Use of antiemetics in the prevention of chemotherapy-induced nausea and vomiting : review and focus on the Belgian situation

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is a common, distressing, debilitating and costly side effect, experienced by up to 90% of patients receiving highly emetogenic drugs. During the last 20 years great advances have been made in the prevention and treatment of CINV. Aprepitant (a neurokinin-1 antagonist) and palonosetron (a 5-HT3 antagonist) are the most recent additions to the available armamentarium. The aim of this paper is to review the most recent findings concerning the pathophysiology and prevention of CINV, and the international guidelines currently in place for its prevention and treatment. Among the treatments available, 5-HT3 antagonists and NK-1 antagonists are compared. In a large meta-analysis (8 studies in 3 592 patients) statistically significant differences in favour of palonosetron compared with first-generation 5-HT3 antagonists have been demonstrated in the prevention of acute, delayed and overall CINV. A recent, large phase III randomized, gender-stratified, double-blind trial in 848 patients receiving a broad range of moderately emetogenic chemotherapy regimens with a variety of tumour types showed superiority of an aprepitant triple regimen compared to a control regimen of ondansetron and dexamethasone. A new combined 5-HT3/NK-1 treatment, called NEPA (palonosetron/netupitant), has provided very promising preliminary data and is awaited with great anticipation by clinicians. The specific Belgian situation in terms of Health Authorities recommendations and reimbursement policies is also presented. It is concluded that further improvements are still desirable, particularly in the prevention and treatment of delayed emesis. (Acta gastroenterol. belg., **2014**, 77, **240-248**).

Key words : anti-emetics, chemotherapy induced nausea and vomiting, aprepitant, 5-HT3 antagonists, and corticosteroids.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common, distressing, debilitating and costly side effect (1,2). Without adequate antiemetic treatment, CINV is experienced by up to 90% of patients receiving highly emetogenic chemotherapy (HEC) (Table 1) (3,4). Characteristics that increase the risk of CINV include female gender, younger age, previous exposure to chemotherapy, and presence of nausea and vomiting with prior chemotherapy (5). On the contrary, patients with a history of high alcohol consumption have a lower risk of CINV (6). Conventionally, a distinction is made between acute CINV, occurring within 24 h of chemotherapy, and delayed CINV which occurs between 24 and 120 h after chemotherapy administration. Following repeated chemotherapy cycles, patients may also experience anticipatory vomiting and nausea (7).

Besides greatly impairing patients' quality of life (QoL) and functional status (8,9), CINV can also result in metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of performance and mental status, wound dehiscence, oesophageal tears, and withdrawal from potentially useful or curative anticancer treatment (6,10).

Pathophysiology and prevention of CINV

Vomiting results from stimulation of a multistep reflex pathway controlled by the brain, and is triggered by afferent impulses to the vomiting centre (located in the medulla) from the chemoreceptor trigger zone, pharynx, gastrointestinal tract (by way of vagal afferent fibres) and cerebral cortex. Vomiting occurs when efferent impulses are sent from the vomiting centre to the salivation centre, abdominal muscles, respiratory centre, and cranial nerves (11). Enterochromaffin cells in the mucosa of the gastrointestinal (GI) tract respond to chemotherapy (as to other potentially toxic chemical or mechanical stimuli) by releasing serotonin which stimulates the 5-HT3 receptors on the afferent fibres of the vagus nerve (6). This causes the chemoreceptor trigger zone to send a signal to areas within the medulla, resulting in increased salivation, respiratory rate, pharyngeal, GI and abdominal muscle contractions and emesis.

In addition, the tachykinin known as substance P (SP), the endogenous ligand acting preferentially on neurokinin-1 (NK-1) receptors, is an important mediator of delayed emesis through both central and peripheral sites of action (6).

Given the central role of serotonin (and especially of the 5-HT3 receptor subtype) in the pathways leading to CINV, the development of agents to selectively block the 5-HT3 receptor was a logical initial step in efforts to control emesis. The first-generation of 5-HT3 receptor antagonists, exemplified by the prototype drug ondansetron, resembled serotonin in structure (12). These agents dramatically improved the QoL of patients undergoing emetogenic chemotherapy and became the standard of care.

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The development of palonosetron, a 5-HT3 receptor antagonist with a structure different from that of serotonin, marked the advent of a second generation of this class of drugs. Compared with earlier 5-HT3 antagonists, palonosetron has a longer half-life (of 40 hours, compared with less than 10 hours for old-generation agents) and at least thirty-fold higher in vitro binding affinity for the 5-HT3 receptor (13). Furthermore, palonosetron triggers internalisation of the receptor, so maintaining functional inhibition even when the drug itself is gone (2,14). Finally, recent evidence indicates that palonosetron, although not directly binding to the NK-1 receptors, is able to inhibit both serotonin and cisplatin enhanced SP- mediated neuronal response (15). The demonstration that palonosetron, but not first- generation 5-HT3 antagonists, also affects the cross-talk between NK-1 and 5-HT3 receptors signalling pathways, provides a further explanation for the demonstrated efficacy of this drug in controlling delayed CINV (15).

In contrast to the primarily peripheral action of serotonin, substance P and one of its cognate receptors (NK-1) are believed to have both central and peripheral sites of action. This concept is supported both pharmacologically and anatomically. The former with the demonstration that the exogenous substance P applied to cells in the nucleus tractus solitarius (NTS) induces emesis ; the latter by an abundance of the peptide and receptor located in the NTS of the mid- brain as well as in the vagal afferents of the gut. Furthermore, the NTS appears to be the hub where vagal afferents converge with inputs from the area postrema and other brain regions presumed to be important in regulating the vomiting response (16,17).

Many other receptor pathways are likely to be involved in the pathogenesis of CINV. One of the other prominent mediators is dopamine. The dopaminergic pathway is further complicated by expression of multiple receptors, of which only two, D2 and D3, appear to elicit emetic responses when activated. This is supported by dose-dependent blockade of emetic events by competitive D2 antagonist such as haloperidol and droperidol (18). As these agents are pure dopamine antagonists, central nervous system toxicity limits front-line application of this class of drugs. Though effective, extrapyramidal side effects frequently lead to treatment discontinuation (16,19). However, there is a place for atypical antipsychotics, less prone to induce extrapyramidal side effects, such as olanzapine, in the treatment of CINV. Recently, it has been shown that olanzapine combined with a single dose of dexamethasone and a single dose of palonosetron was very effective at controlling acute and delayed CINV in patients receiving HEC. Complete response rates were not significantly different from a similar group of patients receiving HEC and an antiemetic regimen consisting of aprepitant, palonosetron and dexamethasone (20).

A class of therapeutic agents, whose mechanisms of action to control CINV have still not been elucidated, is considered the cornerstone of antiemetic therapy. Although minimally effective as a single agent (monotherapy) or in combination with the 5-HT3 receptor antagonists with or without an NK-1 blocking agent, the corticosteroids (usually methylprednisolone or dexamethasone) have been shown to be effective in preventing or controlling emesis and nausea following administration of moderately to highly emetogenic chemotherapy (21,22). Although at times discomforting, the adverse-effect profile seldom causes drug discontinuation. Transient hyperglycaemia, mood alterations, and insomnia are most frequently observed. Pre-existing diabetes should not be a contraindication to glucocorticoid therapy (16).

Guidelines

The Multinational Association of Supportive Care in Cancer (MASCC), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and the European Society of Medical Oncology (ESMO) are regularly publishing and updating guidelines for the prophylaxis and treatment of CINV (10,23-25).

Patients who receive HEC regimens (Table 1) should receive the three-drug combination of a NK-1 antagonist (aprepitant from day 1 to day 3 or fosaprepitant on day 1 only), a 5-HT3 antagonist (day 1 only) and dexamethasone (days 1 through 3 or days 1 through 4). Antiemetic treatment for patients who receive combination chemotherapy should be determined according to the agent with the greatest degree of emetic risk. The combination between anthracycline (doxorubicin or epirubicin) and cyclophosphamide (abbreviated AC) has recently been reclassified as a HEC (23) (Table 2).

The current recommendations for moderately emetogenic chemotherapy (MEC)-induced acute emesis (Table 1) are the following ones : palonosetron (day 1 only) plus dexamethasone (days 1 through 3) are recommended for the prophylaxis of acute nausea and vomiting in patients who receive MEC not including an AC combination. If palonosetron is not available, clinicians may substitute a first generation 5-HT3 receptor antagonist, preferably granisetron or ondansetron. Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving MEC, any one of the 5-HT3 antagonists is appropriate (23) (Table 3).

There is no difference in the effectiveness of oral or intravenous administration of a 5-HT3 receptor antagonist. The recommended oral dose is 16 mg for ondansetron (divided in 2 intakes), 2 mg for granisetron, 100 mg for dolasetron, 5 mg for tropisetron and 0.50 mg for palonosetron. The recommended intravenous dose is 8 mg or 0.15 mg/kg for ondansetron, 1 mg or 0.01 mg/kg for granisetron, 5 mg for tropisetron and 0.25 mg for palonosetron (Tables 2 and 3).

There is a potential clinically relevant difference in the toxicity of the 5-HT3 receptor antagonists. Indeed,

Table 1. — **List of highly emetogenic chemotherapies (HEC) and moderately emetogenic chemotherapies (MEC), as defined by the Multinational Association of Supportive Care in Cancer (MASCC), the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncolog**

Type of chemotherapy	Administration route	Compound
HEC (> 90%)	Intravenous	Carmustine Cisplatin Cyclophosphamide (≥ 1.5 g/m²) Dacarbazine Dactinomycin Mechlorethamine Streptozotocin
	Oral	Hexamethylmelamine Procarbazine
MEC (30%-90%)	Intravenous	Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide (< 1.5 g/m²) Cytarabine (> 1 g/m²) Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin
	Oral	Cyclophosphamide Imatinib Temozolomide Vinorelbine

HEC = Highly emetogenic chemotherapy concerning more than 90% of patients ; MEC = Moderately emetogenic chemotherapy concerning between 30% and 90% of patients. Modified from Roila *et al*. (25) and Basch *et al*. (23).

Table 2. — **Antiemetic dosing recommendations of international scientific societies in highly emetogenic chemotherapy (HEC)**

	Drug	Acute emesis : day 1	Delayed emesis : post-day 1			
			ASCO	MASCC	NCCN	ESMO
NK-1 antagonist	Aprepitant	125 mg p.o.	R	R	R	R
	Fosaprepitant	150 mg i.v.	/	/	/	/
5-HT3 antagonist	Granisetron	2 mg p.o. or 1 mg i.v.	NR	NR	NR	NR
	Ondansetron	16 mg p.o. or 8 mg i.v.	NR	NR	NR	NR
	Palonosetron	0.5 mg p.o. or 0.25 mg i.v.	NR	NR	NR	NR
	Dolasetron	100 mg p.o.	NR	NR	NR	NR
	Tropisetron	5 mg p.o. or 5 mg i.v.	NR	NR	NR	NR
	Ramosetron	0.3 mg i.v.	NR	NR	NR	NR
Corticosteroid	Dexamethasone	12 mg p.o. or i.v.	R	R	R	R
Benzodiazepine	Lorazepam	0.5-2 mg p.o./i.v/s.l.	/	/	R	/
Neuroleptic	Olanzapine	10 mg p.o.	/	/	R	/
H2 blocker or PPI		R	/	/	R	/

NK-1 = Neurokinin-1 ; 5-HT3 = 5-hydroxytryptamine 3 ; H2 = histamine 2 ; PPI = Proton pump inhibitor ; p.o. = oral ; i.v. = intravenous ; s.l. = sublingual ; / = No specific recommendations ; R = Recommended ; NR = Not Recommended ; ASCO = American Society of Clinical Oncology ; MASCC = Multinational Association of Supportive Care in Cancer ; NCCN = National Comprehensive Cancer Network ; ESMO = European Society of Medical Oncology ; Modified from Basch *et al*. (23) and Roila *et al*. (32).

Table 3. — **Antiemetic dosing recommendations of internationally recognized scientific societies in moderately-emetogenic chemotherapy (MEC)**

	Drug	Acute emesis : day 1	Delayed emesis : post-day 1				
			ASCO	MASCC	NCCN	ESMO	ASHP
NK-1 antagonist	Aprepitant	NR	NR	NR	R	NR	NR
5-HT3 antagonist	Palonosetron[5]	0.50 mg p.o. or 0.25 mg i.v.	R[1]	R[1]	R[2]	R[1]	R[4]
	Granisetron	2 mg p.o. or 1 mg i.v.	R[1]	R[1]	R[2]	R[1]	R[4]
	Ondansetron	16 mg p.o. or 8 mg i.v.	R[1]	R[1]	R[2]	R[1]	R[4]
Corticosteroid	Dexamethasone	82 mg p.o. or i.v.	R[1]	R[1]	R[2]	R[1/3]	R[4]
Other drugs	Benzodiazepine	NR	NR	NR	R[2]	NR	NR
	H2 blocker	NR	NR	NR	R[2]	NR	NR
	PPI	NR	NR	NR	R[2]	NR	NR

NK-1 = Neurokinin-1 ; 5-HT3 = 5-hydroxytryptamine 3 ; H2 = histamine 2 ; PPI = Proton pump inhibitor ; p.o. = oral ; i.v. = intravenous ; R = Recommended ; NR = Not Recommended ; [1] = 5-HT3 antagonist OR Dexamethasone ; [2] = Aprepitant with or without dexamethasone OR dexamethasone alone OR 5-HT3 antagonist with or without benzodiazepine, H2 blocker and/or proton pump inhibitor ; [3] = No precision on the type of corticosteroid to be used ; [4] = 5-HT3 antagonist AND dexamethasone ; [5] = palonosetron is the preferred 5-HT3 antagonist in case of non-AC treatment (AC = anthracycline [doxorubicin or epiribicin] + cyclophosphamide) ; ASCO = American Society of Clinical Oncology ; MASCC = Multinational Association of Supportive Care in Cancer ; NCCN = National Comprehensive Cancer Network ; ESMO = European Society of Medical Oncology ; ASHP = American Society of Health-System Pharmacists. Modified from Basch *et al*. (23) and Roila *et al*. (32).

contrary to ondansetron, palonosetron does not prolong the QTc interval in healthy volunteers and cancer patients (26-28). Nevertheless, the European Medicine Agency (EMA) still recommends being careful when using palonosetron in patients with a cardiovascular medical history.

The recommended dose of dexamethasone administered in a two-drug combination with a 5-HT3 receptor antagonist is 8 mg oral or intravenous (Table 3). In a three-drug combination with a 5-HT3 receptor antagonist and a NK-1 receptor antagonist the recommended dose of dexamethasone is 12 mg oral or intravenous on day 1 followed by 8 mg on days 2 to 3 or days 2 to 4. The recommended oral dose is 125 mg for aprepitant. The recommended intravenous dose is 150 mg for fosaprepitant (Table 2). The antiemetic effect of prophylaxis with a 5-HT3 receptor antagonist plus dexamethasone declines during multiple cycles (more than 3) of MEC. The effect of aprepitant in patients treated with AC is maintained during four cycles of chemotherapy (29). A dopamine antagonist can be used as supplement in the subsequent cycles in patients who experience nausea/emesis from MEC after treatment with standard antiemetic therapy (5-HT3 receptor antagonist plus dexamethasone plus or minus a NK-1 receptor antagonist). Moreover, a benzodiazepine can be used as supplement in the subsequent cycles in patients who experience nausea/emesis from MEC after treatment with standard antiemetic therapy (5-HT3 receptor antagonist plus dexamethasone plus or minus a NK-1 receptor antagonist) (23,29).

More recently, Aapro *et al*. (30) have reported a study suggesting that dexamethasone can be omitted on days 2 and 3, reducing steroid exposure without compromising the overall (0-120 h) antiemetic efficacy in breast cancer patients undergoing MEC who have been given a single dose of 0.25 mg palonosetron and 8 mg dexamethasone on day 1. These results have been confirmed by Celio and colleagues who performed a similar study in a mixed patient population treated with common MEC regimens including AC-based chemotherapy (31). As far as prevention of delayed emesis (beyond day 1) is concerned, there are several discrepancies between guidelines. MASCC recommends using aprepitant or dexamethasone when an AC treatment is administered, and to use dexamethasone or a 5-HT3 antagonist when a MEC is administered. The ESMO recommendations are comparable with the exception that there is no precision concerning the type of corticosteroid to use in case of MEC. ASCO recommends using aprepitant in case of AC treatment, and dexamethasone or a 5-HT3 antagonist in MEC. The American Society of Health-System Pharmacists (ASHP) recommends using a 5-HT3 antagonist + dexamethasone for all MECs. NCCN recommends using aprepitant with or without dexamethasone or dexamethasone alone or a 5-HT3 antagonist with or without lorazepam, with or without a H2 blocker or a proton pump inhibitor (32) (Tables 2 and 3).

Comparison between 5-HT3 antagonists

A Cochrane Review of 5-HT3 antagonists used to prevent CINV was recently published (33). Most trials compared ondansetron and granisetron. Few trials including dolasetron and tropisetron were identified, and only one study with palonosetron was included (34). Findings from the review suggest equivalency between ondansetron and granisetron. A meta-analysis from Jordan *et al*. (35) assessed only first-generation 5-HT3 receptor antagonists. This study also indicates equivalency of granisetron and ondansetron and superiority of granisetron compared with tropisetron. A study comparing ramosetron and granisetron was identified (36). Findings

indicate similar rates of complete response during the first 24 h after chemotherapy. Three studies compared palonosetron with first-generation 5-HT3 antagonists (34,37,38). Findings from two larger studies (30,34) suggested that palonosetron provides superior protection against both nausea and vomiting, particularly during the period from 24 to 120 h after chemotherapy. However, the third study yielded non-significant differences, which might be explained by the fact that it was designed as a non-inferiority trial (38). These studies were conducted in combined emetic risk populations, but not a non-AC moderately emetogenic population, and compared palonosetron with a first-generation 5-HT3 receptor antagonist in which dexamethasone has also been included. The preference for palonosetron is therefore an extrapolation from the Saito *et al*. (34) data ; when an NK-1 receptor antagonist is not used in the setting of cisplatin and AC chemotherapy, the combination of palonosetron and dexamethasone is superior to granisetron and dexamethasone. By inference, with non-AC MEC, palonosetron and dexamethasone are also likely to be superior to a first-generation 5- HT3 receptor antagonist and dexamethasone (23). In a systematic review and meta-analysis, eight eligible trials were identified (34,37-43), reporting outcomes on 3 592 patients. Meta- analyses showed statistically significant differences in favour of palonosetron compared with first-generation 5-HT3 antagonists in the prevention of acute, delayed and overall CINV. Subgroup analyses showed statistically significant differences in favour of both 0.25 mg and 0.75 mg of palonosetron in prevention of all phases of CINV. There were no statistically significant differences between 0.25 and 0.75 mg of palonosetron. Compared with the first-generation 5-HT3 antagonists, 0.75 mg of palonosetron induced a significantly higher frequency of constipation (4). Another meta-analysis of five trials by Botrel and colleagues (44) arrived exactly to the same conclusion without even pointing out a statistically significant difference in terms of constipation.

Comparison between NK-1 antagonists

The results of the first phase III aprepitant study (45) has led to recommending the addition of aprepitant to the combination of a 5-HT3-receptor antagonist plus dexamethasone in patients receiving an AC combination. Another study with a small sample size did not show any advantage of aprepitant in addition to ondansetron plus dexamethasone, but given the small sample size, this study was underpowered (46). A recent, large phase III randomized, gender-stratified, double-blind trial in 848 patients receiving a broad range of MEC regimens (non-AC or AC) with a variety of tumour types showed superiority of an aprepitant triple regimen compared to a control regimen of ondansetron and dexamethasone (47). The primary efficacy endpoint was the proportion of patients reporting no vomiting during the 5 days (0-120 h) following initiation of chemotherapy. Significantly more patients in the aprepitant group reported no vomiting compared to the control group 72.6% versus 62.1%. Also in the acute and delayed phases, significantly more patients in the aprepitant group reported no vomiting compared to the control group (92% versus 83.7%) and 77.9% versus 66.8%, respectively. The key secondary endpoint was the overall complete response (no emetic episodes and no administration of rescue therapy) during the 5 days (0-120 h) following initiation of chemotherapy. Significantly more patients in the aprepitant group reported complete response compared to the control group (68.7% vs. 56.3%). In addition, significantly more patients in the aprepitant group reported complete response compared to the control group in both the acute and delayed phases (89.2% versus 80.3%, and 70.8% versus 60.9%), respectively. No significant differences in the incidence of adverse events were identified. This study confirmed and reinforced the results from the first phase III MEC study in breast cancer patients treated with AC chemotherapy. Because the analysis in the AC and non-AC populations were post-hoc analyses, and because of the heterogeneity of chemotherapy in the non-AC population, this study was not considered sufficiently compelling to recommend the standard use of aprepitant with the initial cycle of non-AC chemotherapy.

Fosaprepitant (currently not available in Belgium) is a water-soluble phosphoryl prodrug for aprepitant, which, when administered intravenously, is converted to aprepitant within 30 min of intravenous administration via the action of ubiquitous phosphatases. Owing to the rapid conversion of fosaprepitant to the active form (aprepitant), fosaprepitant 115 mg provided the same aprepitant exposure in terms of AUC as aprepitant 125 mg orally, and fosaprepitant is expected to provide a correspondingly similar antiemetic effect as aprepitant. Clinical studies have suggested that fosaprepitant could be appropriate as an intravenous alternative to the aprepitant oral capsule. In a study in healthy subjects, fosaprepitant 115 mg was generally well tolerated at a final drug concentration of 1 mg/ml, and fosaprepitant 115 mg was AUC bioequivalent to aprepitant 125 mg. Fosaprepitant in the dose of 115 mg has been approved by the US FDA, the EU and the Australian authorities on day 1 of a 3-day oral aprepitant regimen, with oral aprepitant administered on days 2 and 3. Fosaprepitant may be a useful parenteral alternative to oral aprepitant. Further study is needed to clarify the utility of fosaprepitant in the prevention of CINV and to clarify optimal dosing regimens that may be appropriate substitutes for oral aprepitant (48).

Impact of new treatments and guidelines on the management of CINV in gastrointestinal cancers

An open label study evaluated the safety and efficacy of granisetron for prophylaxis of delayed CINV in 30 patients with advanced or recurrent colorectal cancer. Patients were studied during two cycles of a 5-week

regimen with irinotecan and UFT. Sixteen patients (53.3%) experienced delayed CINV in Cycle 1. The incidence of Grade 2 or higher vomiting was 32.1% and 27.7% in Cycles 1 and 2 in males, respectively, and 54.6% and 32.4% in females, respectively. Granisetron was considered effective against delayed Grade 2 or higher vomiting induced by CPT-11/UFT in female patients (49).

Prior to 2009, the majority of gastrointestinal cancer patients treated with MEC (oxaliplatin or irinotecan) plus a fluoropyrimidine regimen received ondansetron and dexamethasone orally on day 1 of chemotherapy for CINV prevention. From 2009, ondansetron was replaced by palonosetron 0.25 mg i.v. The risk of antiemetic failure was reduced from 50.3% to 28.4% (50).

Chemotherapy regimens differ according to the tumour type being treated and are associated with varying degrees of emetogenic potential. In a meta-analysis of 2 813 patients, subjects receiving aprepitant, ondansetron, and dexamethasone, were compared to subjects receiving ondansetron plus dexamethasone. In all tumour types, complete responses were observed in a higher proportion of HEC-treated patients receiving aprepitant compared with active-control patients (genitourinary [61.5% vs 40.6%], gastrointestinal [68.2% vs 44.7%], and lung cancers [73.5% vs 52.8%]). For MEC-treated patients, complete response rates were also higher for aprepitant patients than active-control patients for all tumour types (51).

In Japan, the combination comprising aprepitant, granisetron, and dexamethasone was evaluated in patients with gastric cancer undergoing chemotherapy with cisplatin and S-1.

Fifty-three patients were included. Complete response (no emesis and no rescue medication) was achieved in 88.7, 98.1, and 88.7% of patients in the overall, acute, and delayed phases, respectively (52). Patients treated with a MEC for a GI cancer experienced a significant decrease in CINV when they were switched from granisetron to palonosetron. The incidence of delayed nausea was significantly lower in the palonosetron group (8.7%) than in the granisetron group (37%). Delayed vomiting developed in 10.9% of patients in the granisetron group, but did not occur in the palonosetron group (53).

A study of 113 patients with colorectal cancer receiving MEC or low-emetic risk chemotherapy, demonstrated that the adherence to the MASCC/ESMO guideline was extremely low (3%), the predominant cause of which was the lack of dexamethasone prescription on days 2 and 3 (43%), or throughout the overall chemotherapy period (45%) (54). The same observation was made by Fujii *et al*. (55) in 61 patients with colorectal cancer receiving the first course of MEC. They carried out intervention (treatment with dexamethasone on days 2 and 3) to improve evidence-based antiemetic medication in another 64 patients. The rate of adherence to the antiemetic guidelines was only 6.6% ; non-adherence was due mostly to the lack of dexamethasone treatment on days 2 and 3. In the interventional group, antiemetic medication adherence was markedly enhanced to 89%, which led to a significant enhancement of complete protection from nausea and vomiting during-delayed period from 54% to 74%, although the daily dose of dexamethasone was 4 mg, lower than that recommended by the guidelines (8 mg). These findings suggest that medication intervention to reduce the gap between guidelines and clinical practice improves the emetic control in patients with colorectal cancer receiving MEC.

Reimbursement policy in Belgium

Optimal control of CINV is a high priority in the care of the cancer patient. The Belgian Authorities use the ESMO/MASCC guidelines as a base for reimbursement and this has dramatically increased the level of implementation (56). The Belgian reimbursement conditions have very recently changed after a global revision of the whole class of antiemetics and a new policy will be in place as of 01 March 2014.

A 5-HT3 antagonist will be reimbursed if it can be demonstrated that it is administered for the prevention of nausea and vomiting induced by MEC or HEC (> 30% nausea and vomiting risk) in accordance with the Summary of Product Characteristics or the ESMO/MASCC guidelines (25). The prescribing physician agrees to make available to the medical officer the evidence attesting of the described situation. In Belgium the simultaneous reimbursement of a 5-HT3 antagonist and aprepitant is never authorised after the first day of treatment. Aprepitant is also reimbursed since 2006, if it can be demonstrated that it has been administered in an adult patient for the prevention of acute or delayed nausea and vomiting episodes induced by a HEC involving cisplatin ($\geq$ 50 mg/m^2) or by a MEC, and if it has been associated to a 5-HT3 antagonist on day 1, and with a corticosteroid from day 1 to day 4.

The simultaneous reimbursement of aprepitant and 5-HT3 antagonists, after the first day of treatment, is never authorised. Contrary to 5-HT3 antagonists, aprepitant is not reimbursed in case oxaliplatin is used among the chemotherapeutic agents. This rule established at the time of previous guidelines which were not considering oxaliplatin among MEC, has not been revised by Belgian health authorities in accordance with new guidelines. It constitutes a potential restriction to the use of aprepitant, particularly for the treatment of gastrointestinal cancers in which oxaliplatin is frequently used (Table 4).

Residual issues and ongoing research

For most patients, antiemetic regimens prevent emesis and lessen nausea while patients are undergoing cancer therapy. However, some patients continue to report nausea (57). Identification of new approaches to decrease nausea is required. Limited research on nausea and vomiting control in special populations is available,

Table 4. — **Recently updated Belgian reimbursement conditions of 5-HT3 antagonists and aprepitant, applicable as of 01 March 2014**

Drug	**Reimbursement conditions in Belgium**
All 5-HT3 antagonists (as of 01 March 2014):	HEC & MEC attested by the physician in accordance with the SmPC or the ESMO/MASCC guideline. No reimbursement for other concomitant 5-HT3 antagonists or aprepitant after the first day of treatment.*
Aprepitant:	HEC & MEC, if associated with a 5-HT3 antagonist on day 1 and with a corticosteroid from day 1 to day 4. Simultaneous reimbursement with 5-HT3 antagonists after day 1 is not authorised. No reimbursement if oxaliplatin is used among the chemotherapeutic agents.**

HEC = Highly emetogenic chemotherapy ; MEC = Moderately emetogenic chemotherapy ; SmPC = Summary of Product Characteristics ; ESMO = European Society of Medical Oncology ; MASCC = Multinational Association of Supportive Care in Cancer ; 5-HT3 = 5- hydroxytryptamine 3.

* Belgium is the only European country which does not reimburse the concomitant use of a 5- HT3 antagonist and aprepitant after the first day of treatment.

** This was based on previous international guidelines when oxaliplatin was excluded from MEC. Oxaliplatin is now recognized as a MEC but Belgian reimbursement conditions have not yet been adapted accordingly.

particularly paediatric patients. Similarly, few randomized controlled trials have investigated the role of antiemetics in patients undergoing radiation therapy. Research to improve symptom control in these patients is necessary (23). Patients undergoing multiday chemotherapy are at risk for both acute and delayed nausea and vomiting based on the emetogenic potential of the individual chemotherapy agents and their sequence (58-60). A specific antiemetic regimen for each day is difficult to recommend, especially because acute and delayed emesis may overlap after the initial day of chemotherapy until the last day of chemotherapy. The period of risk for delayed emesis after the conclusion of chemotherapy also depends on the specific regimen and emetogenic potential of the last chemotherapy agent administered in the regimen (10).

Last but not least, research is currently ongoing to develop combined 5-HT3/NK-1 antagonists. NEPA is a fixed-dose, synergistic combination of the new NK-1 antagonist netupitant (300 mg) and palonosetron (0.5 mg). At the occasion of the ASCO 2013 annual meeting the preliminary results of a Phase III study were presented. This clinical trial included 1 455 chemotherapy-naive patients undergoing AC-based chemotherapy who were randomly assigned to receive dexamethasone plus either NEPA or palonosetron. NEPA exhibited superior rates of complete acute (0-24 hour post-chemotherapy) and delayed (25-120 hours post-chemotherapy) antiemetic response (no emesis and no rescue medication ; $p = 0.047$ and $p = 0.001$, respectively). NEPA was also superior to palonosetron during the delayed/overall phases for complete protection, no emesis, and no significant nausea.

These new combined therapies are awaited with great anticipation by oncologists.

Conclusion

During the last 20 years great advances have been made in the prevention and treatment of nausea/vomiting in patients receiving chemotherapy. Aprepitant and palonosetron are the most recent additions to the available armamentarium. Further improvements are still desirable in the prevention and treatment of delayed emesis.

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