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Chemotherapy-induced nausea and vomiting – standards in 2012

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In recent years, new drugs have increased efficacy in the prevention and control of chemotherapy-induced nausea and vomiting (CINV), however, vomiting, and especially nausea continue to be two of the most worrisome adverse effects of antineoplastic treatment. Antiemetic agents that have been identified to significantly improve the prophylaxis and treatment of CINV include the 5-HT₃-receptor antagonists (RA), corticosteroids, neurokinin 1 (NK₁) receptor antagonists, dopamine receptor antagonists, benzodiazepines, neuroleptics and cannabinoids. However, there are still a significant number of patients experiencing CINV, either because of non-adherence to current treatment guidelines or due to the fact that antiemetic prophylaxis for new drugs, targeted therapies and prolonged oral therapy is not yet established appropriately. Due to the emergence of new findings and new antiemetic agents, the MASCC/ESMO and the ASCO updated their treatment guidelines for the prevention of CINV. The combination of anthracyclines and cyclophosphamide (AC) is classified as highly emetogenic and a triple therapy including a 5-HT₃-RA, dexamethasone and an NK₁-RA is recommended. While acute CINV can be sufficiently controlled with the combination of 5-HT₃-RA plus dexamethasone, delayed CINV still remains a significant clinical problem. Palonosetron, a second-generation 5-HT₃-RA, provides superior protection against both, nausea and vomiting, and demonstrated superior long-lasting CINV prevention in the delayed phase. Another recently approved agent is the NK₁-RA fosaprepitant, which has shown equivalency in the prevention of both, acute and delayed CINV to aprepitant, and is used as a single day intravenous prophylaxis. This review provides an update of the revised clinical guidelines for antiemetic treatment and prophylaxis in cancer patients receiving chemotherapy.

Keywords: Antiemetics, Chemotherapy-Induced Nausea and Vomiting (CINV), antiemetic guidelines, palonosetron.

Introduction

In the last two decades, substantial progress has been made in the prevention and treatment of CINV. However, CINV remains still one of the most distressing side effects of chemotherapy, impairing patient's quality of life, leading to non-compliance with treatment, dose reductions, and, as a consequence, may compromise chances of treatment success.

The Multinational Association of Supportive Care in Cancer (MASCC) suggests the classification of the chemotherapeutic agents according to their emetic potential into four emetic risk groups (minimal, low, moderate, and high). As new antineoplastic agents have been developed, these agents have been added to the emetogenic classification scheme (Table 1). With the increasing use of oral agents used in extended regimens of continuous daily use, emetogenicity of these agents has to be newly defined and therefore oral agents are ranked separately from intravenous agents (Table 2), recognizing their different schedules of administration. As oral agents rarely induce delayed emesis, antiemetic prophylaxis is only recommended on day 1.

However, current guidelines are only considering the emetogenic potential of the chemotherapeutic agent itself and not the patient-related risk-factors which might lead to an underestimation of the emetogenic risk and, as a consequence, to an inadequate antiemetic prophylaxis. Furthermore, this classification does not take into account the emetogenic potential of combinations of targeted drugs and does not include nausea, which is not controlled as well as emesis.

Antiemetic agents

Of the various antiemetics currently available, 5-hydroxytryptamine-3(5-HT₃) receptor antagonists, neurokinin-1 (NK₁) receptor antagonists and corticosteroids are the most effective agents [1].

Serotonin (5-HT₃) receptor antagonists

All first-generation 5-HT₃ receptor antagonists (ondansetron, granisetron, tropisetron, dolasetron) are equally effective in

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Tab. 1: Emetogenic classification of intravenous chemotherapeutic agents (Adapted from [18])

High (>90%)	• Carmustine • Cisplatin • Cyclophosphamide $\geq 1.500 \text{ mg/m}^2$ • Dacarbazine • Mechlorethamine • Streptozotocin
Moderate (30%–90%)	• Carboplatin • Cyclophosphamide $< 1.500 \text{ mg/m}^2$ • Cytarabine $> 1.000 \text{ mg/m}^2$ • Daunorubicin • Doxorubicin • Epirubicin • Idarubicin • Ifosfamide • Irinotecan • Oxaliplatin • Azacitidine • Bendamustine • Alemtuzumab • Clofarabine
Low (10%–30%)	• Cytarabine $\leq 100 \text{ mg/m}^2$ • Docetaxel • Etoposide • 5-Fluorouracil • Gemcitabine • Doxorubicin HCL liposome Injection • Methotrexate • Mitomycin • Mitoxantrone • Ixabepilone • Paclitaxel • Pemetrexed • Topotecan • Trastuzumab • Bortezomib • Catumaxumab • Panitumumab • Cetuximab • Temsirolimus
Minimal (<10%)	• Bleomycin • Busulfan • 2-Chlorodeoxyadenosine • Fludarabine • Vinblastine • Vincristine • Vinorelbine • Bevacizumab

the prophylaxis of acute high and moderately emetogenic chemotherapy when given at equivalent doses [2, 3]. However, the first-generation 5-HT₃ receptor antagonists are not effective in the control of delayed CINV, and there is no clinical evidence to justify their use beyond 24 h after chemotherapy for the prevention of delayed emesis [4]. The only 5-HT₃ receptor antagonist which has shown clinical efficacy in controlling delayed CINV is the second-generation 5-HT₃-RA palonosetron.

Palonosetron is characterized by its higher binding affinity to the 5-HT₃ receptor, its significantly longer half-life of approximately 40 h and its ability to trigger 5-HT₃ receptor internalization [5]. Clinical trials on chemotherapy of high and moderately emetogenic potential have shown that palonosetron is at least equivalent to the first-generation 5-HT₃-RA in

Tab. 2: Emetogenic classification of oral chemotherapeutic agents (Adapted from [18])

High (>90%)	• Hexamethylmelamine • Procarbazine
Moderate (30%–90%)	• Cyclophosphamide • Imatinib • Temozolomide • Vinorelbine
Low (10%–30%)	• Capecitabine • Tegafur Uracil (UFT) • Fludarabine • Etoposide • Sunitinib • Everolimus • Lapatinib • Lenalidomide • Thalidomide
Minimal (<10%)	• Chlorambucil • Hydroxyurea • Gefitinib • Erlotinib • Sorafenib • Methotrexate • 6-Thioguanine

the control of acute CINV in moderately [6] – and in highly emetogenic chemotherapy (HEC) [7, 8], and superior in the control of delayed CINV [9, 10]. The study by Aapro et al. [7] demonstrated significantly higher complete response rates during the delayed (24–120 h) and overall phases (0–120 h) when Palonosetron was given with concomitant dexamethasone compared to ondansetron plus dexamethasone in HEC. However, only two-third of patients received pretreatment with dexamethasone. Furthermore, a study by Saito et al. [9] could demonstrate superiority of palonosetron when administered with dexamethasone in the control of CINV in the delayed phase compared to granisetron plus dexamethasone. Regarding the dosage, a recent meta-analysis could prove equivalent in terms of efficacy between the 0.25- and the 0.75 mg doses [11]. Based on these studies, Palonosetron was approved for the prevention of acute CINV in HEC and MEC and, as the only 5-HT₃-RA for the prevention of delayed nausea and vomiting in MEC. However, no study results of palonosetron in combination with an NK₁-RA are available so far.

Neurokinin-1 (NK₁) receptor antagonists

Aprepitant, a selective antagonist of the neurokinin 1 neurotransmitter receptor, demonstrated superior efficacy with an additional improvement in the prevention of acute emesis of 10–15% and 20–30% in delayed CINV, when combined with a 5-HT₃-RA and dexamethasone [12]. Additional NK₁-RA such as casopitant, netupitant and rolapitant have either shown clinical promise or are still under investigation [13]. Fosaprepitant, a single day intravenous antiemetic agent, which is converted within 30 minutes into aprepitant, has demonstrated equivalence with aprepitant for nausea and emesis control in HEC and was recently approved to replace oral aprepitant [14–16]. Of note, a dose of 115 mg fosaprepitant is bioequivalent in its area under the curve to aprepitant 125 mg.

Corticosteroids

The addition of corticosteroids to a 5-HT₃-RA containing antiemetic regimen or an NK₁-RA has markedly enhanced the control rates of both, acute and delayed CINV. Dexamethasone is the preferred steroid in the prophylaxis of acute and delayed CINV of either moderate or high emetogenic potential. For control of acute cisplatin-induced CINV, a single dexamethasone dose of 20 mg is recommended before chemotherapy. When used concomitantly with an NK₁-RA, dexamethasone dose should be adjusted to 12 mg in HEC and 8 mg in MEC [3, 17, 18] as aprepitant causes a 2-fold increase in the area under the plasma concentration curve (AUC).

Updated guidelines in the prevention and therapy of CINV

Due to the emergence of new findings and the implementation of new cytotoxic agents, targeted therapies and the increasing use of oral agents, the Multinational Association of Supportive Care in Cancer (MASCC), the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) updated the emetogenic classification and the clinical antiemetic guidelines [3, 18]. The marginal changes and the management of chemotherapy-induced emesis in different situations (Fig. 1) will be discussed here.

Prevention of acute and delayed CINV in highly emetogenic chemotherapy (HEC)

With the introduction of Aprepitant to a 5-HT₃-RA and dexamethasone regimen, acute and delayed emesis following chemotherapy of high emetogenic risk, could be significantly improved [19–21] most likely due to the improvement of CINV in the first 24 h. This effect could be maintained over multiple cycles of chemotherapy [22, 23], however, the control of nausea was only improved in the delayed period in only one study

[20]. Based on the results of these studies, a triple therapy consisting of single doses of a 5-HT₃-RA, dexamethasone and aprepitant/fosaprepitant given before chemotherapy is recommended. This triple therapy is also a recommended treatment in patients receiving an anthracycline plus cyclophosphamide (AC) combination [21], which was recently reclassified as a highly emetogenic chemotherapy regimen based on the high emetic potential of these two agents.

Antiemetic treatment in HEC

For acute emesis on day 1:

5-HT₃ receptor antagonist:

Preferably Palonosetron 0.50 mg p.o.; 0.25 mg i.v.

Granisetron 2 mg/p.o.; 1 mg or 0.01 mg/kg i.v.

Ondansetron 8 mg p.o. twice daily; 8 mg or 0.15 mg/kg i.v.

Dolasetron 100 mg p.o. only

NK₁ Antagonist:

Aprepitant 125 mg p.o./Fosaprepitant 115 mg i.v.

Corticosteroid:

Dexamethasone 12 mg i.v./p.o.

For delayed emesis on days 2 and 3:

Aprepitant 80 mg/day p.o.

Dexamethasone 4 mg every 12 h p.o. or i.v.

Prevention of acute and delayed CINV in moderately emetogenic chemotherapy (MEC)

In non-AC MEC regimens, the updated ASCO and MASCC/ESMO guidelines recommend the double therapy of a 5-HT₃-RA and a corticosteroid as standard prophylaxis. The addition of aprepitant might be also beneficial in the prevention of CINV in patients with MEC [24] with the additional advantage of abbreviating dexamethasone dosing, however, additional

Fig. 1: Treatment algorithm for prophylaxis of CINV

studies are warranted to further determine the appropriate use of aprepitant in this setting.

Antiemetic treatment in MEC

For acute emesis on day 1:

5-HT₃-RA:

Preferably Palonosetron 0.50 mg p.o.; 0.25 mg i.v.

Corticosteroid:

Dexamethasone 8 mg i.v./p.o.

For delayed emesis on days 2 and 3:

Dexamethasone 4 mg every 12 h p.o.

Prevention of acute and delayed CINV in low and minimal emetogenic chemotherapy

In patients with no prior history of CINV submitted to low emetogenic chemotherapy, a single agent such as dexamethasone (8 mg oral or iv), a 5-HT₃-RA or a dopamine RA should be used as prophylaxis on day one, whereas for days 2 and 3 no prophylaxis is recommended. In chemotherapy with minimal emetogenic potential no antiemetic treatment should be administered routinely.

Multiday chemotherapy

For patients receiving multiday chemotherapy, antiemetics should be administered according to the emetogenic risk class of the antineoplastic agent, and should be given on each day of chemotherapy and for additional 2 days after. Palonosetron is the only 5-HT₃-RA approved for delayed CINV, therefore the combination of palonosetron and dexamethasone daily during each day of chemotherapy might be a promising treatment approach in this setting [25]. However, a specific dosing schedule still needs to be defined. Instead of taking a serotonin antagonist daily, patients can also be offered the granisetron transdermal patch that delivers therapy over multiple days in high- or moderate-risk chemotherapy [26].

The severity of CINV in patients receiving multiday cisplatin-based chemotherapy can be improved by using a combination of a 5-HT₃-RA plus dexamethasone for acute, and dexamethasone alone for delayed nausea and vomiting. The addition of an NK₁-RA to the standard combination of a first-generation 5-HT₃-RA and dexamethasone might have an additional benefit [27] and the recently updated ASCO guidelines recommend the additional use of aprepitant for patients receiving 5-day cisplatin therapy [3].

In addition, olanzapine, a thienobenzodiazepine with a high affinity to several receptors involved in the CINV pathway such as dopamine, serotonin and histamine receptors, has demonstrated activity in the prevention of acute and delayed CINV in patients receiving MEC or HEC [28–30]. The combination of olanzapine with standard 5-HT₃-RA and dexamethasone might be another reasonable treatment strategy to control CINV in multiday chemotherapy regimens.

Antiemetic salvage therapy

In patients who fail antiemetic prophylaxis and/or rescue therapy despite optimal prophylaxis, clinicians should re-evaluate emetic risk, disease status, concurrent illness and

medication. According to the current ASCO and NCCN guidelines, switching to a different 5-HT₃-RA or adding other agents such as lorazepam or alprazolam, dopamine antagonists such as high-dose intravenous metoclopramide or olanzapine or cannabinoids, are reasonable treatment options for patients refractory or intolerant to 5-HT₃-RA, dexamethasone and NK₁-RA [17]. Of note, aprepitant is only approved for the prevention of CINV and should not be used in the treatment of existing nausea and vomiting.

Anticipatory nausea/vomiting

Anticipatory nausea and vomiting occur prior to the administration of chemotherapy and is triggered by the adverse memory of prior CINV. Its incidence ranges from 10–45%, with predominance of nausea. Prevention of CINV with the most active antiemetic regimens is therefore of utmost importance. However, if anticipatory nausea and emesis occur, behavioural therapy with systematic desensitization is suggested [3].

Conclusion

Despite a wide armamentarium of antiemetic drugs, there is still much to be achieved in the prediction and treatment of CINV. Besides the remarkable improvement in the control of vomiting, nausea remains a significant problem in patients receiving moderately and highly emetogenic chemotherapy, also because the emetic risk classification does not include nausea. NK₁-RA and 5-HT₃-RA could not demonstrate major efficacy in the control of nausea and the identification and implementation of antinausea agents into antiemetic regimens is highly warranted.

Patients receiving antiemetic treatment as recommended by international guidelines have an improved control of CINV, leading to a better treatment compliance and improvement in quality of life, however, only 50% of the patients receive antiemetic prophylaxis as recommended by the guidelines, causing a significantly worse protection from CINV, particularly for delayed CINV [31]. Therefore, the implementation of treatment guidelines in clinical practice is the pre-condition for effective prophylaxis of CINV.

Conflict of interest

The author declares that there is no conflict of interest.

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