Prevention of chemotherapy-induced nausea and vomiting: Belgian antiemetic treatment options anno 2018

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SUMMARY

Chemotherapy-induced nausea and vomiting remains an important adverse effect of treatment in daily clinical practice. Recently, new data on combinations of antiemetic agents became available for the prevention of acute and delayed nausea/vomiting in patients receiving highly and moderately emetogenic chemotherapy. As a result, the leading international cancer societies updated their antiemesis guidelines. This text aims at providing guidance regarding these new regimens in the prophylaxis of chemotherapy-induced nausea and vomiting, with a particular focus on highly emetogenic chemotherapy.

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INTRODUCTION

Few side effects of cancer treatments are more feared by patients than nausea and vomiting. Chemotherapy is the most frequent cause of iatrogenic nausea and vomiting. Significant progress has been made, but chemotherapy-induced nausea and vomiting (CINV) remains an important adverse effect of treatment. Several types of CINV have been described.[1-4] *Acute emesis* usually begins within a couple of hours after administration of chemotherapy and peaks in four to six hours. *Delayed emesis* occurs later, more than 24 hours after chemotherapy. A third form of CINV is *anticipatory emesis*; this type of CINV occurs prior to treatment as a conditioned response in patients who experienced nausea and vomiting during previous chemotherapy cycles. Finally, breakthrough CINV is vomiting or nausea despite an appropriate prophylactic treatment.

The development of new antiemetic agents has dramatically changed the landscape of chemotherapy-induced emesis. As a result, adherence to established antiemetic guidelines provides effective relief from CINV in the vast majority of patients, allowing patients to rapidly return to their normal daily activities.[1-5] This significantly improves the quality of

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life of patients, but also reduces the chemotherapy discontinuation rate and can thus improve outcome.

Recently, new data on combinations of antiemetic agents became available for the prevention of acute and delayed nausea/vomiting in patients receiving highly emetogenic chemotherapy (HEC). As a result, the leading international cancer societies updated their antiemesis guidelines. This text aims to provide guidance regarding these new regimens in the prophylaxis of CINV in Belgium. The recommendations regarding all available antiemetic agents will be addressed, taking into account the recently updated NCCN, MASCC/ESMO and ASCO guidelines on antiemetics and the Belgian reimbursement criteria for the different drugs. Finally, the remaining challenges in the management of CINV will be addressed.

The basis for this paper consisted of a small survey conducted among twelve Belgian specialists involved in the prevention and treatment of CINV. The target population of this survey consisted of medical oncologists, haematologists and hospital pharmacists from both the French and Dutch speaking parts of Belgium. The outcome of this survey was then compared with a systematic review of the NCCN, MASCC/ESMO and ASCO guidelines to draft a text reflecting the standard of care in CINV management in Belgium.

METHODS

All data of the survey were mirrored with the NCCN, MASCC/ESMO and ASCO guidelines, and adapted within the reimbursement rules in Belgium.

ESTIMATING THE RISK OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

The most important factor determining the likelihood of acute or delayed emesis during chemotherapy is the intrinsic emetogenicity of the agent(s) that is/(are) administered. Other factors, such as patient age, sex and history of alcohol consumption, play a major clinical role.

In spite of their high predictive value, these factors are surprisingly not reflected in the current guidelines, which only take into account the emetogenic potential of the drug regimen.

The management of CINV has been greatly facilitated by the development of classification schemes that reflect the likelihood of emesis following treatment with particular agents.[6] In these schemes, chemotherapy agents are divided into four categories based upon the risk of emesis in the absence of anti-emetogenic prophylaxis:

- Highly emetogenic agents: >90% risk of emesis (chemotherapy AC is also considered highly emetogenic in the last guidelines)
- Moderately emetogenic agents: >30% to 90% risk of emesis
- Agents with low emetogenicity: 10% to 30% risk of emesis
- Minimally emetogenic agents: <10% risk of emesis

A classification of specific agents according to their emetogenic potential is presented in *Table 1*. Of note, for combination regimens, the emetogenic level is determined by identifying the most emetogenic agent in the combination. In general, this sub-classification of chemotherapeutic agents according to their emetogenic potential is fairly similar in the different established international guidelines on antiemesis.[4,5,7] Among the moderately emetogenic agents, carboplatin takes a particular place. In fact, carboplatin proved to be highly emetogenic in a (substantial) minority of patients, and triple antiemetic therapy is therefore recommended in recent guidelines.

PROPHYLAXIS FOR CINV: CLINICAL DATA IN HISTORICAL PERSPECTIVE

Until the late 1970's, dopamine-receptor antagonists, such as metoclopramide and haloperidol, constituted the basis of antiemetic therapy in patients receiving chemotherapy.[8] The increased use of cisplatin forced investigators to develop more effective antiemetic agents. This first led to the implementation of high-dose metoclopramide and dexamethasone in the antiemetic arsenal, followed by the development of first generation 5-HT_3-receptor antagonists (e.g. ondansetron).[9,10] In the late 1990's, the first international antiemetic guidelines were published by the NCCN, MASCC and ASCO. These guidelines recommended the use of 5-HT_3-receptor antagonists for the prevention of acute and delayed emesis with both highly and moderately emetogenic chemotherapy, although the efficacy of these agents on delayed emesis could be questioned.[11-13]

The treatment algorithms in the prevention of CINV dramatically changed in 2003, when the 2nd generation 5-HT_3-receptor antagonist palonosetron and the NK_1-receptor antagonist aprepitant entered the market. In a large randomised trial, palonosetron was shown to be superior to ondansetron in the prevention of acute and delayed chemotherapy-induced emesis.[14] In two other clinical trials, the combination of the oral NK_1-receptor antagonist aprepitant with ondansetron-dexamethasone was shown to be significantly more effective than ondansetron-dexamethasone alone in patients treated with HEC.[15,16] Following these findings, the combination of an NK_1-receptor antagonist with a 5-HT_3-receptor antagonist and corticosteroids became a standard of care for the prophylaxis of CINV with HEC.

TABLE 1. Overview of chemotherapeutic agents according to their emetogenic potential (MASCC/ESMO guidelines).[4]

Highly emetogenic	Cisplatin Anthracycline + cyclophosphamide (>500 mg/m²) Cyclophosphamide (>1500 mg/m²) Cytarabine (>1000 mg/m²) Carmustine Dacarbazin Mechloretamine Streptozocine		
Moderately emetogenic	Alemtuzumab Azacitidine Bendamustin Carboplatin* Cyclophosphamide (< 1500 mg/m²)	Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Lomustin	Oxaliplatin Procarbazine Romidepsin Temozolomide Thiotepa Trabectedin Cytarabine (<1000 mg/m²)
Low emetogenic	Aflibercept Belinostat Blinatumomab Bortezomib Brentuximab Cabazitaxel Carfilzomib Catumaxomab Cetuximab Cytarabine < 1000 mg/m² Docetaxel	Eribulin Etoposide 5-Fluorouracil Gemcitabine Ipilimumab Ixabepilone Methotrexate Mitomycin Mitoxantrone NAB-paclitaxel Paclitaxel	Panitumumab Pemetrexed Pegylated liposomal doxorubicin Pertuzumab Temsirolimus Topotecan Trastuzumab-emtansine Vinflunine
Minimally emetogenic	Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Cladribine Fludarabine Nivolumab Ofatumumab	Pembrolizumab Pixantrone Pralatrexate Rituximab Trastuzumab Vinblastine Vincristine Vinorelbine	

*In the NCCN guidelines carboplatin AUC4 or more is considered as high-risk for CINV, and also in the ESMO guidelines an NK1-receptor antagonist is advised in contrary to other moderately emetogenic agents.

Olanzapine, an antipsychotic agent that is used in the treatment of schizophrenia and bipolar disorders, was also shown to have antiemetic potential, besides central adverse effects in some patients. In a phase III trial published in 2011 comparing olanzapine with aprepitant (both in combination with palonosetron-dexamethasone) in patients receiving cisplatin or doxorubicin plus cyclophosphamide, olanzapine was shown to be at least as effective as aprepitant in controlling both acute and delayed CINV.[17] Also as breakthrough antiemetic treatment in patients receiving HEC, olanzapine has proven superior efficacy compared with metoclopramide.[18] A large randomised study in the NEJM in 2016 showed additional clinical benefit of adding olanzapine to a triple antiemetic regimen (dexamethasone,

aprepitant or fosaprepitant, and a 5-HT_3-receptor antagonist) in patients receiving HEC.[19]

More recently, clinical trials were completed with two new NK_1-receptor antagonists (netupitant and rolapitant), leading to substantial improvements in the prophylaxis of CINV, especially in the delayed phase.[20] The combination of a single, oral, fixed-dose combination of netupitant (300 mg)/palonosetron (0,50 mg) with dexamethasone was found to be superior to palonosetron-dexamethasone for the prevention of chemotherapy-induced emesis in patients receiving highly emetogenic drugs or the combination of doxorubicin plus cyclophosphamide.[21,22] Moreover, its clinical efficacy was maintained over multiple chemotherapy cycles and the single oral dosing just before chemotherapy administration (without need for steroids after day one for AC) is an advantage for clinical practice.[23] With the combination of rolapitant and granisetron-dexamethasone, the rates of chemotherapy-induced emesis after prophylaxis were significantly lower than those seen with granisetron-dexamethasone alone in patients receiving moderately or highly emetogenic chemotherapy.[24,25]

Subsequent to the redaction of this text, the American Society of Clinical Oncology Clinical Practice Guideline Update of Antiemetics was published in the Journal of Clinical Oncology of July 2017.[26] Key point in this update is the addition of olanzapine to an NK1-receptor antagonist, a 5-HT3-receptor antagonist and steroids for adults who receive HEC (HEC with cisplatin and HEC with AC) or who experience breakthrough nausea and vomiting, which is perfectly in line with international guidelines. However, giving olanzapine front-line to all HEC-patients as is suggested by the new ASCO guidelines, is a point of discussion for all involved panellists. In studies of quadruple therapy, short-working 5-HT3-receptor antagonists were used, and in daily practice with the newer antiemesis agents less nausea and vomiting are encountered with triple therapy. Therefore, this quadruple regimen can be considered in high-risk patients such as treatment with high dose cisplatin and absence of protective characteristics (such as alcohol abuse), anxiety for side effects or CINV during cycle one of chemotherapy with triple therapy.

Other updates are the recommendation to administer dexamethasone on day one only for adults who receive anthracycline and cyclophosphamide chemotherapy, and also the addition of an NK1-receptor antagonist for adults who receive carboplatin AUC≥4 or high-dose chemotherapy. Both updates are also elaborated in our text.

A randomised phase III study evaluating the efficacy of the single-dose combination of netupitant/palonosetron (NEPA) versus an aprepitant regimen for prevention of CINV in patients receiving HEC was recently published in the Annals of Oncology.[27] This represents the first head to head comparison between NEPA and aprepitant (APR) + granisetron (GRAN); both groups received dexamethasone 12 mg on day one and dexamethasone 8 mg on day two and three. NEPA demonstrated non-inferiority to APR/GRAN for overall complete response (NEPA 73.8% *vs.* APR/GRAN 72.4%). No emesis (NEPA 75.0% *vs.* APR/GRAN 74.0%) and no significant nausea rates (NEPA 75.7% *vs.* APR/GRAN 70.4%) were similar between groups, but significantly more NEPA patients did not take rescue medication (NEPA 96.6% *vs.* APR/GRAN 93.5%). NEPA was well tolerated with a similar safety profile to APR/GRAN.

TRANSLATING INTERNATIONAL GUIDELINES TO THE BELGIAN CLINICAL REALITY

As mentioned before, the large international cancer societies (ASCO, NCCN, and ESMO/MASCC) all recently formulated updated versions of their antiemetic guidelines for patients receiving chemotherapy.[3-5] In general, these guidelines show broad agreement on the key principles. They all agree that prophylaxis should be the primary goal of antiemetic therapy, that the duration of prophylaxis should cover the entire risk period, that oral and intravenous administration routes have the same efficacy and that the type of antiemetic treatment is determined on the basis of the emetogenicity of the chemotherapy that is used and by additional patient-related factors (e.g. history of CINV).[28]

A summary of the most recent international guidelines adapted to the Belgian reimbursement rules is shown in *Table 2*; in order to correctly reflect the Belgian situation, only agents that are currently reimbursed in Belgium, are listed in this overview. The international guidelines recommend the use of 5-HT3-receptor and NK1-receptor antagonists with dexamethasone for patients receiving HEC and anthracycline-based chemotherapy regimens. The data on olanzapine are only reflected in the most recent NCCN and ASCO guidelines. The use of olanzapine for CINV is off-label and caution is needed in the elderly and in patients with concomitant use of other antidepressants; a positive effect of olanzapine on anorexia can be an advantage. For patients receiving moderately emetogenic agents, antiemetic prophylaxis with a 5-HT3-receptor antagonist (preferably palonosetron) and dexamethasone is recommended, except for carboplatin AUC ≥4 where the addition of an NK1-receptor antagonist is recommended in the NCCN, ASCO and ESMO/MASCC-guidelines. In *Table 3* the current Belgian reimbursement criteria for the agents mentioned in the antiemetic guidelines discussed above are listed.

TABLE 2. Possible antiemetic strategies in Belgium according to Belgian reimbursement rules and based on the international recommendations on antiemesis for HEC.[3,4,5]

Emetic risk	Acute phase (day of chemotherapy)	Delayed phase (days 2-4)
High	Combined NK_1- and 5-HT_3-receptor antagonist NEPA (300 mg Netupitant and 0,50 mg Palonosetron PO) Corticosteroids Dexamethasone (12 mg PO or IV)∞ Olanzapine (10 mg PO)	Dexamethasone (8 mg PO or IV on d2-4)∞, not needed with AC Olanzapine (10 mg PO on d2-4)
	Combined NK_1- and 5-HT_3-receptor antagonist NEPA (300 mg Netupitant and 0,50 mg Palonosetron PO) Corticosteroids Dexamethasone (12 mg PO or IV)∞	Dexamethasone (8 mg PO or IV on d2-4)∞, not needed with AC
	Olanzapine-containing regimen Olanzapine (10 mg PO) Palonosetron (0,25 mg IV) Dexamethasone (20 mg IV)∞	Olanzapine (10 mg PO on d2-4) Dexamethasone (8 mg PO or IV on d2-4)∞
	NK1-receptor antagonist Aprepitant (125 mg PO) 5-HT_3-receptor antagonist Ondansetron (16-24 mg PO twice, or 8-16 mg IV) Corticosteroids Dexamethasone (12 mg PO or IV)*, ∞ Olanzapine (10 mg PO)	Aprepitant (80 mg PO on d 2-3) Dexamethasone (8 mg PO or IV on d2-4)∞ Olanzapine (10 mg PO on d2-4)
	NK_1-receptor antagonist Aprepitant (125 mg PO) 5-HT_3-receptor antagonist Ondansetron (16-24 mg PO twice, or 8-16 mg IV) Corticosteroids Dexamethasone (12 mg PO or IV)*, ∞	Aprepitant (80 mg PO on d 2-3) Dexamethasone (8 mg PO or IV on d2-4)∞

*This dexamethasone dose is for patients who are receiving recommended three-drug regimen for highly emetogenic chemotherapy. If patients do not receive NK1-receptor antagonist, dexamethasone dose should be adjusted to 20 mg on day 1 and 16 mg on days 2 to 4.

∞Dexamethasone dose may be individualised based upon patient characteristic.

In current clinical practice, there is substantial variation regarding the corticosteroids used and their posology in the antiemetic regimens. Some doctors use dexamethasone, others prefer methylprednisolone, though in most antiemesis studies dexamethasone was implemented. An important aspect that needs to be kept in mind when using corticosteroids together with NK_1-receptor antagonists, is the fact that both aprepitant and netupitant inhibit the metabolism of corticosteroids and may cause higher corticosteroid concentrations. As such, there is a rationale to reduce the dexamethasone or methylprednisolone dose to obtain the same corticosteroid concentrations. However, it

TABLE 3. Belgian reimbursement criteria for NK1- and 5-HT3-receptor antagonists. (www.riziv.fgov.be or www.inami.fgov.be)

Drug	Reimbursement criteria
Zofran® (ondansetron)	• Reimbursed for the prevention of CINV in patients treated with antitumoural agents with a high (> 90% risk of emesis) or moderate emetic risk (> 30% to 90% chance of CINV) according to the SMPC (summary of product characteristics) or according to the ESMO/MASCC guidelines (Roila et al, 2010. Ann Oncol. 21: v232-243; http://www.mascc.org/anti-emetic-guidelines. • Simultaneous reimbursement with palonosetron is not allowed.
Aloxi® (palonosetron)	• Reimbursed for the prevention of CINV in patients treated with antitumoural agents with a high or moderate emetic risk (> 30% chance of CINV) according to the SMPC (summary of product characteristics) or according to the ESMO/MASCC guidelines of (Roila et al, 2010. Ann Oncol. 21: v232-243; http://www.mascc.org/antiemetic-guidelines. • Simultaneous reimbursement with other serotonin antagonists or aprepitant is not allowed.
Emend® (aprepitant)	• Reimbursed for prevention of CINV in patients receiving cyclophosphamide IV (>1500 mg/m^2), hexamethylmelamin, carmustin (≥250 mg/m^2), dacarbazine, streptozocin or cisplatin (≥25 mg/m^2). Should be accompanied by 5-HT3-receptor antagonist on day 1 of chemotherapy and by a corticosteroid on days 1-4. • Reimbursed for prevention of CINV in selected patients receiving combinations of cyclophosphamide (≥500 mg/m^2) with an anthracycline and in patients with an increased CINV risk (history of CINV, younger patients) on carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan or methotrexate. Should be accompanied by a first generation 5-HT3-receptor antagonist and a corticosteroid on day 1 of chemotherapy. • For every chemotherapy cycle, only 1 package is reimbursed (125 mg on day 1, 80 mg on days 2 and 3). • Simultaneous reimbursement with ondansetron during 1 chemotherapy cycle is not allowed.
Akynzeo® (netupitant/palonosetron)	• Reimbursed for prevention of CINV in patients receiving cyclophosphamide IV (>1500 mg/m^2), hexamethylmelamin, carmustin (≥250 mg/m^2), dacarbazine, streptozocin or cisplatin (≥25 mg/m^2). • Reimbursed for prevention of CINV in selected patients receiving a combination of cyclophosphamide (≥500 mg/m^2) with an anthracycline and in patients with an increased CINV risk (history of CINV, younger patients) on carboplatin cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan or methotrexate. • Only 1 capsule, to be taken on day 1 of chemotherapy, is reimbursed per chemotherapy cycle. • Simultaneous reimbursement with serotonin antagonists, aprepitant or palonosetron during 1 chemotherapy cycle is not allowed.

is unclear what the clinical relevance is of somewhat higher or lower corticosteroid doses in terms of antiemetic effect. At first glimpse, the international guidelines on antiemetic therapy seem to be uniform in their recommendations with respect to corticosteroid use. However, when looking into these guidelines in more detail some subtle differences become apparent. The guidelines for corticosteroid use on day one are very similar in the ASCO, NCCN and MASCC/ESMO guidelines and recommend the use of 12 mg dexamethasone (PO or IV) (of note: ASCO recommends only 8 mg dexamethasone on day one with moderately emetic agents). The recommendations with respect to corticosteroids in the delayed phase vary a bit more. With HEC, the general recommendation is to use 8 mg of dexamethasone

(PO or IV) on days two to four. However, based on the specific nature of the chemotherapy that is used (e.g. AC in the MASCC/ESMO guidelines), prophylaxis with dexamethasone on day two and three can be sufficient.[3-5] Of note, when using netupitant in AC treated patients, the MASCC/ESMO guidelines do not recommend any corticosteroid use on days two to four.[4] With moderately emetic chemotherapy, both ASCO and NCCN recommend individualised rather than systematic use of dexamethasone 8 mg (PO or IV) on days two to three. The MASCC/ESMO guidelines on the other hand do not recommend any corticosteroids on days two to three in case of moderately emetic chemotherapy (only in case of oxaliplatin, anthracycline and cyclophosphamide monotherapy, 8 mg of dexamethasone on days two to three can be considered).[2-5] If an NK1-receptor antagonist is not prescribed in HEC, all guidelines advise to give 20 mg of dexamethasone on day one.

REMAINING CHALLENGES

Despite the significant progress that was made in the management of chemotherapy-induced emesis, clinicians still encounter some challenging situations.

CINV PROPHYLAXIS IN PAEDIATRIC AND ADOLESCENT PATIENTS

One important medical need consists of CINV prophylaxis in paediatric and adolescent patients. The 2011 ASCO guidelines on antiemesis state that the combination of a 5-HT3-receptor antagonist plus a corticosteroid is suggested prior to chemotherapy in children receiving chemotherapy of a high or moderate emetic risk.[7] However, due to the variation in pharmacokinetic parameters in children, higher weight-based doses of 5-HT3-receptor antagonists than those used in adults may be required for antiemetic protection. This sometimes leads to difficult situations in clinical practice.

Several studies indicate that the use of an NK1-receptor antagonist in combination with corticosteroids and a 5-HT3-receptor antagonist is safe and effective in adolescent patients.[29,30] This triple therapy is reflected in the MASCC/ESMO consensus recommendations. However, in Belgium both aprepitant and netupitant are only reimbursed for patients older than eighteen years of age. As a result, adolescent patients treated with highly emetogenic agents, currently do not have access to the most effective prophylactic CINV treatment. The previously mentioned small Belgian survey revealed that in Belgian clinical practice adolescent patients under HEC are generally treated with a 5-HT3-receptor antagonist (palonosetron) and dexamethasone. Alternatively, samples of aprepitant are used to manage CINV in these cases.

Other problems regarding CINV treatment in children are:

1. The lack of randomised controlled trials in children, leading to less evidence in the use of different medications.
2. In childhood cancer more multiday chemotherapy regimens are used. As there is a lack of consensus in the treatment of CINV in multiday chemotherapy regimens in adults, there is no consensus at all in children.
3. The attitude of paediatric haemato-oncologists to avoid the use of dexamethasone for different reasons: potential interference with apoptosis, the risk of fungal infections and the distribution of chemotherapy across the blood-brain barrier.
4. Alizapride is used a lot in the paediatric population, with good results. It is a drug not available in the United States, and therefore not present in the different guidelines.

MANAGING CINV IN MULTIDAY CHEMOTHERAPY REGIMENS

Another challenge in (Belgian) clinical practice consists of CINV management in patients receiving multiday chemotherapy. The 2011 ASCO guidelines state that these patients should be treated with antiemetics appropriate for the emetogenic risk class of the chemotherapy, which should be administered for each day of the chemotherapy and for two days thereafter.[7] Unfortunately, with respect to the efficacy of the different antiemetic agents, limited data are available in the setting of chemotherapy regimens over four to five days. In the latest NCCN guidelines, the recommendations for CINV prophylaxis with multiday chemotherapy consist of dexamethasone given on every day of the chemotherapy, to be continued for two to three days after chemotherapy, in combination with a 5-HT_3-receptor antagonist administered prior to the first and subsequent doses of moderately or highly emetogenic chemotherapy.[5] In addition to this, an NK_1-receptor antagonist may be added. However, only limited data exist to support the administration of aprepitant beyond day three of multiday chemotherapy.[5] The updated MASCC/ESMO guidelines also briefly touch upon multiday chemotherapy.[4] In these guidelines a combination of a 5-HT_3-receptor antagonist plus dexamethasone plus aprepitant is recommended for the prevention of acute CINV, followed by dexamethasone to prevent delayed nausea and vomiting. In this setting, the 5-HT3-receptor antagonist should be dosed at days one to five, except for palonosetron, which should be dosed on days one, three and five only. However, the level of evidence for this recommendation is only moderate.[4]

KEY MESSAGES FOR CLINICAL PRACTICE

1. CINV in HEC and MEC remains an important adverse effect of anticancer treatments.
2. Chemotherapy AC/EC is considered highly emetogenic in the last guidelines.
3. According to the recently updated ASCO guidelines, the most potent strategy for HEC nowadays involves the combination of a NK1-receptor antagonist, a 5-HT3-receptor antagonist, olanzapine and steroids.
4. Prescription of olanzapine to all HEC patients seems not obligatory with the recent advent of the very potent antiemetic combination netupitant/palonosetron, stratification according risk seems feasible in daily practice.
5. It is unclear what the clinical relevance is of corticosteroid doses in terms of antiemetic effect.

Moreover, in Belgium there is reimbursement for only one package of aprepitant or netupitant/palonosetron per chemotherapy cycle. In addition, the combination of aprepitant and palonosetron is not reimbursed in Belgium. An alternative strategy that is sometimes used, consists of six days of aprepitant (+ ondansetron and a corticosteroid); also the use of olanzapine may be considered in this setting.

MANAGING BREAKTHROUGH NAUSEA AND VOMITING

Notwithstanding the satisfactory efficacy of the available antiemetic regimens in most situations, a minority of patients does experience breakthrough nausea and/or vomiting despite optimal prophylaxis. When this occurs, it often presents as a challenging situation. In this light, adequate patient education is crucial in order to stress the importance of treatment compliance when using treatments that contain oral drugs that are taken at home on the days following the chemotherapy.

The general principle in dealing with breakthrough emesis is to add an agent from a different drug-class to the antiemetic regimen used in the prophylaxis of CINV. Recommended drugs that can be added, are steroids and/or dopamine-antagonists with a preference for olanzapine if not already used. Metoclopramide, alizapride, domperidone and haloperidol can be used instead of olanzapine to avoid the sedative side effect of olanzapine (which in general is more pronounced in older patients), but is clearly inferior to olanzapine as breakthrough antiemetic treatment in patients receiving HEC.[4,5,7] If olanzapine 10 mg daily is considered too toxic, the 5 mg dose daily can be considered a feasible alternative.[31] An important note in this setting is that when the oral route is difficult in case of ongoing vomiting, olanzapine is also available in sublingual and parenteral formulation.

Prior to the next chemotherapy cycle, it is also important to reassess the antiemetic strategy, if the chosen strategy failed to protect the patients during their first chemotherapy cycle. In case of a failure, possible strategies are then to change the antiemetic regimen in function of the previous antiemetic drugs used.[5] The most potent strategy for HEC involves the combination of a 5-HT3-receptor antagonist, an NK1-receptor antagonist, olanzapine and steroids.

ANTICIPATORY NAUSEA AND VOMITING

Anticipatory CINV occurs before patients receive the next chemotherapy cycle. Because it is primarily considered to be a conditioned response, anticipatory emesis typically occurs after a negative chemotherapy experience in the past. This again underlines the importance of an optimal antiemetic prophylaxis before the first chemotherapy cycle. As is stated in the updated MASCC/ESMO guidelines on antiemesis: 'the best approach for the prevention of anticipatory nausea and vomiting is the best possible control of acute and delayed nausea and vomiting'.

For prevention of anticipatory CINV in selected high-risk patients, upfront intensification of the standard antiemetic prophylaxis according to the risk of the treatment has to be considered. To counter anticipatory CINV once established, antianxiety agents such as lorazepam and alprazolam are often given.[4,5] In addition to this, behavioural therapy (e.g. progressive muscle relaxation training) with systematic desensitisation has also been suggested.[7,4]

CONCLUSIONS

Recently, new data on combinations of antiemetic agents became available for the prevention of acute and delayed nausea/vomiting in patients receiving (HEC). As a result, the leading international cancer societies updated their antiemetic guidelines. The recommendations regarding all available antiemetic agents are addressed in this article, taking into account the recently updated NCCN, MASCC/ESMO and ASCO guidelines on antiemetics and the Belgian reimbursement criteria for the different drugs.

The combination of steroids, NK1-receptor antagonists and 5-HT3-receptor antagonists (the latter two even available as a single, oral, fixed-dose combination), and the additional clinical benefit of adding olanzapine to a triple antiemetic regimen in patients receiving HEC, are the two most recent promising therapeutic strategies in the fight against CINV.

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