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SPECIAL SECTION

Emetic risk classification and evaluation of the emetogenicity of antineoplastic agents—updated MASCC/ESMO consensus recommendation

Karin Jordan[1,2] · Alexandre Chan[3] · Richard J. Gralla[4] · Franziska Jahn[5] · Bernardo Rapoport[6,7] · Christina H. Ruhlmann[8,9] · Paula Sayegh[10] · Paul J. Hesketh[11]

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Abstract

Purpose Our goal was to identify new anticancer agents approved by the US Food and Drug Administration (FDA) and the European Medical Agency (EMA) since the 2016 MASCC/ESMO antiemetic update and classify their emetic potential.

Methods The MASCC/ESMO Expert Panel classified the emetogenicity of the identified new antineoplastic agents based on nonsystematic reviews of randomized controlled trials, analysis of product labeling, and evaluation of emetic classification in other international guidelines and informal consensus. The emetogenic classification system for oral anticancer agents was revised into two emetic risk categories (minimal–low; moderate–high) to be consistent with the system reported by ASCO (American Society of Clinical Oncology) in their 2017 guideline update. The previously employed four emetic risk classification categories for intravenously administered antineoplastic agents were retained for this update.

Results From June 2015 to January 2023, 107 new antineoplastic agents (44 intravenously administered and 63 orally administered agents) were identified. The reported incidence of vomiting varied significantly across studies for many agents, especially for oral anticancer agents.

Conclusion The MASCC/ESMO Expert Panel acknowledges the limitations of our efforts to classify the emetic potential of anticancer agents, especially the imprecision associated with oral agents. However, we have attempted to provide a reasonable approximation of the emetic risk associated with new antineoplastic agents by searching the available literature and reviewing other available international antiemetic guidelines.

Keywords Emetogenicity · Nausea · Vomiting · Risk classification · Antineoplastic agents

✉ Karin Jordan
karin.jordan@med.uni-heidelberg.de

[1] Department of Hematology, Oncology and Palliative Medicine, Ernst von Bergmann Hospital Potsdam, Charlottenstraße 72, 14467 Potsdam, Germany

[2] Department of Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany

[3] School of Pharmacy & Pharmaceutical Sciences, University of California Irvine, Irvine, CA, USA

[4] Albert Einstein College of Medicine, Bronx, NY, USA

[5] Department of Hematology and Oncology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany

[6] Medical Oncology Centre of Rosebank, Johannesburg, South Africa

[7] Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

[8] Department of Oncology, Odense University Hospital, Odense, Denmark

[9] Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[10] OU Health Stephenson Cancer Center, Oklahoma City, OK, USA

[11] Division of Hematology and Oncology, Lahey Hospital & Medical Center, Burlington, MA, USA

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Introduction

In 1997, an emetogenic classification schema for anticancer agents was introduced and has formed the basis for subsequent antiemetic prophylaxis recommendations by guideline panels [4, 6]. Since the 2004 Perugia Antiemetic Consensus Conference, chemotherapy agents were divided into four categories based on the risk of emesis in the absence of antiemetic prophylaxis (Table 1) [9, 10]. Of note, nausea was not incorporated into this schema. Many new antineoplastic agents have been introduced since the last MASCC/ESMO antiemetic guideline update in 2016 [7, 11].

It remains a challenge to accurately define the emetic risk associated with antineoplastic agents [3, 8]. The data on emesis in various trials of anticancer agents are usually highly heterogenous (different tumor types, advanced versus non-advanced disease, systemic treatment naïve or previously treated, used alone or in combination with other agents, different antiemetic prophylaxis if given or not reported, different reporting system, e.g., CTCAE (Common Terminology Criteria of Adverse Events) all grades versus only grade 3/4). Oral anticancer agents provide additional challenges. Most oral agents tend to be used in extended regimens of daily use rather than the single bolus administration schedule commonly employed with intravenous agents. As these agents are typically administered continuously over protracted periods, traditional concepts of acute and delayed nausea and vomiting lose their relevance in these settings.

In the current update, the following questions related to antineoplastic agent emetogenicity were addressed:

1. Identify new antineoplastic agents approved by the FDA and/or EMA since the last update (time frame: June 2015 to January 2023).
2. Characterize the emetic potential of new intravenously administered antineoplastic agents and place them at an appropriate level in the four-level classification schema.
3. Modify the original four-level classification system for oral agents to a two-level system (minimal to low and moderate to high) [5] and place both prior and new oral antineoplastic agents into the appropriate level.

Methods

As the initial step, new antineoplastic agents approved by the FDA and/or EMA since the last update from June 2015 to January 2023 (data cut off) were identified by two independent reviewers. The data source was the FDA summary (https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products) and the EMA summary (https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/search_api_aggregation_ema_therapeutic_area_name/Cancer/field_ema_public_date/%5B2022-05-31T22%3A00%3A00Z%20TO%202023-01-20T22%3A59%3A59Z%5D?sort=field_ema_computed_date_field&order=desc).

Next, information on the incidence of vomiting was obtained by (1) a nonsystematic review of randomized controlled trials, (2) a review of information available in the summary of product characteristics, and (3) through informal consensus of the panel members. In addition, a detailed comparison of emesis classification schemas in the updated ASCO and NCCN antiemetic guidelines was conducted. In cases where data was inconclusive, the corresponding pivotal key phase II/III studies of the respective antineoplastic agent were reviewed. If clinical studies of an antineoplastic agent showed broad differences in the incidence of vomiting, results of the "worst outcome" were selected.

The intravenous anticancer agents were classified as being at minimal, low, moderate, or high emetic risk in accordance with the summarized vomiting rates.

Oral anticancer agents were placed into one of two emetic categories, minimal–low risk and moderate–high risk (Table 2). Of note, the emetic risk classification only refers to adult patients.

Results

Within the defined time frame, 107 new antineoplastic agents were identified. The reported incidence of vomiting varied considerably across studies, especially for oral anticancer agents. The emetic potential of the oral anticancer

Table 1 MASCC/ESMO emetic risk groups 2016*

Intravenous agents	Emetic risk	Oral agents	Emetic risk
High	Risk in nearly all patients (> 90%)	High	Risk in nearly all patients (> 90%)
Moderate	Risk in 30 to 90% of patients	Moderate	Risk in 30 to 90% of patients
Low	Risk in 10 to 30% of patients	Low	Risk in 10 to 30% of patients
Minimal	Fewer than 10% at risk	Minimal	Fewer than 10% at risk

*Proportion of patients experiencing emesis in the absence of effective antiemetic prophylaxis. The incidence of nausea is not part of the risk classification

Table 2 MASCC/ESMO emetic risk groups 2023*

Intravenous agents	Emetic risk	Oral agents**	Emetic risk
High	Risk in nearly all patients (> 90%)	High/moderate	Risk in more than 30% of patients
Moderate	Risk in 30 to 90% of patients		
Low	Risk in 10 to 30% of patients	Low/minimal	Risk in fewer than 30% of patients
Minimal	Fewer than 10% at risk		

*Proportion of patients experiencing emesis in the absence of effective antiemetic prophylaxis. The incidence of nausea is not part of the risk classification

**The emetic potential of the oral anticancer agents is based upon a full course of therapy and not a single dose within the first cycle

agents was based upon a full course of therapy and not a single dose.

All agents in Tables 3 and 4 are listed in alphabetical order.

For intravenous agents No highly emetogenic intravenous agents were identified. Eight moderately emetogenic intravenous agents were identified (arsenic trioxide, cytarabine/daunorubicin liposomal, dinutuximab beta, irinotecan peg-liposomal, lurbinectedin, naxitamab, sacituzumab-govitecan, trastuzumab-deruxtecan). For sacituzumab-govitecan and trastuzumab-deruxtecan, the emetic potential appears to be at the high end of the moderate category, most closely resembling that of carboplatin. As such, those two new classified agents received an asterisk in the table to highlight this point.

Twenty-one intravenous agents were classified as low emetogenic (amivantamab, axicabtagene-ciloleucel, copanlisib, decitabine, elotuzumab, enfortumab-vedotin, gemtuzumab-ozogamicin, inotuzumab-ozogamicin, isatuximab, loncastuximab-tesirine, margetuximab, melphalan-flufenamide, mirvetuximab-soravtansine, moxetumomab-pasudotox, necitumumab, nelarabine, tafasitamab, tagraxofusp, teclistamab, tisagenlecleucel, tisotumab-vedotin). Fifteen intravenous agents were classified as minimally emetogenic (asparaginase,[1] atezolizumab, avelumab, belantamab-mafodotin, cemiplimab, daratumumab, dostarlimab, durvalumab, emapalumab, ipilimumab, mosunetuzumab, obinutuzumab, polatuzumab-vedotin, ramucirumab, tremelimumab).

For oral agents Fourteen oral agents were identified as high–moderate (abemaciclib, adagrasib, avapritinib, cabozantinib, enasidenib, fedratinib, lenvatinib, lomustine, midostaurin, mobocertinib, niraparib, ribociclib, rucaparib, selinexor). Selinexor also received an asterisk to indicate the emetic potential to be at the higher end of the high–moderate risk category. Forty-nine agents were classified as low–minimal (acalabrutinib, alectinib, alpelisib, apalutamide, asciminib, bexarotene, brigatinib, capmatinib, cobimetinib, dacomitinib, darolutamide, duvelisib, encorafenib, entrectinib, erdafitinib, estramustine, futibatinib, gilteritinib, glasdegib, infigratinib, ivosidenib, ixazomib, larotrectinib, lorlatinib, neratinib, nintedanib, olutasidenib, osimertinib, palbociclib, panobinostat, pemigatinib, pexidartinib, pralsetinib, relugolix, ripretinib, selpercatinib, sonidegib, sotorasib, talazoparib, tazemetostat, tepotinib, tivozanib, topotecan, trametinib, trifluridine/tipiracil, tucatinib, umbralisib, venetoclax, zanubrutinib).

Combination antineoplastic regimens For combination antineoplastic regimens, the emetic level is determined by identifying the most emetic agent in the combination. One exception to this rule remains the combination of cyclophosphamide and anthracycline (AC regimen). Both are moderately emetogenic agents; however, the regimen is highly emetic when coadministered. It has to be acknowledged that the studies defining the AC regimens as highly emetogenic were conducted almost exclusively in women with breast cancer. It is still a matter of debate whether AC used as a component of combination regimens such as the CHOP (doxorubicin plus cyclophosphamide, vincristine, and prednisone) regimen in patients with non-Hodgkin lymphomas is also highly emetic.

Discussion

Classifying antineoplastic agents according to their emetic potential remains imprecise and challenging. This process is hindered by the fact that the potential of an administered antineoplastic agent to cause emesis has been established rigorously for only a few agents. Due to limitations further discussed below, the third Antiemetic Perugia Consensus Conference decided to change from the original Hesketh classification schema from 1997 with five emetic risk groups

[1] asparaginase erwinia chrysanthemi (crisantaspase) and asparaginase (calaspargase pegol)

Table 3 Emetogenic potential of single intravenous antineoplastic agents

High	Anthracycline/cyclophosphamide combination[a]	
	Carmustine	
	Chlormethine (mechlorethamine)	
	Cisplatin	
	Cyclophosphamide ≥ 1500 mg/m^2	
	Dacarbazine	
	Streptozocin	
Moderate	Alemtuzumab	Idarubicin
	Arsenic trioxide	Ifosfamide
	Azacitidine	Irinotecan
	Bendamustine	Irinotecan peg-liposomal
	Busulfan	Lurbinectedin
	Carboplatin*	Naxitamab
	Clofarabine	Oxaliplatin
	Cyclophosphamide < 1500 mg/m^2	Romidepsin
	Cytarabine > 1000 mg/m^2	Sacituzumab-govitecan**
	Cytarabine/daunorubicin liposomal	Temozolomide[b]
	Daunorubicin	Thiotepa[c]
	Dinutuximab beta	Trabectedin
	Doxorubicin	Trastuzumab-deruxtecan**
	Epirubicin	
Low	Aflibercept	Ixabepilone
	Amivantamab	Loncastuximab-tesirine
	Axicabtagene-ciloleucel	Margetuximab
	Belinostat	Melphalan-flufenamide
	Blinatumomab	Methotrexate
	Bortezomib	Mirvetuximab-soravtansine
	Brentuximab-vedotin	Mitomycin
	Cabazitaxel	Mitoxantrone
	Carfilzomib	Moxetumomab-pasudotox
	Catumaxomab	Necitumumab
	Cetuximab	Nelarabine
	Copanlisib	Paclitaxel
	Cytarabine ≤ 1000 mg/m^2	Paclitaxel nab-albumin
	Decitabine	Panitumumab
	Docetaxel	Pemetrexed
	Doxorubicin peg-liposomal	Pertuzumab
	Elotuzumab	Tafasitamab
	Enfortumab-vedotin	Tagraxofusp
	Eribulin	Teclistamab
	Etoposide	Temsirolimus
	5-Fluorouracil	Tisagenlecleucel
	Gemcitabine	Tisotumab-vedotin
	Gemtuzumab-ozogamicin	Topotecan
	Inotuzumab-ozogamicin	Trastuzumab-emtansine
	Isatuximab	Vinflunine
Minimal	Asparaginase[#]	Nivolumab
	Atezolizumab	Obinutuzumab
	Avelumab	Ofatumumab
	Belantamab-mafodotin	Pembrolizumab
	Bevacizumab	Pixantrone
	Bleomycin	Polatuzumab-vedotin
	Cemiplimab	Pralatrexate
	Cladribine (2-chlorodeoxyadenosine)	Ramucirumab
	Daratumumab	Rituximab
	Dostarlimab	Trastuzumab
	Durvalumab	Tremelimumab
	Emapalumab	Vinblastine
	Fludarabine	Vincristine
	Ipilimumab	Vinorelbine
	Mosunetuzumab	

[a]The combination of an anthracycline and cyclophosphamide in patients with breast cancer is highly emetogenic

[b]No direct evidence found for temozolomide IV; as all sources indicate a similar safety profile of oral temozolamide, the classification was based on oral temozolomide

[c]Classification refers to individual evidence from pediatric trials

[*]Emetic potential appears to be at the high end of the moderate category

[**]Emetic potential appears to be at the high end of the moderate category, most closely resembling that of carboplatin

[#]Asparaginase erwinia chrysanthemi (crisantaspase) and asparaginase (calaspargase pegol)

Table 4 Emetogenic potential of single oral antineoplastic agents*

High/moderate	Abemaciclib	Lenvatinib
	Adagrasib	Lomustine
	Avapritinib	Midostaurin
	Bosutinib	Mobocertinib
	Cabozantinib	Niraparib
	Ceritinib	Olaparib
	Crizotinib	Procarbazine
	Cyclophosphamide	Ribociclib
	Enasidenib	Rucaparib
	Fedratinib	Selinexor**
	Hexamethylmelamine	Temozolomide
	Imatinib	Vinorelbine
Low/minimal	Acalabrutinib	Methotrexate
	Afatinib	Neratinib
	Alectinib	Nilotinib
	Alpelisib	Nintedanib
	Apalutamide	Olutasidenib
	Asciminib	Osimertinib
	Axitinib	Palbociclib
	Bexarotene	Panobinostat
	Brigatinib	Pazopanib
	Capecitabine	Pemigatinib
	Capmatinib	Pexidartinib
	Chlorambucil	Pomalidomide
	Cobimetinib	Ponatinib
	Dabrafenib	Pralsetinib
	Dacomitinib	Regorafenib
	Darolutamide	Relugolix
	Dasatinib	Ripretinib
	Duvelisib	Ruxolitinib
	Encorafenib	Selpercatinib
	Entrectinib	Sonidegib
	Erdafitinib	Sorafenib
	Erlotinib	Sotorasib
	Estramustine	Sunitinib
	Etoposide	Talazoparib
	Everolimus	Tazemetostat
	Fludarabine	Tegafur/uracil
	Futibatinib	Tepotinib
	Gefitinib	Thalidomide
	Gilteritinib	Tioguanin (6-thioguanine)
	Glasdegib	Tivozanib
	Hydroxyurea	Topotecan
	Ibrutinib	Trametinib
	Idelalisib	Trifluridine/tipiracil
	Infigratinib	Tucatinib
	Ivosidenib	Umbralisib
	Ixazomib	Vandetanib
	Lapatinib	Vemurafenib
	Larotrectinib	Venetoclax
	Lenalidomide	Vismodegib
	Lorlatinib	Vorinostat
	Melphalan (L-Phenylalanine mustard)	Zanubrutinib

*Classified emetic potential of oral agents based upon a full course of therapy and not a single dose within the first cycle

**Emetic potential appears to be at the high end of the moderate category

Table 5 Common terminology criteria: term vomiting

Adverse event	Grade				
	1	2	3	4	5
Vomiting*	1 – 2 episodes (separated by 5 min) in 24 h	3 – 5 episodes (separated by 5 min) in 24 h	≥ 6 episodes (separated by 5 min) in 24 h; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

*Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth

to four broad emetogenic risk groups (high, moderate, low, minimal) [2, 6].

During the classification process, the following challenges noted during prior guideline updates were continuously present:

- A lack of specific information on nausea/vomiting in clinical trial publications,
- Listing only CTCAE grade 3/4 nausea and/or vomiting or the combination of both,
- Reporting all grades only of nausea and/or vomiting,
- Not specifying the observation period when the toxicity data were collected,
- Missing information on whether antiemetic prophylaxis or treatment was administered,
- Limited data for single antineoplastic agents as many agents are given as combination regimens,
- Inclusion of heavily pre-treated patient populations makes it difficult to differentiate whether the vomiting is due to the antineoplastic agent or due to advanced cancer itself (example: imatinib in CML, chronic phase imatinib is of low emetogenic potential, in blast crisis, imatinib is of moderate emetogenic potential),
- Lack of information about intercurrent illnesses or concomitant medications, which cause nausea and emesis,
- Failure to report the time frame of emetic outcomes, thus providing little basis to determine the potential of a new antineoplastic agent to induce acute or delayed nausea and vomiting or even anticipatory nausea and vomiting,
- No detailed information about patient-related variables in correlation to the incidence of nausea and vomiting, such as sex, age, anxiety, and history of alcohol consumption,
- The tendency to underestimate the incidence of emesis that occurs in the days after the patient has left the clinic and is no longer under direct observation.

The reported incidence of vomiting with three new antineoplastic agents (sacituzumab-govitecan, trastuzumab-deruxtecan, and selinexor) deserves special mention. The two intravenously administered agents (sacituzumab-govitecan and trastuzumab-deruxtecan) warrant classification in the high–moderate emetogenic range analogous to carboplatin. The oral agent selinexor warrants classification in the higher end of the moderate–high-risk category.

Characterizing emetic potential for oral antineoplastic agents is especially problematic and challenging. These agents are typically administered chronically over protracted periods. Traditional concepts of acute and delayed nausea and vomiting lose their relevance in these settings.

One other limiting factor is the standard toxicity reporting systems. In clinical studies, the CTCAE criteria are often used (Table 5). For example, CTCAE grade 1 describes 1–2 episodes of vomiting in 24 h. Although this information would be critically important in evaluating the emetic potential of a given agent, grade 1 and 2 CTCAE toxicities are rarely reported in publications. The suggestion of the prior MASCC/ESMO guideline panel to record the frequency and intensity of nausea and vomiting using standard antiemetic methodology rather than the less informative Common Terminology Criteria was never adopted in clinical trials [2]. Further, the CTCAE criteria represent a classical clinician-reported outcome, and it is well-known that clinicians often underreport symptoms experienced by the patient [1]. In contrast, patient-reported outcomes usually identify a higher incidence and severity of treatment-related symptoms.

Finally, it should be acknowledged that the MASCC/ESMO antiemetic prophylaxis guideline recommendations at present can only be applied to intravenously administered antineoplastic agents, given the paucity of antiemetic trials specifically designed for orally administered antineoplastic agents.

Of note, several intravenous agents (carboplatin, sacituzumab-govitecan, trastuzumab-deruxtecan) are significantly more emetogenic than most moderate agents and may warrant consideration to be classified in a separate category between the moderate and high categories in the future. This may allow more precise antiemetic prophylaxis recommendations.

Acknowledging these limitations, we have attempted to provide a reasonable approximation of the emetic risk associated with systemic antineoplastic agents. Ultimately, this process will only improve if appropriate information on nausea, vomiting, and concomitant medication (e.g., antiemetic prophylaxis or treatment) is collected and reported for phase II and III clinical studies in new antineoplastic agents.

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