 receptor antagonist be administered in a standard dose before and at least during the first day after the RT in combination with dexamethasone or

without corticosteroid. In other situations, preventive therapy based on corticosteroids, metoclopramide antihistaminic drugs, benzodiazepines (and in the case of no effect, also of the inhibitors of the 5-HT3 receptor) should be started only in patients who have symptoms (II, A) [4, 5, 13].

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