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Special Paper

Guidelines for Anti-emetic Therapy: Acute Emesis

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Anti-emetic therapy has become integral to the management of patients with cancer. Goals related to complete emesis control include providing treatment that reduces hospitalisation and time in the ambulatory setting, care that is convenient for the patient and therapy that enhances patients' quality of life. A panel of clinical, health economic and basic scientists with expertise in various oncology disciplines reviewed published literature to develop evidence-based consensus guidelines for the prevention and treatment of chemotherapy-induced emesis. Currently, serotonin receptor antagonists and corticosteroids are the two categories of anti-emetics that are most effective, have the fewest side-effects and are convenient to use. These agents are recommended in combination for highly emetogenic chemotherapy regimens and as single agents or in combination for moderately to highly emetogenic chemotherapy. When possible, these agents may be given orally in single doses; current evidence does not support dose escalation for either category of anti-emetics. In special situations, such as the use of high-dose chemotherapy combination regimens, the most emetogenic component of the regimen should dictate the choice of anti-emetic. Appropriate anti-emetic use described in these guidelines represents both good medical practice and a sensible economic approach to care. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

In recent years, anti-emetic therapy has become integral to the management of patients with cancer. Current anti-emetic therapy allows oncologists to achieve routinely the goal of completely preventing nausea and vomiting in many patients receiving chemotherapy. Clinical and basic research over the past 20 years has led to steady improvements in the control of nausea and vomiting. Newer, more effective anti-emetic agents commonly used today are also safer, associated with few of the side-effects observed with older regimens and more convenient for patients to receive and healthcare professionals to administer.

Increased anti-emetic usage has been accompanied by increases in the classes and numbers of anti-emetic agents, as well as the indications for anti-emetic therapy. Identifying a cancer patient's emetic risk has become critical to appropriate anti-emetic management.

Several aspects of clinical care play a role in the selection of an appropriate anti-emetic regimen. Goals related to complete emesis control include providing: (1) treatment that reduces hospitalisation and time in the ambulatory setting; (2) care that is convenient for the patient; and (3) therapy that enhances patient quality of life. Importantly, oncologists are encouraged to achieve these goals with minimal or no impact on overall treatment costs.

PRACTICE GUIDELINES

Practice guidelines can be defined as systematically developed strategies that assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances. Considerations of validity, reliability, reproducibility,

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clinical applicability, clinical flexibility, clarity, multidisciplinary process, evidentiary review and documentation are necessary to develop good clinical practice guidelines. Effective guidelines may promote access to better care as well as decrease medical care costs [1].

Evidence can differ in level and grade and is, thus, rated according to specific criteria (Table 1) [2]. Importantly, guidelines cannot always describe individual patient variations and are not designed to replace physician judgement in decisions about particular patients or particular clinical situations. Clinical practice guidelines cannot include all proper methods of care or exclude other treatments reasonably directed at obtaining similar results. Importantly, not all relevant questions regarding cancer-related emesis have been addressed in the context of clinical trials. In some cases, specific areas of research need are identified in these guidelines. As ongoing research is completed, useful clinical trial results will be incorporated into any guideline updates.

These guidelines describe anti-emetic administration in clinical practice. They do not necessarily apply to interventions rendered in the context of clinical trials, because clinical studies are designed to evaluate novel and innovative therapies in a disease in which better treatment is vitally important. Because they are developed via review and synthesis of the most current literature, practice guidelines also identify important questions for further research and those settings in which investigational therapy should be considered.

METHODS

Panel members Perugia consensus conference

The Panel (see appendix) included experts in clinical medicine, clinical research, outcomes/health services research, medical decision-making and health economics, all of whom had additional expertise in anti-emetics and supportive care. Clinical oncology experts represented relevant disciplines, including medical oncology, paediatric oncology and oncological pharmacy practice in oncology.

Data collection and literature review

To create these guidelines, MEDLINE and other database searches were conducted using key words related to the individual emetic problems to collect appropriate articles. Pertinent published literature as of July 1997 was retrieved and reviewed; directed searches were also made of the primary articles.

Evidence-based consensus development

The panel identified guideline topics, developed a strategy for guideline completion and reviewed the literature. The panel emphasised the inclusion of prospective randomised clinical trials. The expert panel's recommendations are based on current emetic treatment and prevention methods.

ACUTE CHEMOTHERAPY-INDUCED EMESIS

Definitions provide a proper context to discuss the evidence of emetic control. Although several methods are available to measure emesis (vomiting), counting the number of emetic episodes is the most frequent measure used. With currently available anti-emetic agents, the most important endpoint is complete emetic control (i.e. no vomiting). Studies have documented the strong accuracy and reliability of the complete control endpoint [3–5]. Complete vomiting control is highly correlated with patients' perception of emesis and satisfaction with emetic control [6, 7], further validating this as an important emetic measure. Although the neuropharmacological basis for emetic control is now better understood, many questions remain.

In comparison, mechanisms responsible for mediating nausea are less well described. Only the patient can judge nausea, or the perception that emesis may occur, making its description more subjective. Various questionnaires, incorporating either visual analogue or categorical scales, are widely used to describe nausea. The incidence of nausea correlates well with that of vomiting, although chemotherapy-induced nausea occurs more often than vomiting [7]. Many large, randomised clinical trials have demonstrated that complete control rates are higher for vomiting than nausea [3–5, 8–11].

Although the concept of 'total control' (no vomiting or nausea) is attractive, results of recent large studies indicate that total control essentially corresponds to the complete control rate of nausea [5, 10, 12]. Thus, this category does not appear to provide additional practical information.

Lesser control rates, such as major control (none to two or one to two emetic episodes) or minor control (three to five emetic episodes), have been useful historically [3, 4, 13, 14] and may continue to be valuable in particularly difficult emetic situations. However, the panelists reached a consensus and advised the use of complete control rates in the guideline process and to evaluate most clinical emetic situations.

Table 1. *Type and grading of evidence for recommendations* [2]

Level	Type of evidence for recommendation
I	Evidence obtained from meta-analysis of multiple well-designed controlled studies; randomised trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study; randomised trials with high false-positive and/or -negative errors (low power)
III	Evidence obtained from well-designed quasi-experimental studies, such as non-randomised controlled single-group pre-post, cohort, time, or matched case–control series
IV	Evidence from well-designed non-experimental studies, such as comparative and correlation descriptive and case studies
V	Evidence from case reports and clinical examples
Category	**Grade of evidence**
A	There is evidence from type I or consistent findings from multiple studies of types II, III, or IV
B	There is evidence of types II, III, or IV and findings are generally consistent
C	There is evidence of types II, III, or IV but findings are inconsistent
D	There is little or no systematic empirical evidence
NG	Grade not given

Anti-emetic agents: highest therapeutic index

The serotonin receptor antagonists and corticosteroids are the two agent classes included in this category (Table 2). Both are highly effective with few adverse effects when used properly and can be safely administered in combination when indicated [15, 16]. The significant improvements in anti-emetic ease of administration and effectiveness in clinical practice largely result from the use of these agents. Currently, these are the two most effective anti-emetic classes.

Serotonin receptor antagonists. This section separately describes agent equivalence, drug dosage, schedule and route of administration. Specific guidelines for unique acute emetic situations will be provided in a subsequent section.

Agent equivalence. There are four serotonin receptor antagonists currently available commercially in many countries: dolasetron, granisetron, ondansetron and tropisetron. Other serotonin receptor antagonists are available in individual countries or are being evaluated clinically. Each agent acts by selectively inhibiting the type 3 serotonin (5-hydroxytryptamine, 5-HT_3) receptor, for which each has a high affinity [17–20]. This inhibition results in the clinically relevant anti-emetic activity that occurs with each of these drugs. The serotonin receptor antagonists also share a similarly mild adverse-effect profile [13, 14, 21, 22]. The most common adverse effects observed in clinical practice include mild headache, transient transaminase elevations and constipation or diarrhoea [13, 14, 21, 22].

Several, large, well-designed randomised trials with high power demonstrated that the serotonin receptor antagonists are equivalent in terms of anti-emetic efficacy and safety [3–5, 9–11, 15, 23–25]. The panel was unanimous in this conclusion. (*Type of evidence*: I; *grade of evidence*: A.)

The overall conclusion is based on the superior available evidence for dolasetron, granisetron and ondansetron. Although tropisetron studies were less rigorously performed (evidence type II, grade B), the panel agreed that the evidence was sufficient to support its confidence in the above-stated conclusion.

Drug dosage. Numerous studies have evaluated possible ideal dosage regimens for the serotonin receptor antagonists. Although few studies have carefully evaluated appropriate tropisetron dosages [26, 27], dosing of dolasetron [28–34], granisetron [35–38] and ondansetron [39–43] has been extensively evaluated. Toxicity has not been a criterion for determining dosage because all of these agents have excellent safety profiles across large dosing ranges. Clearly, the efficacy of these drugs is weakened at lower than optimal doses (Table 2). Further, higher doses do not enhance anti-emetic activity once all 5-HT_3 receptors become saturated. An important corollary to these observations is that sufficient doses of each drug must be administered to guarantee maximum efficacy, and the dose will not change, regardless of the setting in which a serotonin receptor antagonist is recommended. The unanimous conclusion of the panel was that the lowest fully effective dose for each agent should be administered. (*Type of evidence*: I; *grade of evidence*: A.)

Drug dosage has been studied most extensively with dolasetron, granisetron and ondansetron. Although there is a less rigorous degree of evidence, a similar conclusion was reached for tropisetron.

Drug schedule. Several recent studies have evaluated administration of multiple versus single anti-emetic doses [30, 34, 35, 44–47]. If equally effective, single-dose administration with the lowest fully effective dose improves convenience and patient compliance, provides economic benefit

Table 2. Anti-emetic agents, doses and administration schedules

Anti-emetic agent	Dose range	Schedule*	Evidence (type, grade)
Agents with highest therapeutic index			
Serotonin receptor antagonists			
Dolasetron	100 mg or 1.8 mg/kg i.v.	One time, prior to CT	I, A
	200 mg p.o.	One time, prior to CT	II, A
Granisetron	1 mg or 0.010 mg/kg i.v.	One time, prior to CT	I, A
	2 mg† p.o.	One time, prior to CT	I, A
Ondansetron	8 mg or 0.15 mg/kg i.v.	One time, prior to CT	I, A
	Oral doses not well studied for acute emesis, (usually 8 mg doses in delayed or RT emesis)	(Two to three times daily in delayed or RT emesis)	
Tropisetron	5 mg i.v.	One time, prior to CT	III, B
	5 mg p.o.	One time, prior to CT	III, B
Corticosteroids			
Dexamethasone	8 mg–20 mg i.v.	One time, prior to CT	I, A
	4–20 mg p.o.	One time, prior to CT	II, III, B
Methylprednisolone	40–100 mg i.v.	One time, prior to CT	III, B
Agents of lower therapeutic index			
Dopamine receptor antagonists			
Metoclopramide	2–3 mg/kg i.v.	Prior to and 2 h after CT	I, A
	20–0.5 mg/kg p.o. for delayed emesis or RT	Two to four times daily for delayed emesis	
Prochlorperazine	10–30 mg i.v.	Every 3–4 h	II,B
	10–20 mg p.o.	Every 3–4 h	III–IV, C

*For acute chemotherapy-induced emesis. †Within first 24 h of chemotherapy. i.v. intravenous; p.o., oral; CT, chemotherapy; RT, radiation therapy.

and decreases the potential for adverse effects. Large, randomised studies with granisetron [35] and ondansetron [44–47] verify the equivalence of single-dose and multiple-dose schedules for each individual agent. The efficacy of dolasetron is optimal using single-dose administration schedules [30, 34] and the single-dose activities of dolasetron, ondansetron and granisetron are equivalent [3, 11, 15, 23, 48], confirming that all three agents can be administered via the single-dose administration schedule. The panel unanimously concluded that single-dose regimens are as effective as multiple-dose schedules. (*Type of evidence*: I; *grade of evidence*: A.)

Tropisetron generally has been administered as a single dose [22, 24, 49, 50] and few formal dosing comparisons have been conducted. Although this represents a lower level of evidence, the panel reached the same conclusion as with the other three 5-HT_3 receptor antagonists.

Route of administration. The majority of conclusions regarding drug equivalence, dosage and schedules are based on intravenous (i.v.) administration. However, formal trials are now being reported describing comparisons between the oral and i.v. administration routes for a number of serotonin receptor antagonists [51, 52]. Results of pharmacological testing of the 5-HT_3 receptor antagonists demonstrate that each is well absorbed when administered orally, with 50–80% bioavailability [13, 14, 21, 22]. Because 5-HT_3 receptors occur in the enterochromaffin cells in the gut [53] and vagal afferent fibres are also found in this area [54], these agents may be particularly suited for oral administration.

Large, randomised studies demonstrated comparable efficacy between a single oral granisetron dose and a single i.v. ondansetron dose in patients receiving highly emetogenic or moderately emetogenic chemotherapy [10, 51]. The very small differences observed were further decreased when both agents were administered concomitantly with corticosteroids [51]. Another large randomised study also demonstrated similar efficacy between oral dolasetron and oral ondansetron in patients receiving moderately emetogenic chemotherapy [4]. Both ondansetron and tropisetron are orally active; however, only less formal studies have evaluated the oral forms of these agents [55–57]. Oral and i.v. routes are similar in efficacy, especially when these agents are administered with corticosteroids [51]; however, the level of evidence is somewhat lower for this comparison than for those previously described. (*Type of evidence*: I–II; *grade of evidence*: A–B.)

Ongoing trials will probably increase the level of evidence and more completely evaluate the efficacy of oral ondansetron.

Corticosteroids. Similar to serotonin receptor antagonists, corticosteroids have a high therapeutic index when administered for acute chemotherapy-induced emesis [15]. These drugs are among the most frequently employed anti-emetics, and single-agent administration is appropriate in some settings. They are particularly useful when given in combination with serotonin receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy [15, 58, 59]. Issues of equivalence and route of administration and drug dose and schedule will be discussed together.

Agent equivalence and route of administration. Dexamethasone and methylprednisolone are the two corticosteroids most frequently studied as anti-emetics [60]. Occasionally, clinical reports have incorporated prednisone or other corticosteroids. Although efficacy has been demonstrated with these agents [61, 62], comparative trials have not been conducted. The advantages of dexamethasone include the availability of low-cost generic equivalents in many countries and numerous dosage formulations. Formal trials comparing oral and parenteral corticosteroid formulations have not been conducted. Acceptable oral bioavailability and efficacy in many indications has encouraged oral corticosteroid use for emesis in anti-emetic settings where efficacy of the parenteral formulations has been reported. In the absence of comparative trials, most clinicians prefer dexamethasone or methylprednisolone because of the published experience with these agents. (*Type of evidence*: IV and expert consensus; *grade of evidence*: B.)

Drug dose and schedule. The limited number of comparative trials [63] conducted to explore these issues have generally been designed as dose-ranging rather than randomised studies. Results suggest that single doses have equivalent efficacy to multiple-dose regimens [64]. Although only a few small studies have been conducted, there is no evidence demonstrating benefit in beginning corticosteroid therapy a long time (e.g. the prior day) before chemotherapy. In addition, there is no evidence to date that dexamethasone doses > 20 mg are more effective than lower doses. Numerous trials have evaluated 8–10 mg dexamethasone doses [65]; it is unclear whether there is a dose–response in various anti-emetic settings for dexamethasone doses ranging from 8–20 mg (Table 2) [66]. Adverse effects of single corticosteroid doses are generally low, although glucose elevation and sleep disturbances have been reported. Until further evidence is available from ongoing formal comparative studies, the panel reached the consensus that single-dose regimens are appropriate and that dexamethasone doses ranging from 8–20 mg are appropriate. (*Type of evidence*: III; *grade of evidence*: B.)

Anti-emetic agents: lower therapeutic index

Several classes of anti-emetic agents are somewhat or significantly less effective than the serotonin receptor antagonists or corticosteroids. These agents generally have more adverse effects than those discussed previously and are less selective than the serotonin receptor antagonists. Several agents in this class share a possible anti-emetic mechanism of action, antagonism of dopamine type 2 (D2) receptors. Metoclopramide, a substituted benzamide that has many actions mediated via dopamine receptors, is also a serotonin receptor antagonist at higher doses (Table 2) [67]. The anti-emetic efficacy of metoclopramide is similar although slightly lower than that of the selective serotonin receptor antagonists [68–71]. However, adverse effects such as dystonic reactions lower its therapeutic index [60, 69]. The panel unanimously agreed that, in acute chemotherapy-induced emesis, particularly in moderate to severe risk settings, there are few patients for whom these agents are appropriate as first-choice anti-emetic drugs. They should be reserved for specific circumstances, including known intolerance to serotonin receptor antagonists or corticosteroids. (*Type of evidence*: I; *grade of evidence*: A.)

Adjunctive drugs

Several classes of sedatives or minor tranquilizers have been administered as anti-emetics, including barbiturates and benzodiazepines [15, 60]. Barbiturates have failed to demonstrate significant anti-emetic activity in clinical trials. Benzodiazepines, generally lorazepam, have been widely

administered both in combination and as single agents [72–74]. Clinical trials, including randomised, blinded studies evaluating lorazepam in combination regimens, demonstrated that lorazepam has only minor anti-emetic activity [74]. However, lorazepam's anti-anxiety effects were significant and considered a useful addition to efficacious anti-emetic combinations. Lorazepam is considered a helpful adjunct to anti-emetic therapy rather than an effective anti-emetic.

Antihistamines, most commonly diphenhydramine and hydroxyzine, have been administered both as anti-emetics and adjunctive agents to prevent dystonic reactions following dopamine antagonist administration. These drugs do not demonstrate significant anti-emetic activity in clinical trials [73, 74]. Diphenhydramine may be useful to prevent or treat dystonic reactions, although its role in this setting is limited because dopamine receptor antagonists are no longer a first choice to prevent emesis. (*Type of evidence*: II; *grade of evidence*: B.)

Anti-emetic combinations

Extensive research demonstrates that certain anti-emetic combinations are significantly more effective than single agents with highly emetogenic chemotherapy. Results of repeated highly powered, multicentre, randomised clinical trials demonstrate that the combination of corticosteroids and a serotonin receptor antagonist provides the best anti-emetic protection with a low incidence of adverse effects [46, 58, 59, 75–80]. These combinations are the regimens of choice for patients receiving cisplatin or non-cisplatin chemotherapy of moderate to high emetic risk. The panel unanimously recommended that in these patients, a corticosteroid should be administered concomitantly when a serotonin receptor antagonist is indicated unless use of the former agent is strongly contraindicated. (*Type of evidence*: I; *grade of evidence*: A.)

Older, well-conducted randomised trials also show that corticosteroids plus agents in the 'lower therapeutic index' category (e.g. metoclopramide) demonstrate superior efficacy compared with the single agent in high risk emetic situations [81–84]. However, a large randomised trial demonstrated that a serotonin receptor antagonist/corticosteroid combination was superior to a high-dose metoclopramide/corticosteroid combination in these settings, both in terms of greater efficacy and fewer adverse effects [85].

Risk factors for acute emesis

Two major factors predict risk of emesis or differences in anti-emetic control: patient characteristics and the chemotherapeutic agent used for treatment.

Patient characteristics. Several patient factors predict poorer anti-emetic control: poor control with prior chemotherapy [3, 4, 86], female gender [3, 4, 87], a history of low chronic alcohol intake [88, 89] and younger age [4, 63, 90]. Although age is less consistently identified as a predictive factor in clinical trials, most panelists indicated that age should be considered in conjunction with other factors when planning appropriate anti-emetic therapy. Chronic alcohol intake may include a prior or current history of high alcohol use. High use is frequently defined as alcohol intake > 100 g/day for several years; the emetic risk with chemotherapy decreases as alcohol intake increases [88, 89]. Patients may present with several risk factors. Patients with ovarian cancer are likely to have several characteristics that indicate a lower chance for complete emetic control. Multivariate analysis has confirmed the predictive impact of these factors [91].

Classification of acute emetic risk by chemotherapeutic agent. Prospective documentation of emetogenic potential has been rigorously identified for only a few chemotherapeutic agents. General categories defined from experience instead of specific data are helpful, but do not precisely differentiate agents. A recent publication has attempted to categorise both single agents and chemotherapy combinations based on the actual incidence of emesis [91]. Although this approach was viewed positively by the panel, a consensus could not be reached because clear documentation of emetogenic potential is not available for most chemotherapeutic agents and combinations. This issue is further complicated by the fact that, except for cisplatin, existing data include too few patients for a multivariate analysis by gender, alcohol intake history or age.

A classification based on anti-emetic recommendations is necessary to create guidelines. The rationale for a classification by emetic risk of the chemotherapy agent is described in the following paragraphs (Table 3). These treatment-related categories allow general consensus, although difficulties occur in properly categorising agents that border two risk categories.

Severe emetic risk. The literature provides clear evidence-based documentation of emetic incidence with cisplatin [92, 93]. This is valuable in anti-emetic studies for several reasons: (1) cisplatin is widely used in oncology; (2) cisplatin causes emesis in all patients (> 99% without anti-emetic therapy); and (3) cisplatin provides a 'worst case' model in anti-emetic clinical trials. Thus far, clinical trials demonstrate that an anti-emetic's effectiveness in preventing emesis with other chemotherapeutic agents is positively correlated with its efficacy in cisplatin-induced emesis. Although universal with cisplatin, other factors may influence the emetic risk. Emetic control decreases as cisplatin dose increases [92]. Other problems, such as delayed emesis, also appear to increase with cisplatin dose. Based on these observations, cisplatin is generally considered the most emetogenic chemotherapeutic agent available. The anti-emetic treatment guideline for cisplatin is independent of dose or infusion duration. Based on the careful documentation of cisplatin-induced emesis in numerous well-conducted trials, the panel was unanimous in its treatment recommendation. *Guideline*: combination of a 5-HT_3 antagonist + a corticosteroid. (*Type of evidence*: I; *level of evidence*: A.)

Complete control of acute cisplatin-induced emesis using the recommended regimen has been documented to range from 65 to 80% in large, multicentre randomised trials [58, 76, 78, 79, 94].

Moderate to high emetic risk. Risk documentation for several chemotherapy agents in this category (e.g. cyclophosphamide, carboplatin) is well established (Table 3). If the classification was based on emetic incidence instead of treatment recommendations, some of these agents (dacarbazine, nitrogen mustard, very high-doses of cyclophosphamide) could be placed in a separate higher risk group in which the emetic risk is > 90%.

Other commonly used agents in this category include the anthracyclines, nitrosoureas and cytosine arabinoside. Especially when administered in higher-doses, these agents will

cause emesis in most patients who do not receive effective anti-emetic therapy [92]. The panel unanimously agreed on the treatment recommendations for all agents in this category. Guideline: combination of a 5-HT_3 antagonist + a corticosteroid. (*Type of evidence*: I, II, III and expert consensus; *level of evidence*: A–B.)

The type and level of evidence varied by agent. Good level 1 data are identified for cyclophosphamide, the anthracyclines and combinations of these agents. In these instances, several large randomised multicentre trials documented complete control rates ranging from 85–90% using the recommended regimen for acute emesis [10, 26, 77, 80]. A lower level of evidence was identified for other agents (e.g. dacarbazine).

Low emetic risk. Several frequently used chemotherapeutic agents in this category are shown in Table 3. Many (but not most) patients demonstrate an emetic response to these drugs without anti-emetic therapy. However, the emesis is more controllable than that experienced with drugs in higher risk categories [92]. Some panel members considered the first few drugs on this list to border the higher risk category in terms of emetogenic potential. Similarly, some panel members categorised the last few drugs as having a very low risk of emesis. Evidence for emetic risk for newer agents in this category is often derived from phase I and II chemotherapeutic trials rather than comparative anti-emetic studies. *Guideline*: a corticosteroid. (T*ype of evidence*: III, IV, and expert consensus; *level of evidence*: B, D.)

The efficacy of anti-emetic therapy administered in conjunction with these lower risk chemotherapeutic agents has not been formally documented. The experience of the panel indicates that complete emetic control rates > 90% should be expected following a single dose of a corticosteroid.

Very low risk emesis. Few anti-emetic studies have been performed with these chemotherapeutic agents (Table 3), which is understandable considering the low perception of risk (< 10% for most drugs) [92]. All of the agents in this category have been used for ≥ 20 years; thus, the drug evaluation process generally did not include a quantification of emetic incidence. Although most hormonal agents are not included, tamoxifen is listed because it is so frequently administered and is associated with a very low emetic risk. Some panelists would move a few of the agents listed at the beginning to the low risk category. *Guideline*: no anti-emetic

Table 3. Chemotherapeutic agents, anti-emetic risk categories and guidelines for acute emesis

Emetic category	Chemotherapy agents	Anti-emetic guideline	Evidence (type/grade)
Severe risk	Cisplatin	5-HT_3 antagonist + corticosteroid*	I, A†
Moderate to high risk	Dacarbazine	5-HT_3 antagonist + corticosteroid*	II–III, A–B†
	Actinomycin-D		(Range for the class)
	Nitrogen mustard		
	Carboplatin		II, B
	Cyclophosphamide		II, B
	Lomustine		
	Carmustine		
	Daunorubicin		
	Doxorubicin		II, B
	Epirubicin		II, B
	Idarubicin		
	Cytosine arabinoside		
	Ifosfamide		
Low risk	Mitoxantrone	Corticosteroid*	III–IV, B–D†
	Paclitaxel		(Range for the class)
	Docetaxel		
	Mitomycin		
	Irinotecan		
	Topotecan		
	Gemcitabine		
	Etoposide		
	Teniposide		
	Vinorelbine		
Very low risk	Methotrexate	No routine use of anti-emetics	V, D†
	6-Thioguanine		(For the class)
	6-Mercaptopurine		
	Bleomycin		
	L-Asparaginase		
	Vindesine		
	Vinblastine		
	Vincristine		
	Busulfan		
	Chlorambucil		
	Melphalan		
	Hydroxyurea		
	Tamoxifen		

*See Table 2 for anti-emetic doses, schedules and routes of administration. †See text for details. 5-TH_3, 5-hydroxytryptamine.

is routinely needed for most patients. (*Type of evidence*: V and expert consensus; *level of evidence*: D.)

As with all categories, individual patients may require anti-emetic regimen alteration, especially those who experienced poor emetic control with prior chemotherapy. Panelists expect that anti-emetic control should exceed 95% in this group. Occasionally, patients may require a single corticosteroid dose or intermittent administration of an oral substituted benzamide or phenothiazine.

Emetic risk and combination chemotherapy. With combination chemotherapy, the drug in the combination with the highest emetic risk should dictate the choice of anti-emetic therapy [15, 92]. For example, patients receiving cisplatin plus a low risk agent should be given anti-emetics appropriate for cisplatin. Patients receiving a low risk agent and an anthracycline should be given anti-emetics recommended for non-cisplatin moderate to high risk drugs. The panel unanimously agreed on this recommendation. *Guideline*: when administering combination chemotherapy, the patient should receive anti-emetics appropriate for the chemotherapeutic agent with the highest emetic risk. (*Type of evidence*: I; *level of evidence*: A.)

The panel could not reach a consensus concerning added emetic risk if patients receive chemotherapy combinations in which all drugs are in either the low risk or the very low risk category. Although no definitive evidence currently exists, some clinicians suggest that these combinations may increase the emetic risk (i.e. from low risk to moderate to high risk or from very low risk to low risk). The panelists believed that oncologists should be cognisant of this issue and should carefully evaluate the emetic history of patients receiving these combinations. Most experts would treat most patients receiving these combinations with anti-emetics appropriate for the chemotherapeutic agent with the highest emetic risk.

Emetic risk and multiple consecutive day chemotherapy. Emetic control decreases when highly emetogenic chemotherapy is administered on several consecutive days. Although not completely understood, the consideration of both delayed and anticipatory emesis to an already highly emetogenic regimen may in part explain this phenomenon. Serotonin receptor antagonists are particularly useful in high risk and moderate risk settings because use of these agents avoids the increased risk of dystonic reactions that occurs (especially in younger patients) following consecutive day dopamine antagonist administration. A special anti-emetic regimen has not been described for this setting. *Guideline*: if the chemotherapy can be given as effectively and safely on 1 day, the likelihood of controlling emesis improves. Anti-emetics appropriate for the chemotherapy risk class (as outlined above) should be administered each day of the chemotherapy. (*Type of evidence*: II, III; *level of evidence*: B.)

If appropriate for the chemotherapy administered, anti-emetics for delayed emesis should be given after chemotherapy completion. Paradoxically, in older studies using ineffective anti-emetics, emetic incidence declined with each day of chemotherapy.

OUTSTANDING QUESTIONS

Consensus recommendations have been presented on the appropriate use of 5-HT_3 antagonists, alone and in combination with other agents, for the prevention and treatment of acute chemotherapy-induced emesis and nausea. Despite reaching a consensus on several issues, two major issues regarding acute emesis and nausea remain to be determined. Firstly, it is necessary to reach a consensus on a definitive emetogenic classification system. Further work should be performed on refining the current classification system proposed by Hesketh and colleagues [92] and prospectively evaluating new chemotherapeutic agents for their emetogenic potential. Secondly, despite the availability of the 5-HT_3 antagonists, many patients continue to experience emesis and nausea after chemotherapy, mostly due to late breakthrough or delayed emesis. Practice guidelines for the treatment of delayed emesis need to be developed. Overall, future improvements in the prevention and treatment of chemotherapy-induced emesis and nausea will probably be related to advancing our understanding of the underlying pathophysiology of emesis and nausea.

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APPENDIX
PANEL MEMBERS

M. Aapro,	Italy, Switzerland
P.L.R. Andrews,	U.K.
E. Ballatori,	Italy
P. de Mulder,	The Netherlands
A. del Favero,	Italy
M.A. Dicato,	Luxembourg
A. du Bois,	Germany
P.C. Feyer,	Germany
D.R. Gandara,	U.S.A.
R.J. Gralla,	U.S.A.
S. Groshen,	U.S.A.
S.M. Grunberg,	U.S.A.
J. Herrstedt,	Denmark
P.J. Hesketh,	U.S.A.
R.A. Joss,	Switzerland
J. Klastersky,	Belgium
M.G. Kris,	U.S.A.
M. Martin,	Spain
M.E. Marty,	France
G.R. Morrow,	U.S.A.
R.J. Naylor,	U.K.
I.N. Olver,	Austria
F. Roila,	Italy
S. Sallan,	U.S.A.
J.F. Smyth,	U.K.
T.R. Spitzer,	U.S.A.
A. Stewart,	U.K.
M. Tonato,	Italy
D. Walsh,	U.S.A.
D. Warr,	Canada

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