

## 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients

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### introduction

Despite the considerable progress achieved in the last 30 years, vomiting and, especially, nausea, continue to be two of the most distressing side-effects of cancer chemotherapy. In the late 1990s, several professional organisations published recommendations on the optimal antiemetic prophylaxis in patients submitted to chemotherapy and/or radiotherapy. The European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) published the results of the third Consensus Conference on antiemetics held in Perugia in June 2009 in *Annals of Oncology* in 2010 [1]. An update of these recommendations, including studies published from 1 January 2009 to 30 June 2015, was discussed in Copenhagen in June 2015 and is presented in this paper. The methodology for the guideline process is described in detail in the 2010 publication [1]. To change a 2010 recommendation or for a new guideline recommendation to be accepted, a consensus of at least 67% of the expert panellists was needed. As a general rule, the panel considered changes of 10% or greater to be sufficient to warrant the changing of a recommendation.

ESMO levels of Evidence [I–V] and Grades of Recommendation [A–D] are given according to the ESMO-adapted version of the grading of the Infectious Diseases Society

of America. The MASCC Levels of Scientific Confidence was classified as

- high: repeated, randomised trials that were appropriately sized and well conducted
- moderate: at least one randomised trial, supported by well-conducted, phase II trials, or possibly several well-conducted phase II studies;
- low: formal clinical trials of a level less than that expressed above;
- very low: clinical impression only;
- no confidence possible.

The MASCC Levels of Consensus are given as high, moderate or low.

### levels of emetogenicity

The emetogenicity of chemotherapy agents is used as a framework for defining antiemetic treatment guidelines. In the past, a number of classifications have been proposed in which chemotherapy agents have been divided into three to five emetogenic levels. The literature has provided a very limited source of useful information in the development of these classifications, given the imprecise, inconsistent and extremely limited ways in which information on emesis and nausea has been recorded in most therapeutic trials. Most classifications have not differentiated between the various types of emesis, such as acute, delayed, breakthrough and anticipatory, and few have accounted for important treatment- and patient-related variables, such as

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chemotherapy dose, rate and route of administration, gender, age and history of alcohol consumption.

A four-level classification of intravenous (i.v.) chemotherapy agents has been accepted by registration authorities and groups producing recommendations on antiemetics: high (emetic risk >90%), moderate (30%–90%), low (10%–30%), and minimal (<10%) [2]. However, the broad range of expected emesis in the moderate level has posed an increasing challenge to efforts to provide a single recommendation for antiemetic treatment appropriate for the entire moderate category [3].

Numerous new antineoplastic agents, especially oral agents, have been introduced since the last MASCC/ESMO antiemetic guideline update, and have to be incorporated into the emetogenic classification. Such efforts continue to be hampered by the limited recording of ‘common’ toxicities such as emesis during antineoplastic drug development and the unregulated use of prophylactic antiemetics during antineoplastic drug development even before the emetogenicity of the agents is established. Furthermore, information might be incomplete or uninterpretable when only severe vomiting or nausea or combined nausea and vomiting are listed. Patients in trials with new agents are often heavily pretreated with other antitumour agents and therefore may also be more prone to develop emesis. Many agents tend to be used in extended regimens of daily oral use, and therefore, we decided that for oral agents, the emetic potential was based upon a full course of therapy and not a single dose.

A systematic search identified 42 new antineoplastic agents and 168 studies could be extracted in the established period. There was adequate evidence to allow 41 of 42 new agents to be classified in alphabetical order and according to emetogenic risk (Table 1). This represents a change from prior MASCC/ESMO antiemetic guideline updates as the relative emetogenicity of agents within a given emetic level is not shown because of the mentioned constraints.

No new highly emetogenic agents were identified. Seven new moderately emetogenic agents were identified (i.v.: temozolomide, trabectedin, romidepsin, thiotepea; oral: bosutinib, crizotinib, ceritinib). Twenty-six new agents were classified as having a low emetogenic risk potential (i.v.: aflibercept, belinostat, blinatumomab, brentuximab, cabazitaxel, carfilzomib, eribulin, ipilimumab, nab-paclitaxel, pegylated liposomal doxorubicin, pertuzumab, trastuzumab-emtansine, vinflunine; oral: afatinib, axatinib, dabrafenib, dasatinib, ibrutinib, idelalisib, nilotinib, olaparib, pazopanib, ponatinib, regorafenib, vandetanib, vorinostat). Finally, eight new agents were classified as minimally emetogenic (i.v.: nivolumab, ofatumumab, pembrolizumab, pixantrone; oral: pomalidomide, ruxolitinib, vemurafenib, vismodegib). The emetic risk classification only refers to adult patients.

The update committee also recommended reclassification of the combined anthracycline–cyclophosphamide (AC) regimen for breast cancer patients as a special category within highly emetogenic, because delayed phase treatment is different from cisplatin regimens.

## prevention of acute and delayed nausea and vomiting induced by highly emetogenic chemotherapy

Previous MASCC/ESMO consensus guidelines recommended a three-drug regimen including single doses of a 5-HT<sub>3</sub>-receptor

antagonist (RA), dexamethasone and aprepitant given before chemotherapy to prevent acute nausea and vomiting following chemotherapy of high emetic risk and dexamethasone plus aprepitant or aprepitant alone to prevent delayed nausea and vomiting in cisplatin-treated/ and AC-treated patients, respectively [1]. Since then two new neurokinin (NK)<sub>1</sub> RAs, netupitant and rolapitant, have been approved by the US Food and Drug Administration (FDA, netupitant as NEPA combined with palonosetron and rolapitant) and the European Medicines Agency (EMA, netupitant as NEPA combined with palonosetron) and an i.v. formulation of aprepitant, fosaprepitant, has been marketed.

### cisplatin-treated patients

Five studies have been carried out since 2009. A double-blind, randomised, non-inferiority study compared the efficacy and tolerability of a single i.v. dose of fosaprepitant (150 mg), with the 3-day oral aprepitant administration in 2247 cancer patients submitted to cisplatin-based chemotherapy [4]. The complete response rate (no vomiting and no rescue treatment) was not significantly inferior with fosaprepitant compared with aprepitant. In particular, complete response was achieved in 89.0% versus 88.0% of patients on day 1, in 74.3% versus 74.2% on days 2–5 and in 71.9% versus 72.3% on days 1–5, respectively. Subsequent studies confirmed the equal efficacy of the 150 mg single i.v. dose of fosaprepitant [5] and the 3-day oral regimen of aprepitant in cisplatin-based chemotherapy [6].

NEPA, an oral combination of the NK<sub>1</sub> RA, netupitant, and the 5-HT<sub>3</sub> RA, palonosetron, has been evaluated in a randomised, double-blind, dose-ranging phase II study in 694 cisplatin-treated patients [7]. Three different oral doses of netupitant (100, 200 and 300 mg) plus oral palonosetron 0.50 mg were compared with oral palonosetron 0.50 mg, all given on day 1. A standard 3-day oral aprepitant regimen plus a single i.v. dose of ondansetron 32 mg was included as an exploratory arm. In the NEPA and aprepitant arms, patients received 12 mg oral dexamethasone on day 1 and 4 mg twice daily on days 2–4 and in the palonosetron arm, the dose of dexamethasone was 20 mg orally day 1 followed by 8 mg twice daily on days 2–4. The primary end point was complete response on days 1–5 which was significantly superior with all NEPA doses with respect to palonosetron (87.4% NEPA<sub>100</sub>, 87.6% NEPA<sub>200</sub>, and 89.6% NEPA<sub>300</sub> and 76.5% with palonosetron), while complete response was achieved in 86.6% of patients receiving aprepitant and ondansetron. Complete response on days 2–5 was also significantly superior in the NEPA (and aprepitant) arms compared with palonosetron. On day 1, the complete response was 93.3%, 92.7% and 98.5%, respectively, versus 89.7% with palonosetron and 94.8% with aprepitant and ondansetron. On day 1, only NEPA 300 mg and aprepitant plus ondansetron were significantly superior to palonosetron alone. Therefore, a dose of 300 mg NEPA was selected for the phase III trial carried out in cisplatin and AC-treated cancer patients.

A randomised, double-blind, dose-finding study carried out in 454 patients submitted to cisplatin evaluated four different oral doses of rolapitant (9, 22.5, 90 and 180 mg respectively) in comparison with placebo, all combined with i.v. ondansetron 32 mg and oral dexamethasone 20 mg on day 1 followed by dexamethasone 8 mg twice daily on days 2–4 [8]. The primary

**Table 1.** Emetogenic potential of single intravenous antineoplastic agents

	IV chemotherapy		Oral chemotherapy <sup>a</sup>
High	Anthracycline/cyclophosphamide combination <sup>b</sup>		Hexamethylmelamine
	Carmustine		Procarbazine
	Cisplatin		
	Cyclophosphamide $\geq 1500 \text{ mg/m}^2$		
	Dacarbazine		
	Mechlorethamine		
	Streptozocin		
Moderate	Alemtuzumab	Epirubicin	Bosutinib
	Azacitidine	Idarubicin	Ceritinib
	Bendamustine	Ifosfamide	Crizotinib
	Carboplatin	Irinotecan	Cyclophosphamide
	Clofarabine	Oxaliplatin	Imatinib
	Cyclophosphamide $< 1500 \text{ mg/m}^2$	Romidepsin	Temozolomide
	Cytarabine $> 1000 \text{ mg/m}^2$	Temozolomide <sup>c</sup>	Vinorelbine
	Daunorubicin	Thiotepa <sup>d</sup>	
	Doxorubicin	Trabectedin	
	Low	Aflibercept	Ipilimumab
Belinostat		Ixabepilone	Axatinib
Blinatumomab		Methotrexate	Capecitabine
Bortezomib		Mitomycin	Dabrafenib
Brentuximab		Mitoxantrone	Dasatinib
Cabazitaxel		Nab-paclitaxel	Everolimus
Carfilzomib		Paclitaxel	Etoposide
Catumaxumab		Panitumumab	Fludarabine
Cetuximab		Pemetrexed	Ibrutinib
Cytarabine $\leq 1000 \text{ mg/m}^2$		Pegylated liposomal doxorubicin	Idelalisib
Docetaxel		Pertuzumab	Lapatinib
Eribulin		Temsirolimus	Lenalidomide
Etoposide		Topotecan	Olaparib
5-Fluorouracil		Trastuzumab-emtansine	Nilotinib
Gemcitabine		Vinflunine	Pazopanib
			Ponatinib
			Regorafenib
			Sunitinib
			Tegafur uracil
			Thalidomide
		Vandetanib	
		Vorinostat	
Minimal	Bevacizumab	Pembrolizumab	Chlorambucil
	Bleomycin	Pixantrone	Erlotinib
	Busulfan	Pralatrexate	Gefitinib
	2-Chlorodeoxyadenosine	Rituximab	Hydroxyurea
	Cladribine	Trastuzumab	Melphalan
	Fludarabine	Vinblastine	Methotrexate
	Nivolumab	Vincristine	L-phenylalanine mustard
	Ofatumumab	Vinorelbine	Pomalidomide
			Ruxolitinib
			Sorafenib
		6-Thioguanine	
		Vemurafenib	
		Vismodegib	

<sup>a</sup>Classified emetic potential of oral agents based upon a full course of therapy and not a single dose.

<sup>b</sup>The combination of an anthracycline and cyclophosphamide in patients with breast cancer should be considered highly emetogenic.

<sup>c</sup>No direct evidence found for temozolomide i.v.; as all sources indicate a similar safety profile to the oral formulation, the classification was based on oral temozolomide.

<sup>d</sup>Classification refers to individual evidence from paediatric trials.

end point was complete response on days 1–5 which was significantly increased with all doses of rolapitant. The greatest benefit was observed with rolapitant 180 mg (62.5% versus 46.7% on days 1–5, 87.6% versus 66.7% on day 1 and 63.6 versus 48.9 on days 2–5), and this dose was selected for the phase III studies.

Two phase III studies (HEC-1 and HEC-2), published as a single paper, have evaluated rolapitant in cisplatin-treated patients [9]. The two phase III studies had the same design and compared a combination of granisetron 10 µg/kg i.v. and oral dexamethasone 20 mg on day 1 and 8 mg twice daily on days 2–4 with granisetron and dexamethasone in the same doses and schedules plus rolapitant 180 mg orally. The dose of dexamethasone was not reduced in the experimental arm because rolapitant is not an inducer or inhibitor of CYP3A4. The primary end point of these studies was the complete response on days 2–5 which was significantly superior in the rolapitant arms in both studies (HEC-1 73% versus 58% and HEC-2 70% versus 62%). Complete responses on day 1 and days 1–5 were also significantly superior with rolapitant in the HEC-1 study (84% versus 74% and 70% versus 56%), but not in the HEC-2 study (83% versus 79% and 68% versus 60%). Combining data from these two trials, the addition of rolapitant significantly improved the effect of granisetron plus dexamethasone compared with placebo in all primary and secondary end points.

In conclusion, the addition of an NK<sub>1</sub> RA in patients receiving cisplatin chemotherapy increased the complete response on day 1 by 4%–14%, on days 2–5 by 8%–21% and on days 1–5 by 8%–20% [1, 7, 9]. This increase is not only statistically significant but also clinically relevant because of the potential positive impact on the rates of complete response achieved in the first cycle on the subsequent cycles of chemotherapy. The magnitude of the differences observed between the studies could be affected by differences in the control arm (e.g. differences in 5-HT<sub>3</sub> RA used). Furthermore, part of the antiemetic effect on days 2–5 could also be due to a dependence effect from day 1 (the better the results obtained on day 1, the higher the chance of complete responses on days 2–5). Therefore, for the prevention of non-AC highly emetogenic chemotherapy, a three-drug regimen including single doses of a 5-HT<sub>3</sub> RA, dexamethasone and an NK<sub>1</sub> RA (aprepitant, fosaprepitant, netupitant or rolapitant), given before chemotherapy is recommended [MASCC level of confidence: high; MASCC level of consensus: high; ESMO level of evidence I; ESMO grade of recommendation: A]. In patients receiving non-AC highly emetogenic chemotherapy treated with a combination of an NK<sub>1</sub> RA, a 5-HT<sub>3</sub> RA and dexamethasone to prevent acute nausea and vomiting, dexamethasone on days 2–4 is suggested to prevent delayed nausea and vomiting [MASCC level of confidence: high; MASCC level of consensus: moderate; ESMO level of evidence I; ESMO grade of recommendation: B].

Recently, a double-blind study, specifically designed to investigate cisplatin-induced delayed nausea and vomiting, compared the effect of aprepitant with metoclopramide in 303 chemotherapy-naïve patients receiving the same antiemetic prophylaxis on day 1 consisting of i.v. palonosetron 0.25 mg, dexamethasone 12 mg and oral aprepitant 125 mg before chemotherapy [10]. Patients were randomised to oral dexamethasone 8 mg (days 2–4) plus oral aprepitant 80 mg (days 2–3) or to oral metoclopramide 20 mg four times daily plus oral dexamethasone 8 mg twice daily (both days 2–4). Complete response on days 2–5 was

the primary end point. No significant differences were observed on day 1. On days 2–5, the complete response rates were not significantly different (80.3% with aprepitant plus dexamethasone versus 82.5% with metoclopramide plus dexamethasone). Also no significant differences were observed with respect to the secondary efficacy end point and toxicity. Therefore, if aprepitant 125 mg is used on day 1, then dexamethasone 8 mg × 1 (days 2–4) + aprepitant 80 mg × 1 (days 2–3) or dexamethasone 8 mg × 2 (days 2–4) + metoclopramide 20 mg × 4 (days 2–4) is recommended. Note that this dosage of metoclopramide derives from the results of the phase III study mentioned above and some regulatory authorities like the EMA now recommend a maximum of 0.5 mg/kg total daily dose.

These changes aim mainly to reduce the risk of neurological side-effects.

### AC-treated female patients with breast cancer

Two studies have been carried out since 2009. A randomised double-blind phase III study in 1455 patients (98% with breast cancer), undergoing AC chemotherapy compared NEPA (oral netupitant 300 mg and palonosetron 0.5 mg) plus oral dexamethasone 12 mg with oral palonosetron 0.5 mg plus oral dexamethasone 20 mg [11]. The primary end point was the complete response achieved during the delayed phase which was significantly superior with netupitant (76.9% versus 69.5%). Even complete response on day 1 (88.4% versus 85.0%) and on days 1–5 (74.3% versus 66.6%) were significantly superior with the addition of netupitant. Although the benefit was <10% as concerns both the primary and secondary efficacy parameters, these differences seem to be clinically relevant, because a significantly higher number of patients in the NEPA arm reported that nausea and vomiting had no impact on daily living when compared with patients in the palonosetron arm.

A randomised, double-blind phase III study in 1369 patients submitted to a combination of AC or non-AC moderately emetogenic chemotherapy (MEC) evaluated rolapitant [12]. Oral granisetron (2 mg daily on days 1–3) and dexamethasone (20 mg on day 1) were compared with oral rolapitant (180 mg on day 1) plus oral granisetron and dexamethasone in the same doses and schedules as in the control arm. The primary end point was complete response on days 2–5. Protocol-specified subgroup analysis in women with breast cancer receiving AC (53%) and patients of different diagnosis receiving non-AC (47%) chemotherapy was planned. Rolapitant significantly improved the effect of granisetron and dexamethasone both in the entire population and in women with breast cancer receiving AC chemotherapy; complete response on days 2–5 was achieved by 71% versus 62% of the total population and by 67% versus 60% of AC-treated patients. Also the rates of patients obtaining a complete response on days 1–5 were significantly improved by rolapitant in the entire population and in the AC subgroup, whereas no significant difference was seen on day 1 in either group [12].

Therefore, the addition of an NK<sub>1</sub> RA in patients receiving AC chemotherapy for breast cancer increased the complete response on day 1 by 0%–7%, on days 2–5 by 6%–9% and on days 1–5 by 8%–9% [1, 11, 12]. The improvement in the delayed and overall phases is not only statistically significant but also

clinically relevant because of the potential positive impact on the complete response rates in the subsequent cycles of chemotherapy. Similar to the cisplatin studies, the differences in the magnitude of benefit could be influenced by differences in the control arm. Also as with the cisplatin-based studies, none of the AC chemotherapy studies were designed specifically for the investigation of delayed nausea and vomiting, and a carry-over effect of a day 1 difference cannot be excluded.

In conclusion, in women with breast cancer receiving AC chemotherapy, a three-drug regimen including single doses of a 5-HT<sub>3</sub> RA, dexamethasone and an NK<sub>1</sub> RA (aprepitant, fosaprepitant, netupitant or rolapitant), given before chemotherapy is recommended [MASCC level of confidence: high; MASCC level of consensus: high; ESMO level of evidence I; ESMO grade of recommendation: A].

A randomised double-blind study evaluated aprepitant versus dexamethasone for the prophylaxis of delayed emesis in 580 chemotherapy-naïve women with breast cancer, who received adjuvant AC and i.v. palonosetron 0.25 mg, dexamethasone 8 mg and oral aprepitant 125 mg as antiemetic prophylaxis on day 1 [13]. Patients on days 2–3 received oral dexamethasone 4 mg twice daily or oral aprepitant 80 mg daily. No significant differences were observed on day 1. On days 2–5, the complete response rates, the primary end point, were identical in both arms (79.5%). Also no significant differences were observed with respect to the secondary efficacy end point, but significantly more patients complained of heartburn and insomnia in the dexamethasone group on days 2–5. The use of steroids in the delayed phase tends to be reduced, because of the side-effects, and it should be noted that the netupitant–palonosetron and rolapitant studies did not use dexamethasone on days 2 and 3.

Therefore, in women with breast cancer treated with a combination of a 5-HT<sub>3</sub> RA, dexamethasone and an NK<sub>1</sub> RA to prevent acute nausea and vomiting, aprepitant or dexamethasone should be used on days 2 and 3 but not if fosaprepitant, netupitant or rolapitant has been used on day 1 [MASCC level of confidence: moderate; MASCC level of consensus: moderate; ESMO level of evidence II; ESMO grade of recommendation: B]. If an NK<sub>1</sub> receptor antagonist is not available for the prophylaxis of nausea and vomiting induced by AC chemotherapy, palonosetron is the preferred 5-HT<sub>3</sub> RA [14].

### are there differences among the NK<sub>1</sub> RAs?

Aprepitant and netupitant are inhibitors of CYP3A4 and as a consequence, both significantly increase the exposure to oral dexamethasone; hence, reduction in oral dexamethasone doses is recommended during co-administration (from 20 to 12 mg). Rolapitant is not an inhibitor or inducer of CYP3A4 and therefore does not require a reduced dose of dexamethasone when co-administered. However, rolapitant is a moderate inhibitor of CYP2D6. At present, no comparative studies have been carried out to identify differences in efficacy and toxicity between the three NK<sub>1</sub> RAs. Therefore, when available, the choice may be dependent on the respective convenience and cost.

### other highly emetogenic chemotherapy

These agents include mechlorethamine, streptozocin, cyclophosphamide  $\geq 1500$  mg/m<sup>2</sup>, carmustine and dacarbazine. Even

**Table 2.** Recommended doses of serotonin (5-HT)<sub>3</sub> receptor antagonists

Agent	Route	Antiemetics
Ondansetron	IV	8 mg or 0.15 mg/kg
	Oral	16 mg <sup>a</sup>
Granisetron	IV	1 mg or 0.01 mg/kg
	Oral	2 mg (or 1 mg <sup>b</sup> )
Dolasetron	Oral	100 mg
Tropisetron	IV	5 mg
	Oral	5 mg
Palonosetron	IV	0.25 mg
	Oral	0.5 mg

<sup>a</sup>Randomised studies have tested the 8 mg twice daily schedule.

<sup>b</sup>The 1 mg dose is preferred by some panellists.

**Table 3.** Recommended doses of corticosteroids<sup>a</sup> (dexamethasone)

Dexamethasone	Dose and schedule
High risk	
Acute emesis	20 mg once [12 mg when used with (fos) aprepitant or netupitant] <sup>b</sup>
Delayed emesis	8 mg bid for 3–4 days [8 mg once daily when used with (fos)aprepitant or netupitant]
Moderate risk	
Acute emesis	8 mg once
Delayed emesis	8 mg daily for 2–3 days (many panellists give the dose as 4 mg bid)
Low risk	
Acute Emesis	4–8 mg once

<sup>a</sup>While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice.

<sup>b</sup>The 12 mg dose of dexamethasone is the only one tested with (fos) aprepitant/netupitant in large, randomised trials.

if no randomised studies have evaluated the NK<sub>1</sub> RAs against emesis induced by these drugs, adding an NK<sub>1</sub> RA to the combination of a 5-HT<sub>3</sub> RA and dexamethasone for all non-cisplatin and non-AC highly emetogenic chemotherapy is recommended.

### dose, schedule, route of administration and safety of antiemetics

Suggested doses, schedules and route of administration of the 5-HT<sub>3</sub> RAs, the NK<sub>1</sub> RAs and dexamethasone in the prevention of acute and delayed nausea and vomiting induced by highly emetogenic chemotherapy are reported in Tables 2–4. With the 5-HT<sub>3</sub> RAs, electrocardiography changes, particularly QTc prolongation, are a class effect. The risk may differ between these agents and palonosetron seems to induce the lowest risk [15]. Due to cardiac adverse effects, FDA warnings against both the i.v. dose of dolasetron (Drug Safety Communication, December

**Table 4.** Recommended doses of neurokinin (NK)<sub>1</sub> receptor antagonists

NK1 receptor antagonist	Dose and schedule
Aprepitant <sup>a</sup> and fosaprepitant: acute emesis	Aprepitant: 125 mg once on the day of chemotherapy <sup>a</sup> Or Fosaprepitant: 150 mg i.v., once on the day of chemotherapy
Aprepitant <sup>a</sup> and fosaprepitant: delayed emesis	Aprepitant: 80 mg orally, once daily for the 2 days after chemotherapy; or none if fosaprepitant is used
Rolapitant	180 mg orally once on the day of chemotherapy
Netupitant	300 mg netupitant/0.5 mg palonosetron orally once on the day of chemotherapy

<sup>a</sup>Aprepitant 165 mg as a single dose before chemotherapy (and none days 2–3) is registered by EMA and other authorities, but no randomised clinical trials have tested this dose schedule.

2010) and the high 32 mg i.v. dose of ondansetron (Drug Safety Communication, June 2012) have been released. These formulations have therefore been withdrawn [15]. A transdermal formulation of granisetron has been evaluated versus daily oral granisetron (2 mg/day for 3–5 days) in a randomised, double-blind study carried out in 582 patients submitted to multiple-day moderately or highly emetogenic chemotherapy [16]. The transdermal formulation of granisetron was non-inferior to 3–5 days of daily oral granisetron. A patch providing 3.1 mg granisetron/24 h for up to 7 days has been marketed.

Finally, two large randomised, double-blind studies confirmed non-inferiority of the oral 0.5 mg palonosetron dose compared with the i.v. 0.25 mg dose in patients receiving cisplatin-based chemotherapy [17] or different antineoplastic agents with a moderate emetogenic potential [18]. Concerning NK<sub>1</sub> RAs, a study in 16 young, healthy volunteers showed that the 5-day NK<sub>1</sub> receptor binding affinity of a single dose of oral aprepitant 165 mg was as high as a single i.v. dose of fosaprepitant 150 mg [19]. It is unknown if the results can be extrapolated to cancer patients, who are older than the healthy volunteers in the study and typically require 4–6 different drugs each day, heightening the risk of drug–drug interactions with the oral formulation. Nevertheless, the single oral dose was approved by the EMA, but not the FDA. No clinical trial has investigated the 165 mg single oral dose.

The EMA has recommended a change in the use of metoclopramide due to the risk of neurological effects such as short-term extrapyramidal disorders [EMA/443003/2013]. The EMA recommends metoclopramide not to be used in children below 1 year of age and for adults to be used in a daily maximum dose of 30 mg (e.g. 10 mg × 3 orally) for a maximum of 5 days. The authors of this guideline believe that 10 mg of metoclopramide is not superior to placebo in the effect against chemotherapy-induced nausea and vomiting and that higher doses are tolerable, when given for 2–3 days.

## olanzapine

Studies of low to moderate quality have investigated the antiemetic efficacy and tolerability of olanzapine, an approved anti-psychotic drug that blocks multiple neurotransmitters in the central nervous system: dopamine D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub> receptors, serotonin 5-HT<sub>2a</sub>, 5-HT<sub>2c</sub>, 5-HT<sub>3</sub> and 5-HT<sub>6</sub> receptors, α<sub>1</sub> adrenergic receptors, muscarinic receptors and histamine H<sub>1</sub> receptors. A phase III open trial, carried out in patients submitted to cisplatin ≥70 mg/m<sup>2</sup> or cyclophosphamide ≥500 mg/m<sup>2</sup> and doxorubicin ≥50 mg/m<sup>2</sup>, compared olanzapine with aprepitant in the prevention of chemotherapy-induced emesis [20]. Patients were randomised to receive oral olanzapine 10 mg, palonosetron 0.25 mg i.v. and dexamethasone 20 mg i.v. on day 1 and oral olanzapine 10 mg on days 2–4 or oral aprepitant 125 mg, palonosetron 0.25 mg i.v. and dexamethasone 12 mg i.v. on day 1 and oral aprepitant 80 mg on days 2–3 and oral dexamethasone 4 mg bid on days 2–4. In 251 patients, the complete response was not significantly different between the two antiemetic regimens on day 1 (97% versus 87%) on days 2–5 (77% versus 73%) and on days 1–5 (77% versus 73%), respectively. The rate of no nausea on days 1–5 was superior with olanzapine (69% versus 38%). Unfortunately, this study had a number of shortcomings: it was an open study and, therefore, not ideal to evaluate the impact on subjective end points such as nausea. Due to the small sample size, the study was only powered to investigate large differences such as a 15% difference in complete response on days 1–5. It was not defined if the study was designed as a superiority, non-inferiority or equivalence study. More recently, a phase II study [21] and a randomised, double-blind phase III study published as an abstract only (at the time of writing) [22] reported high complete response rates and high protection rates against nausea in patients receiving cisplatin-based or AC chemotherapy, when olanzapine was combined with a three-drug combination of a 5-HT<sub>3</sub> RA, dexamethasone and the NK<sub>1</sub> RA aprepitant.

In conclusion, olanzapine seems to be useful in the prophylaxis of delayed nausea [superior to (fos)aprepitant] and equal to (fos)aprepitant in the prevention of acute symptoms. Olanzapine may be considered with a 5-HT<sub>3</sub> RA plus dexamethasone, particularly when nausea is an issue, but using the 10 mg dose, patient sedation may be a concern [MASCC level of confidence: low; MASCC level of consensus: low; ESMO level of evidence II; ESMO grade of recommendation: B].

## prevention of acute and delayed nausea and vomiting induced by MEC

Previous MASCC/ESMO guidelines recommended palonosetron plus dexamethasone for the prophylaxis of acute nausea and vomiting. Furthermore, for MEC known to be associated with a significant incidence of delayed nausea and vomiting, patients should receive antiemetic prophylaxis for delayed emesis; in this case, multiday oral dexamethasone was the preferred treatment [1].

## the prophylaxis of MEC-induced acute nausea and vomiting

Studies evaluating palonosetron versus other 5-HT<sub>3</sub> RAs have almost exclusively been carried out in patients receiving cisplatin

or breast cancer patients receiving AC. Therefore, there is a lack of comparative studies in MEC agents as defined in this guideline.

A meta-analysis of randomised trials concluded that palonosetron in the above reported patient population was superior to other 5-HT<sub>3</sub> RAs [23]. A limitation of the published data is that most of the palonosetron clinical trials did not permit the administration of corticosteroids. Thus, there is no definitive evidence demonstrating an advantage of the use of palonosetron with respect to the other 5-HT<sub>3</sub> RAs, when both are combined with dexamethasone. Therefore, for the prevention of acute emesis in MEC-treated patients, a 5-HT<sub>3</sub> RA plus dexamethasone is recommended [MASCC level of confidence: moderate; MASCC level of consensus: moderate; ESMO level of evidence II; ESMO grade of recommendation: B].

### the prophylaxis of MEC-induced delayed nausea and vomiting

The recommendation for dexamethasone beyond 24 h for MEC was based upon a study by the Italian Group for Antiemetic Research [24]. This study concluded that in patients who did not vomit or had experienced moderate to severe nausea in the first 24 h, there was a benefit for oral dexamethasone 4 mg twice/day on days 2–5. Unfortunately, results according to the different MEC agents used have not been published. There are no data evaluating the role of dexamethasone or other antiemetics for preventing delayed emesis in MEC.

Two recent studies have been published evaluating the need for prophylaxis in the delayed phase with irinotecan. A placebo-controlled study in 68 patients showed a small, non-statistically significant difference in favour of dexamethasone (82.9% versus 78.8%) [25]. An observational study in 44 colorectal cancer patients treated with irinotecan, folinic acid and 5-fluorouracil and receiving dexamethasone 8 mg i.v. and a 5-HT<sub>3</sub> RA on day 1 showed 86% complete response on day 1 and 82% complete response during the delayed emesis period [26]. The relatively good control in these studies suggests that prophylaxis for delayed emesis in irinotecan-based chemotherapy may not be warranted.

In conclusion, no new data have emerged that allow the identification of patients at sufficiently high risk of delayed emesis to warrant prophylaxis. Previous data have demonstrated that some but not all patients may have reduced nausea or vomiting with the addition of dexamethasone beyond 24 h. Some new data are available for carboplatin and will be reviewed below. For other MEC agents, it can be concluded that: in patients receiving MEC with a known potential for delayed emesis (e.g. oxaliplatin, doxorubicin, cyclophosphamide), the use of dexamethasone for days 2–3 can be considered [MASCC level of confidence: low; MASCC level of consensus: moderate; ESMO level of evidence III; ESMO grade of recommendation: C]. No routine prophylaxis for delayed emesis can be recommended for all other patients receiving MEC [MASCC level of confidence: no confidence possible; MASCC level of consensus: high; ESMO level of evidence IV; ESMO grade of recommendation: D].

### which MEC should receive prophylaxis including an NK<sub>1</sub> RA?

A randomised trial evaluating the role of an NK<sub>1</sub> RA added to a 5-HT<sub>3</sub> RA and dexamethasone versus a 5-HT<sub>3</sub> RA plus

dexamethasone has been carried out in 848 MEC-treated patients. Approximately one half of the patients received AC which, at the time, was not considered highly emetogenic [27]. The primary efficacy end point, no vomiting during the first 5 days, was significantly superior in patients receiving the NK<sub>1</sub> RA. Among those receiving non-AC-based chemotherapy regimens, more patients in the aprepitant group reported no vomiting compared with those in the control group in all phases (overall: 83.2% versus 71.3%; acute: 96.5% versus 91.6%; delayed: 84.5% versus 73.9%) [27]. No statement of statistical significance was provided as this was a *post hoc* analysis. In any case, not all MEC-treated patients may have a sufficiently high risk of emesis to warrant prophylactic therapy including an NK<sub>1</sub> RA from cycle 1.

A double-blind, placebo-controlled, study evaluating fosaprepitant (150 mg i.v.) plus oral ondansetron (8 mg before chemotherapy and 8 mg after 8 h) plus oral dexamethasone (12 mg) versus oral ondansetron, at the same doses in the first 24 h plus 8 mg every 12 h on days 2 and 3, plus oral dexamethasone (20 mg) in 1015 patients receiving non-AC MEC has recently been published [28]. Fosaprepitant significantly increased the complete response on days 2–5, the primary end point (78.9% versus 68.5%), as well as the complete response on days 1–5 (77.1% versus 66.9%) but not the complete response on day 1 (93.2% versus 91%). On days 1–5, the percentage of patients with no vomiting and no significant nausea was significantly superior with fosaprepitant. No subgroup analyses have been reported.

### carboplatin

Six studies, two published only as abstracts, evaluated the role of adding an NK<sub>1</sub> RA to a 5-HT<sub>3</sub> RA plus dexamethasone in carboplatin-treated patients. One recently published study [29] and the two abstracts all presented a subgroup analysis or *post hoc* analysis of studies involving both AC- and non-AC-treated patients. From these studies, it seems that in carboplatin-treated patients, adding an NK<sub>1</sub> RA increased the complete response by ~10%–15%.

In a phase II study ( $n=91$ ), the combination of granisetron (1 mg i.v.) plus dexamethasone (20 mg i.v. on day 1 and 8 mg i.v. on days 2 and 3) was compared with aprepitant (125 mg orally on day 1 and 80 mg on days 2 and 3) plus granisetron (same dose) and dexamethasone (12 mg i.v. on day 1 and 4 mg i.v. on days 2 and 3) [30]. Almost all of the patients (89/91) received carboplatin-based chemotherapy and most of them had a gynaecological cancer. The complete response was superior but not statistically significant with aprepitant (62% versus 52% on days 1–5, 98% versus 96% on day 1 and 62% versus 52% on days 2–5).

A phase III, double-blind study in 297 chemotherapy-naïve patients with ovarian, endometrial or cervical cancer, scheduled to receive carboplatin plus paclitaxel, randomised patients to aprepitant or placebo, both combined with a 5-HT<sub>3</sub> RA plus dexamethasone [31]. Adding aprepitant significantly increased the complete response (61.6% versus 47.3%), no vomiting (78.2% versus 54.8%) and no significant nausea (85.4% versus 74.7%).

Finally, a phase II open-label study evaluated aprepitant combined with a 5-HT<sub>3</sub> RA plus dexamethasone (8 mg on days 1–3) versus a 5-HT<sub>3</sub> RA plus dexamethasone alone in 134 patients with advanced non-small-cell lung cancer who received

carboplatin-based first-line chemotherapy [32]. The primary end point was the complete response rate on days 1–5; it was numerically superior in patients receiving aprepitant (80.3% versus 67.2%), but this difference was not statistically significant.

In conclusion, to prevent carboplatin-induced acute nausea and vomiting, a combination of an NK<sub>1</sub> RA, dexamethasone and a 5-HT<sub>3</sub> RA is recommended [MASCC level of confidence: moderate; MASCC level of consensus: moderate; ESMO level of evidence II; ESMO grade of recommendation: B]. If patients receive fosaprepitant, netupitant or rolapitant on day 1, no antiemetic prophylaxis for delayed emesis is required. If patients receive aprepitant on day 1, aprepitant on days 2 and 3 is recommended [MASCC level of confidence: moderate; MASCC level of consensus: moderate; ESMO level of evidence II; ESMO grade of recommendation: B].

### oxaliplatin

The first double-blind trial to evaluate the role of an NK<sub>1</sub> RA for oxaliplatin was carried out in 710 colorectal cancer patients receiving casopitant or placebo [33]. Casopitant 90 mg i.v. on day 1 or placebo were administered in combination with ondansetron 8 mg bid oral on days 1–3 and dexamethasone 8 mg i.v. on day 1. The incidence of vomiting on days 1–5 was low in both arms (11% and 10% in the placebo and casopitant arms, respectively) with the vast majority of emesis occurring in the delayed phase. Both groups received ondansetron on days 2–3 which may have increased the control of delayed emesis.

A different conclusion about the value of an NK<sub>1</sub> RA was reported in a more recent antiemetic study for oxaliplatin-induced emesis [34]. An open-label randomised trial in 413 patients compared a 5-HT<sub>3</sub> RA (day 1 only) and dexamethasone (administered on days 1–4) + aprepitant versus a 5-HT<sub>3</sub> RA and dexamethasone. The primary end point was no vomiting. Significantly more patients in the aprepitant group achieved no vomiting overall and in the delayed phase than those in the control group (95.7% versus 83.6%, and 95.7% versus 84.7%, respectively).

These two large randomised trials came to apparently conflicting conclusions about the role of NK<sub>1</sub> RA for oxaliplatin-based chemotherapy. In view of the discordant results, no recommendation can be made about combining an NK<sub>1</sub> RA to dexamethasone and a 5-HT<sub>3</sub> RA for the prophylaxis of oxaliplatin-induced emesis.

### prevention of nausea and vomiting induced by multiple-day cisplatin chemotherapy

Multiday chemotherapy studies have included drugs such as dactinomycin, dacarbazine, ifosfamide and cisplatin. Only a few small studies have been carried out with this type of chemotherapy schedule. In patients with germ cell tumours, the i.v. combination of a 5-HT<sub>3</sub> RA plus dexamethasone has been shown to induce ~55%–83% complete protection from vomiting during the 3–5 days of cisplatin administration and this combination has proven to be superior to i.v. high-dose metoclopramide plus dexamethasone, alizapride plus dexamethasone and to a 5-HT<sub>3</sub> RA alone [1].

Using a combination of a 5-HT<sub>3</sub> RA plus dexamethasone, patients receiving consecutive 5 days of cisplatin for testicular cancer will have little or no nausea or vomiting during the first 3 days of chemotherapy. The worst nausea is seen on days 4 and 5 as well as on days 6, 7 and 8. Whether this all reflects delayed nausea from days 1 and 2 is unknown.

A double-blind randomised crossover study enrolling 69 evaluable germ cell tumour patients receiving cisplatin-based chemotherapy for 5 consecutive days has been published [35]. All patients received a 5-HT<sub>3</sub> RA for 5 days and dexamethasone 20 mg on the first 2 days of chemotherapy. Then the patients were randomised to aprepitant 125 mg on day 3 and 80 mg on days 4–7 plus dexamethasone 4 mg twice/day on days 6–8 or placebo on days 3–7 plus dexamethasone 8 mg twice/day on days 6–7 and 4 mg twice/day on day 8. The complete response was significantly superior with aprepitant compared with placebo (42% versus 13% of patients). At least one emetic episode was observed significantly more often with placebo (47% versus 16%,  $P < 0.001$ ). The visual analogue scale (VAS) score for nausea was better, but not significantly superior with aprepitant. Aprepitant was also preferred by the patients (38 versus 11 patients). Toxicity was not increased by aprepitant. Confirmatory supportive evidence with aprepitant was seen in phase II trials conducted in Australia and Japan [36, 37]. The optimal dose and schedule of aprepitant, 5-HT<sub>3</sub> RA as well as of dexamethasone remains to be identified.

Therefore, patients affected by metastatic germ cell tumours receiving multiple-day cisplatin should receive a 5-HT<sub>3</sub> RA plus dexamethasone plus aprepitant for the prevention of acute nausea and vomiting and dexamethasone for delayed nausea and vomiting [MASCC level of confidence: moderate, MASCC level of consensus: moderate; ESMO level of evidence: II, ESMO grade of recommendation: B].

### prevention of acute and delayed nausea and vomiting induced by chemotherapy with low and minimal emetogenic potential

Many of the newer targeted therapies fit into the category of agents of low and minimal emetogenic potential. For patients treated with low or minimally emetogenic chemotherapy, there is little evidence from clinical trials supporting the choice of a given antiemetic therapy or of any treatment at all. Furthermore, the degree of nausea and/or vomiting related to these agents has not been well documented, nor are there prospective trials that clearly outline the incidence and severity of nausea and vomiting for each drug.

Since the previous MASCC/ESMO guideline, only a prospective cohort study evaluating the efficacy of granisetron to prevent acute nausea and vomiting with chemotherapy of low emetogenic potential has been reported [38]. In this study, patients received dexamethasone or metoclopramide or granisetron before low emetogenic chemotherapy. The patients receiving granisetron achieved a higher complete response rate in the acute phase, but no difference was shown for acute nausea or delayed nausea and vomiting. No guidelines have recommended routine antiemetic prophylaxis against delayed emesis for low

emetogenic chemotherapy. Despite this, a study reports that after antiemetic prophylaxis, only 6% of low emetogenic chemotherapy patients presented acute emesis but 22.8% had delayed emesis [39]. Another study showed that patients receiving low emetogenic chemotherapy had increasing delayed emesis from cycle 1 to cycle 4 (from 25% to 50%) [40].

In conclusion, a single antiemetic agent, such as dexamethasone, a 5-HT<sub>3</sub> RA or a dopamine RA, such as metoclopramide may be considered for prophylaxis in patients receiving chemotherapy of low emetic risk [MASCC level of confidence: no confidence possible; MASCC level of consensus: moderate; ESMO level of evidence: II; ESMO grade of recommendation: B].

No antiemetic should be routinely administered before chemotherapy to patients without a history of nausea and vomiting receiving minimally emetogenic chemotherapy [MASCC level of confidence: no confidence possible; MASCC level of consensus: high; ESMO level of evidence: IV; ESMO grade of recommendation: D].

No antiemetic should be administered for prevention of delayed nausea and vomiting induced by low or minimally emetogenic chemotherapy [MASCC level of confidence: no confidence possible; MASCC level of consensus: high; ESMO level of evidence: IV; ESMO grade of recommendation: D]. If a patient experiences acute or delayed nausea or vomiting after low or minimally emetogenic chemotherapy, it is advised that, with subsequent chemotherapy treatments, the regimen for the next higher emetic level be given.

## breakthrough chemotherapy-induced emesis and refractory emesis

Antiemetics are most effective when used prophylactically. Therefore, it is preferable to use maximally effective antiemetics as first-line therapy rather than withholding more effective antiemetics for later use at the time of antiemetic failure. Breakthrough chemotherapy-induced emesis, defined as emesis and/or nausea occurring on the day of chemotherapy despite guideline-recommended prophylaxis, remains an unsolved problem. In a study, 108 out of 276 patients treated with highly emetogenic chemotherapy experienced breakthrough nausea and vomiting, despite prophylaxis with palonosetron 0.25 mg i.v. plus fosaprepitant 150 mg i.v. and dexamethasone 12 mg i.v. on day 1 and 8 mg orally on days 2–4 [41]. The 108 patients with breakthrough nausea and vomiting were randomised to either olanzapine 10 mg orally for 3 days versus a low dose of metoclopramide, 10 mg orally three times daily for 3 days. No further emesis during the 72 h observation period was shown by 70% of patients receiving olanzapine versus 31% of those treated with metoclopramide. Furthermore, 68% had no nausea with olanzapine compared with 23% with metoclopramide. Olanzapine induced mild to moderate sedation. A supportive phase II study was recently published [42]. For the treatment of breakthrough nausea and vomiting, it is recommended to use an antiemetic with a different mechanism of action than that of the antiemetic(s) used for prophylaxis. The available evidence for breakthrough nausea and vomiting suggests the use of olanzapine 10 mg orally daily for 3 days. The mild to moderate sedation in this patient population, especially elderly patients, is a potential problem with olanzapine [MASCC level of confidence:

moderate; MASCC level of consensus: moderate; ESMO level of evidence: II; ESMO grade of recommendation: B].

A few trials have investigated patients with refractory emesis defined as emesis in the previous cycle of chemotherapy, but without emesis before the subsequent cycle of chemotherapy. A number of approaches have been utilised including switching to a different 5-HT<sub>3</sub> RA or adding other agents such as dopamine RA or benzodiazepines [1]. In two randomised trials, metopimazine improved the efficacy of ondansetron and of ondansetron plus methylprednisolone. Some studies have documented antiemetic activity of NK<sub>1</sub> receptor antagonists in patients who did not achieve complete protection from emesis when treated with dexamethasone and a serotonin receptor antagonist alone [1]. Again, it seems a reasonable approach to add an antiemetic with a different mechanism of action than that of those used in the previous cycle of chemotherapy.

## prevention of anticipatory nausea and vomiting

Anticipatory nausea is believed to be a learned response to chemotherapy. In a randomised, double-blind study evaluating patients in the last 3 days before chemotherapy, anticipatory vomiting occurred in 3% and anticipatory nausea in 9% at any time during the entire course of adjuvant CMF/CEF chemotherapy for breast cancer [43]. In a recent Asian-Pacific study of 598 adult cancer patients, anticipatory vomiting was infrequent (1.5%–2.3%), while anticipatory nausea continues to be more commonly reported than anticipatory vomiting (up to 13.8%) and the risk increases with each successive chemotherapy treatment cycle received [44]. Similarly, in a European survey, anticipatory nausea was reported in 8.3%, 10.1% and 13.8% of 991 adult cancer patients over three consecutive chemotherapy blocks [45]. A history of poor chemotherapy-induced nausea and vomiting control can increase the risk of anticipatory nausea and vomiting by 3.7 times by the second chemotherapy block and by 3.3 times by the third chemotherapy block [44]. Past experience with nausea and vomiting due to various causes (e.g. anticipatory nausea and vomiting in previous chemotherapy blocks, pregnancy, motion sickness) has been identified as a risk factor for anticipatory nausea and vomiting [46]. In addition, anxiety may play a role in predisposing patients to anticipatory nausea and vomiting [44, 45], but this has not been consistently described in all studies or in all chemotherapy cycles [47].

Once it develops, anticipatory nausea and vomiting is difficult to control by pharmacological treatment. Therefore, the panel recommended that the best approach for the prevention of anticipatory nausea and vomiting is the best possible control of acute and delayed nausea and vomiting [MASCC level of confidence: moderate; MASCC level of consensus: high; ESMO level of evidence: III, ESMO grade of recommendation: A].

Three studies evaluating three separate pharmacological interventions with benzodiazepines (alprazolam, diazepam and lorazepam) have been summarised in a systematic review [47]. Benzodiazepines are recommended to reduce the occurrence of anticipatory nausea and vomiting [MASCC level of confidence: moderate, MASCC level of consensus: moderate; ESMO level of evidence: II, ESMO grade of recommendation: A].

**Table 5.** Radiotherapy emetic risk levels and MASCC/ESMO antiemetic guidelines update

Emetic risk level	Area of treatment	Antiemetic guideline	MASCC level of scientific confidence/level of consensus	ESMO level of evidence/grade of recommendation
High	Total body irradiation	Prophylaxis with a 5-HT <sub>3</sub> -RA + DEX	High/high (for the addition of DEX: moderate/high)	II/B (for the addition of DEX: III/C)
Moderate	Upper abdomen, craniospinal	Prophylaxis with a 5-HT <sub>3</sub> -RA + optional DEX	High/high (for the addition of DEX: moderate/high)	II/A (for the addition of DEX: II/B)
Low	Cranium	Prophylaxis or rescue with DEX	Low/high	IV/D
	Head and neck, thorax region, pelvis	Prophylaxis or rescue with DEX, a dopamine RA or a 5-HT <sub>3</sub> -RA	Low/high	IV/D
Minimal	Extremities, breast	Rescue with DEX, a dopamine receptor antagonist or a 5-HT <sub>3</sub> -RA	Low/high	IV/D
Concomitant CRT	In patients undergoing concomitant CRT, the antiemetic prophylaxis should be according to the guidelines for CINV for the used chemotherapy. However, in case the emetic risk of RT is higher than that of the concomitant CT, then the risk level of RT has to be chosen to tailor the antiemetic treatment		Low/high	IV/D

5-HT<sub>3</sub>-RA, 5-HT<sub>3</sub>-receptor antagonist; CINV, chemotherapy-induced nausea and vomiting; CT, chemotherapy; CRT, chemoradiotherapy; DEX, dexamethasone; RT, radiotherapy.

Behavioural interventions may also play an important role in the management of anticipatory symptoms [48]. Behavioural therapies, in particular progressive muscle relaxation training, systematic desensitisation and hypnosis, may be used to treat anticipatory nausea and vomiting [MASCC level of confidence: moderate, MASCC level of consensus: moderate; ESMO level of evidence: II, ESMO grade of recommendation: B].

### prevention of nausea and vomiting induced by high-dose chemotherapy

Chemotherapy-induced nausea and vomiting in patients treated with high-dose chemotherapy with stem cell support has several contributing causes, including the use of prophylactic antibiotics and opioids prescribed for concurrent mucositis management. An additional confounding factor is the use of total-body irradiation. Until recently, only phase II studies of a 5-HT<sub>3</sub> RA alone or combined with dexamethasone were published and the interpretation of these studies was problematic due to the various chemotherapy regimens used, small sample sizes, duration of high-dose chemotherapy, different patient populations and tumour types included. The natural history of chemotherapy-induced nausea and vomiting in patients undergoing high-dose chemotherapy and stem cell transplantation is largely unknown. Most patients undergoing high-dose chemotherapy with stem cell support have experienced nausea and vomiting with prior chemotherapy or irradiation. Following the positive results of phase II trials in patients receiving high-dose BEAM (carmustine, etoposide, cytarabine, melphalan) [49] or high-dose melphalan [50] before hematopoietic stem cell transplantation, two phase III trials have recently been published [51, 52]. The first study evaluated 179 patients treated with a high-dose cyclophosphamide preparative regimen before stem cell transplant. Patients were randomised to receive ondansetron and dexamethasone with or without aprepitant administered daily

and for 3 days after the completion of the preparative regimen. The study showed a significant reduction in emesis without increasing toxicity or use of rescue medication. In fact, the complete response rate (no vomiting and no or mild nausea) was 82% with the aprepitant arm versus 66% with placebo. However, there was no difference in the mean nausea VAS score and in the amount of rescue antiemetics used [51]. The other phase III study evaluated patients with multiple myeloma randomised to receive either aprepitant administered at a dose of 125 mg orally on day 1 and 80 mg orally on days 2–4; granisetron (given at a dose of 2 mg orally on days 1–4), and dexamethasone (given at a dose of 4 mg orally on day 1 and 2 mg orally on days 2–3) or placebo [52]. The placebo arm utilised dexamethasone at a dose of 8 mg orally on day 1 and 4 mg orally on days 2–3. The high-dose chemotherapy consisted of melphalan at a dose of 100 mg/m<sup>2</sup> administered intravenously on days 1–2. The autologous stem cell transplant was carried out on day 4. A total of 362 patients entered the study. The complete response on days 1–5 after melphalan administration was significantly higher in the aprepitant arm compared with the control group (58% versus 41%). The absence of major nausea (94% versus 88%) and emesis (78% versus 65%) on days 1–5 was significantly improved by aprepitant. In conclusion, for patients receiving high-dose chemotherapy for stem cell transplant, a combination of a 5-HT<sub>3</sub> RA with dexamethasone and aprepitant (125 mg orally on day 1 and 80 mg on days 2–4) is recommended before chemotherapy [MASCC level of confidence: high; MASCC level of consensus: high; ESMO level of evidence: I; ESMO grade of recommendation: A].

### prevention of radiotherapy-induced nausea and vomiting

Several observational studies have demonstrated that radiotherapy-induced nausea and vomiting (RINV) is under-treated, with few patients receiving antiemetic prophylaxis [53–55].

The emetic risk of radiotherapy is divided into four risk levels: high, moderate, low and minimal (Table 5). The risk levels depend on the site of radiation, and do not take into account radiation dose, fractionation or technique or other proposed risk factors such as field size. The risk classification is mainly based on incidence of emesis in clinical studies and expert opinions. Two observational studies by the Italian Group for Antiemetic Research in Radiotherapy identified that irradiated site (upper abdomen), field size  $>400\text{ cm}^2$  and concomitant chemotherapy are independent risk factors for development of RINV [54, 55]. The only identified patient-related risk factor for RINV is the previous treatment with chemotherapy.

### risk classification

In the current guidelines, the following changes on the risk classification took place, mainly based on expert opinions:

- (i) total nodal irradiation was previously classified as high emetic risk, but as this radiotherapy field technique is no longer in use, it was decided to exclude this.
- (ii) In the moderate emetic risk level, half body irradiation (HBI) and upper body irradiation (UBI) were also excluded. Both HBI and UBI include the upper abdomen, and as it is the irradiation of the upper abdomen that gives the moderate risk of RINV, it would be sufficient just to mention the upper abdomen.
- (iii) Craniospinal irradiation was previously in the low emetic risk level. No randomised antiemetic studies in craniospinal radiotherapy are available, but the risk of RINV in craniospinal radiotherapy is unlikely to be less than for large field vertebral irradiation for which data from randomised trials have demonstrated that prophylaxis with a 5-HT<sub>3</sub> RA is superior compared with prophylaxis with a dopamine RA or placebo. Therefore, it was decided to reclassify craniospinal radiation to the moderate risk category.
- (iv) The lower thorax region is in the low emetic risk level. In a study [54], the risk of nausea and/or vomiting was 31% in 126 patients receiving thorax radiotherapy and no distinction between the upper and lower region was made. Thus, it was decided to remove the word 'lower'.

### antiemetic treatment options

Since the previous guidelines, no randomised, controlled antiemetic studies in RINV have been published. In 2012, a systematic review and meta-analysis evaluated prophylaxis with 5-HT<sub>3</sub> RA in single or multiple fraction radiotherapy [56]. Nine studies were included in the analysis, and different sites of irradiation were included. The authors concluded that 5-HT<sub>3</sub> RAs are superior to placebo or dopamine RAs in the prevention of emesis during radiotherapy. The evidence is less concrete for the control of nausea. The dose and duration of prophylaxis with a 5-HT<sub>3</sub> RA remain unclear, as well as comparisons between different 5-HT<sub>3</sub> RAs. Thus, this analysis does not change existing guidelines recommendations.

A systematic review, focusing on timing and duration of the prophylaxis of RINV with a 5-HT<sub>3</sub> RA, evaluated 25 prophylaxis studies in high, moderate and low emetic risk radiotherapy [57]. Due to the heterogeneity of the studies (e.g. reported end points, emetic risks, fractionation), no correlation between

duration of the prophylaxis and response rates could be made. The updated recommendations are summarised in Table 5.

Previously, the recommendation for the low emetic risk level (cranium, head and neck, thorax region and pelvis) included prophylaxis or rescue with a 5-HT<sub>3</sub> RA. Due to the very heterogeneous sites of irradiation in the low-risk group, the limited number of studies including these sites and mainly addressing efficacy of 5-HT<sub>3</sub> RAs, it was decided that the guideline should not be restricted to recommend a 5-HT<sub>3</sub> RA, but the choice could also be dexamethasone or a dopamine RA. In clinical practice, the antiemetic treatment of choice in cranial irradiation would be a corticosteroid (due to the oedema), and therefore, this was included in the guideline. For minimal risk, and again based on expert opinion, it was decided not to restrict the recommendation to a dopamine RA or a 5-HT<sub>3</sub> RA, but also to include dexamethasone.

### concurrent chemoradiotherapy

In patients receiving chemoradiotherapy (CRT), it is advised to prescribe antiemetics according to the emetic risk of the chemotherapy unless it is considered that the risk of nausea and vomiting induced by the radiotherapy is higher. Recently, the first randomised, double-blind study in women with cervical cancer compared palonosetron, dexamethasone and placebo with palonosetron, dexamethasone and fosaprepitant during 5 weeks of fractionated radiotherapy and weekly cisplatin in a dose of 40 mg/m<sup>2</sup> [58]. There was a significantly lower cumulative risk of emesis in the fosaprepitant group compared with the placebo group [sub-hazard ratio 0.58 (95% confidence interval 0.39–0.87);  $P=0.008$ ]. Further studies in concurrent CRT are warranted.

### prevention of acute chemotherapy-induced nausea and vomiting in children

The previous MASCC/ESMO guidelines recommended that paediatric patients receiving chemotherapy of high or moderate emetogenic potential should receive antiemetic prophylaxis with a combination of a 5-HT<sub>3</sub> RA and dexamethasone [1].

Although antiemetic studies in children are few, the results of some new paediatric trials are now available. Paediatric studies continue to present many limitations such as the classification of emetogenicity based on experience in adults rather than children, evaluation of only acute chemotherapy-induced nausea and vomiting and definitions of acute complete control which vary among studies. Furthermore, among studies that assessed nausea, no study used a validated paediatric nausea assessment instrument to evaluate nausea severity.

Recently, two studies evaluated the benefit of adding aprepitant to ondansetron for the prophylaxis of chemotherapy-induced vomiting. In a randomised double-blind, placebo-controlled study in 96 children receiving highly emetogenic chemotherapy, chemotherapy-induced vomiting was evaluated from administration of the first chemotherapy dose to 24 h after the last dose of chemotherapy in children receiving multiple-day chemotherapy. A significantly higher complete response rate (no vomiting and no retching) was achieved with ondansetron plus dexamethasone plus aprepitant when compared with ondansetron plus dexamethasone (48% versus 12%) [59]. The second trial compared ondansetron plus aprepitant with/

without dexamethasone versus ondansetron plus placebo with/without dexamethasone [60]. A complete response rate (no vomiting, no retching and no use of rescue medications) of 65% was reported in the ondansetron plus aprepitant arm versus 51% in the ondansetron arm for the first 24 h after administration of the first chemotherapy dose. However, the number of children who received dexamethasone in each group is unknown and the dose of dexamethasone, when given, was uncontrolled and varied widely. As a result, it is difficult to ascertain the contribution of aprepitant itself to chemotherapy-induced vomiting control in this trial. Interestingly, the study reported a reduced rate of vomiting control in children who received dexamethasone.

Therefore, in children receiving chemotherapy of high emetic risk, an antiemetic prophylaxis with a 5-HT<sub>3</sub> RA (granisetron, ondansetron, tropisetron or palonosetron) plus dexamethasone plus aprepitant is recommended [MASCC level of confidence: high; MASCC level of consensus: high; ESMO level of evidence: II; ESMO grade of recommendation: B].

The use of dexamethasone is prohibited in many paediatric oncology protocols (e.g. leukaemia and brain tumours) due to concerns regarding potential interference with apoptosis, fungal infection and distribution of chemotherapy across the blood–brain barrier. Therefore, children who cannot receive dexamethasone should receive a 5HT<sub>3</sub> RA plus aprepitant [MASCC level of confidence: moderate; MASCC level of consensus: high; ESMO level of evidence: II; ESMO grade of recommendation: B].

Aprepitant may not be an option for all children receiving highly emetogenic chemotherapy. An oral liquid aprepitant formulation is not always available. Intravenously administered fosaprepitant cannot be routinely recommended currently since paediatric experience is scant. When aprepitant administration is not feasible or desirable, the guideline recommends a 5-HT<sub>3</sub> RA plus dexamethasone be given to children receiving highly emetogenic chemotherapy [MASCC level of confidence: moderate; MASCC level of consensus: high; ESMO level of evidence: II; ESMO grade of recommendation: B].

Children receiving MEC should receive antiemetic prophylaxis with a 5-HT<sub>3</sub> RA plus dexamethasone [MASCC level of confidence: moderate; MASCC level of consensus: high; ESMO level of evidence: II; ESMO grade of recommendation: B]. Furthermore, children who cannot receive dexamethasone should receive a 5-HT<sub>3</sub> RA and aprepitant [MASCC level of confidence: moderate; MASCC level of consensus: high; ESMO level of evidence: II; ESMO grade of recommendation: B].

In children receiving chemotherapy of low emetogenicity, antiemetic prophylaxis with a 5-HT<sub>3</sub> RA is recommended [MASCC level of confidence: moderate; MASCC level of consensus: moderate; ESMO level of evidence: II; ESMO grade of recommendation: B]. In children receiving chemotherapy of minimal emetogenicity, no antiemetic prophylaxis is recommended [MASCC level of confidence: moderate; MASCC level of consensus: high; ESMO level of evidence: V; ESMO grade of recommendation: D].

## antiemetics in advanced cancer

The causes of nausea and vomiting in advanced cancer can be multifactorial (elevated intracranial pressure due to brain tumours, cerebral metastases or meningeal carcinomatosis,

biochemical syndromes such as hypercalcaemia, hyponatraemia, vestibular dysfunction, gastric stasis-related, such as with ascites, hepatomegaly, paraneoplastic neuropathy, opioid-induced, malignant bowel obstruction, etc.). Hence, a careful assessment which includes a detailed history, physical examination and investigations for reversible causes is paramount. Of those with a reversible cause, about half are drug-related, mostly induced by opioids. There are two therapeutic approaches [61]. One is empirical; starting with one drug and if unsuccessful adding or rotating to another. The second is aetiological; that is management tailored to the suspected cause and/or likely receptors involved in generating nausea and/or vomiting. Concerning antiemetic treatment, when malignant bowel obstruction is excluded, the evidence base in this field is minimal with largely poor quality trials or uncontrolled trials and case studies. The level of evidence in most studies is very low. While not documented, experience suggests that clinicians favour metoclopramide as first-line therapy due to small randomised trials [62, 63]. Haloperidol is often used as a second-line therapy, followed by levomepromazine and olanzapine which has some evidence of benefit in prospective studies. Unlike chemotherapy-induced nausea and vomiting, there is no evidence that combining antiemetics improves responses over monotherapy, although this needs formal research confirmation.

In conclusion, the antiemetic treatment of choice in advanced cancer is metoclopramide [MASCC level of confidence: high, MASCC level of consensus: moderate; ESMO level of evidence: III, ESMO grade of recommendation: C]. Alternative options include haloperidol, levomepromazine or olanzapine [MASCC level of consensus: high, MASCC level of confidence: low; ESMO level of evidence: V, ESMO grade of recommendation: D].

## nausea and vomiting in malignant bowel obstruction

Patients with nausea and vomiting due to malignant bowel obstruction unfit for surgery can be managed medically through two pharmacological approaches:

- (i) Anti-secretory drugs like anticholinergics (hyoscine hydrobromide, hyoscine butylbromide HB, glycopyrrolate) and/or somatostatin analogues octreotide ± glucocorticoids.
- (ii) Antiemetics alone or combined with anti-secretory drugs.

Few studies have assessed efficacy, while there are no comparative studies on different approaches. From 2009 to 2015, four randomised trials (three double-blind) were published evaluating octreotide [64–67] and all showed a reduction in nausea and/or vomiting episodes.

In conclusion, the drug recommended in bowel obstruction is octreotide, dosed around the clock, and given alongside a conventional antiemetic (with the committee recommending haloperidol) [MASCC level of consensus: high, MASCC level of confidence: high; ESMO level of evidence: II, ESMO grade of recommendation: A]. If octreotide plus an antiemetic is suboptimal, the use of anticholinergic anti-secretory agents (e.g. scopolamine butylbromide, glycopyrronium bromide) and/or corticosteroids is recommended as either an adjunct or as an alternative intervention [MASCC level of consensus: high (moderate for corticosteroids), MASCC level of confidence: moderate (low for corticosteroids);

ESMO level of evidence: IV, ESMO grade of recommendation: D]. Metoclopramide should be used with caution in partial bowel obstruction and should not be used in complete bowel obstruction [MASCC level of consensus: low, MASCC level of confidence: low; ESMO level of evidence: V, ESMO grade of recommendation: D].

### opioid-induced nausea and vomiting

Nausea and vomiting are common side-effects of opioid analgesics with up to 19% incidence of moderate/severe nausea and 40% vomiting. Opioid-induced nausea and vomiting may be an initiation side-effect, with tolerance after 5–7 days of therapy, but others consider it chronic. There are no randomised, controlled trials of prophylactic antiemetics for those starting opioids and several antiemetics appear active in managing opioid-induced nausea and vomiting [68]. In conclusion, no recommendation can be made about specific antiemetics in opioid-induced nausea and vomiting, although various antiemetics may help. Opioid rotation and route switching may be effective approaches. There are no data to support antiemetic prophylaxis in this situation [MASCC level of consensus: high, MASCC level of confidence: low; ESMO level of evidence: V; ESMO grade of recommendation: D].

### summary

The 2016 MASCC/ESMO guidelines on antiemetics updated the classification of the emetogenic potential of antineoplastic agents adding 42 new drugs many of which are orally administered. The MASCC antiemetic guideline recommendations at present can only be applied to intravenously administered antineoplastic agents, given the virtual absence of antiemetic trials with orally administered antineoplastics and the considerable uncertainty in defining the emetogenic risk of oral agents. The recommendations for the prophylaxis of nausea and vomiting induced by different chemotherapeutic agents were updated. Two new NK<sub>1</sub> RAs have achieved FDA (netupitant and rolapitant) and EMA (netupitant) approval and their role in the prophylaxis of acute and delayed nausea and vomiting induced by cisplatin, AC or carboplatin is discussed. In future research, it would be interesting to plan randomised double-blind comparative studies among the three NK<sub>1</sub> RAs to identify if the two new drugs have an advantage over the more established aprepitant or if they produce the same outcomes. Also the new NK<sub>1</sub> RAs should be investigated prospectively in settings other than cisplatin and AC chemotherapy.

Two studies suggested that aprepitant and metoclopramide were equally effective in the prophylaxis of cisplatin-induced delayed nausea and vomiting and that dexamethasone was as effective as aprepitant in women with breast cancer receiving an AC combination, given the fact that aprepitant was applied on day 1.

Adding an NK<sub>1</sub> RA to the previous standard regimen consisting of a 5-HT<sub>3</sub> RA plus dexamethasone has been addressed in multiple-day cisplatin-based chemotherapy and high-dose chemotherapy. Finally, a new classification of the emetogenic potential of radiotherapy according to irradiated sites and an update of the recommended antiemetic treatments has been reported as well as the use of fosaprepitant in combined CRT (Table 5).

Control of vomiting has markedly improved during the past few years. Therefore, in the future, attention should shift to the

control of nausea, at present the greatest remaining emetogenic challenge. In fact, although nausea and vomiting seem to appear and respond in parallel, they are not the same phenomena. While vomiting can be objectively measured in terms of number of emetic episodes, nausea is a subjective phenomenon that requires different measurement tools and definitions. It has also been recognised that the standard primary end point for antiemetic trials, complete response, is defined as ‘no vomiting and no use of rescue medication’ and this does not refer to nausea or protection from nausea at all. Preliminary clinical trials of several agents such as olanzapine, amisulpride and ginger have also suggested that some agents may be more effective against acute and delayed nausea than against acute and delayed vomiting. Identification and characterisation of antinausea agents and rational inclusion of these agents into antiemetic regimens may be the primary challenge in coming years.

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