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REVIEW ARTICLE

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Methodology of antiemetic trials: response assessment, evaluation of new agents and definition of chemotherapy emetogenicity

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Abstract Establishing appropriate and practical methodology is a key to progress in the investigation of chemotherapy-induced nausea and vomiting. Critical issues include patient response assessment, proper trial design for evaluating new agents, and the definition of chemotherapy emetogenicity. In assessing antiemetic response, the primary end-point should be complete control of emesis and nausea. Emesis and nausea should be independently assessed with the period of observation defined (acute, delayed, anticipatory). Emesis can be evaluated by measuring the number of emetic episodes either by direct observation or by patient self-report using patient-completed diaries. Nausea should be measured by patient self-report with the standard parameters, including frequency and intensity. New antiemetic drug development should proceed in an orderly progression from open-label phase I–II trials defining tolerance and minimally fully effective dose to phase III comparative trials. A randomized, parallel, double-blind study is the preferred design for the latter, and the comparator arm should always include the current best available treatment. Antiemetic placebos are no longer acceptable with chemotherapy regimens known to produce emesis in a majority of patients. None of the emetogenic classifications proposed to date adequately accounts for all known important patient- and treatment-related prognostic variables. A modification of a recently reported schema is proposed for use in making antiemetic treatment recommendations and defining the emetogenic challenge in clinical trials.

Key words Antiemetic · Emesis · Emetogenicity · Methodology · Nausea

Introduction

Significant progress has been made over the past 15 years in the development of more effective and better tolerated means of preventing chemotherapy-induced nausea and vomiting in cancer patients [15]. Control of emesis remains less than optimal, however, in a number of situations, including delayed emesis following cisplatin and emesis induced by very-high-dose chemotherapy. Therefore, there is a need to evaluate additional novel treatment approaches and new agents.

Establishing and employing practical methodology is a key to progress in the investigation of emesis and its control. Progress in the past was impeded by lack of a focus on the major end-points and by varying methodology of questionable psychometric properties. Appropriate trial design improves the efficiency of new treatment evaluation, maximizes the interpretability of trial results and allows for meaningful comparison of results

across studies. Sound methodology also minimizes the chance that patients participating in antiemetic trials will be placed at unacceptable risk for emesis or excessive toxicity.

A number of reviews have previously addressed the issue of antiemetic trial methodology [1, 14, 28, 31, 32]. Although there is reasonable consistency among the latter on many issues, variation among antiemetic trials with respect to key methodologic issues continues to be seen. This manuscript will review a number of areas relating to antiemetic trial methodology, including patient response assessment, evaluation of new agents and definition of chemotherapy emetogenicity. Consensus recommendations of the Fifth Perugia International Cancer Conference pertaining to these latter areas will be presented.

Assessment of patient response

Methods of data collection

Vomiting and retching (non-productive vomiting), collectively termed emesis, can be objectively quantitated by measuring the number of emetic episodes (Table 1). Direct observation of the patient is an accurate and reliable technique to quantitate emetic episodes [13]. For patients treated in settings where prolonged direct observation is not possible, daily diary cards completed by patients have also proven reliable [12, 29], and are preferable to follow-up by telephone or questioning at the next clinic visit [29].

In delayed emesis trials, the use of questionnaires completed by the patient at home each day during the period of interest (usually 4–7 days) has been an effective method with high patient acceptance. Yield is increased by daily telephone contact.

The recording of emetic episodes when vomiting and retching occur almost continuously has been a vexing problem, with innumerable definitions used to characterize discrete emetic episodes [17, 21, 22]. One definition that simplifies this process considers a discrete emetic episode (vomiting and/or retching) to have ended when at least 1 min has passed since retching or vomiting ceased [21].

Other parameters that have been measured with respect to emesis include volume of emesis, duration of emesis (either from the time of chemotherapy administration or from the initial episode, to the cessation of emesis) and the time of onset of the first emetic episode.

The assessment of nausea has been a more challenging problem than that of emesis, given its subjective nature. Despite the good correlation between vomiting and nausea, they are distinct entities and should be separately evaluated. Although observer rated reports of nausea have occasionally been employed [20, 26], the preferred method of assessment is patient self-report. The three primary characteristics of nausea that have been most commonly measured include frequency, intensity and duration. Frequency is easily determined by patients' providing a simple yes/no answer to specific questioning or through the use of a multi-point scale. Intensity of nausea has been assessed most commonly by means of visual analog or descriptive ordinal scales [3, 11, 27]. Two studies simultaneously assessing nausea with different scales found a high correlation between a four-point descriptive scale (none, mild, moderate, severe) and visual analog scales [8, 16]. One of these stud-

Table 1 Consensus recommendations on assessment of patient response (*EE* emetic episodes)

Recommendation	Level of consensus	Confidence level
Methods of data collection (see text for details)	High	High
Periods of assessment		
Acute: 24 h after chemotherapy	High	Moderate to high
Delayed: >24 h after chemotherapy	High	Moderate
Composite: 1–3 days after chemotherapy	Moderate to high	Moderate
End Points		
Primary		
Complete prevention of emesis (Complete response 0 EE)	High	High
Complete prevention of nausea	High	High
Secondary		
Major response (0–2 EE)	Moderate to high	Moderate
Other		
(See text for details	Low	Low

ies also evaluated the sensitivity of these scales and found them to be comparable [8].

Duration of nausea has been reported much less commonly in antiemetic trials than frequency and intensity [9]. Potential problems with this parameter include the need to rely on patient recall, which can be affected both by the frequency of assessments and concurrent medications and events. In addition, there is no commonly accepted method of measuring nausea duration.

Delfavero et al, have described two additional means of measuring nausea that provide composite measurements. These include entity and quantity of nausea [8]. To employ these composite measurements, assessments of nausea are carried out at a number of intervals during the study period. Entity is defined as the sum of all values of intensity of nausea recorded at each evaluation time point. Quantity is defined as the sum of the products of the intensity times the duration recorded at each evaluation time point. The potential advantage of the composite measurements is their greater sensitivity compared with unidimensional parameters. Therefore, they may provide a means to detect subtle clinical differences in comparative trials. Their major disadvantages, which argue against their general acceptance at present, is their added complexity and the limited experience with these measurements to date.

Period of assessment

Periods of assessment for various emetic problems have been defined empirically (Table 1). Acute chemotherapy-induced emesis is the most common problem. It has been defined as that emesis occurring in the first 24 h after the administration of chemotherapy. The 24-h period serves to separate evaluation of the problem from that of delayed emesis. This definition is useful in delineating both problems, but is not necessarily based on an identified physiological or neuropharmacological difference. It is also useful in that most emesis occurs during this period if effective treatment is not given. Assessment also includes the evaluation of nausea during the period of the emetic problem.

Late-onset emesis is a subtype of acute emesis that has been defined for agents such as cyclophosphamide and carboplatin, which tend to induce emesis much later than most chemotherapy agents, typically at 12 h or more after chemotherapy [11, 25].

Delayed emesis is differentiated from acute or late-onset emesis by an arbitrary definition. It is defined as that emesis starting (or persisting) after the initial 24-h period. This definition has served us well in the identification of the problem and been helpful in the study of control of delayed emesis. There are several theories on the neuropharmacology of the problem; however, these hypotheses remain controversial. The exact time of onset of delayed emesis is not clear, but it has been suggested that it may commonly begin a few hours earlier than the definition. The period of assessment for delayed emesis has varied with different chemotherapy regimens. Following cisplatin, the period of assessment has most commonly extended from the 2nd to the 5th day after chemotherapy. With other chemotherapy regimens, assessment periods have most commonly extended from 3 to 5 days after chemotherapy. As long as the pathophysiology of both acute and delayed emesis remains unclear, cutoffs between these two entities will always be arbitrary and recommendations for clinical studies will remain vague. One way to overcome these limitations is to focus on total control of emesis over a chemotherapy course as a whole. For practical reasons the observation period might be limited to 3 days following chemotherapy administration, because almost all patients who vomit will start vomiting within the first 3 days.

Anticipatory or conditioned emesis is often defined as that emesis beginning prior to the administration of chemotherapy in patients who have previously received chemotherapy. It is clear that poor control of acute or delayed emesis predisposes to this problem.

Response criteria

Primary end-points

The gold standard for antiemetic response is the complete prevention of all emesis and nausea. Emesis is best quantitated by assessing the number of emetic (vomiting/retching) episodes.The primary end-point for emesis is *complete* response, defined as no emetic episodes during the specified observation period (Table 1).

Given its subjective and distinctive nature, nausea should be assessed independently of emesis. Notably, control of nausea has consistently been inferior to control of emesis in clinical trials, with complete nausea control rates approximately 10% lower than complete control rates for emesis [8]. The primary efficacy endpoints should be the frequency and intensity of nausea. The latter can be determined equally well with descriptive ordinal or visual analog scales.

A new category of *total control* has recently emerged and is defined as the complete control of both emesis and nausea. It is unclear whether this new category adds substantially to existing response criteria, as *total control* rates in most reports is typically very similar to the complete control rate of nausea.

Secondary end-points

A number of additional response categories have been defined by the number of emetic episodes. These include: *major* (≤2 emetic episodes), *minor* (3–5 emetic episodes), and *failure* (›5 emetic episodes). The major response category continues to be useful in assessing antiemetic treatment benefit and should be retained as a secondary end-point for response. The clinical utility of the traditional minor and failure categories has become increasingly suspect as antiemetic treatment for conventional-dose chemotherapy has improved. A new failure category, defined as more than two emetic episodes, should be considered. In addition, use of rescue antiemetics and withdrawal from the study should also be classed as failure. After the use of rescue antiemetics, patient observation should continue for the full study period nonetheless, with a complete recording of the total number of emetic episodes.

The complete and major control categories have been helpful in assessing delayed emesis in addition to acute emesis. In delayed emesis, it can be useful to report the number of episodes by each of the first 4 or 5 days after chemotherapy, and control over the entire delayed emesis risk period. In assessing anticipatory nausea or vomiting it is sufficient simply to report on the presence or absence of the problem.

Other end-points

Other parameters that have been measured with respect to emesis include volume and duration of emesis. However, neither can be recommended for primary or secondary end-points. Volume of emesis is difficult to measure, is dependent on oral intake and is not clinically useful [31]. Duration of emesis has been recorded by a number of groups, but no standard definition has yet emerged to characterize this parameter. Time to first emetic episode (mean or median) has also been employed in assessing response. Although not a primary end-point, it may occasionally have value in comparative antiemetic trials.

Other parameters that have been employed in assessing nausea include duration, time to nausea and composite measurements, such as entity and quantity. None should be considered as primary or secondary end-points at the present time.

Evaluating new agents

New antiemetic drug development should follow an orderly and logical progression beginning with open-label phase I/II tolerance and dose-finding trials and progressing through phase III comparative trials (Table 2).

Table 2 Consensus recommendations on evaluation of new agents

Recommendation	Level of consensus	Confidence level
1. Phase I/II trials should always precede phase III trials	High	High
2. Phase I/II trials should define minimal fully effective dose	High	High
3. Phase III trials should employ a double-blind, randomized parallel design	High	High
4. Phase III trials should use best available treatment as comparators	High	High
5. Placebo comparators are not appropriate for trials of acute emesis with moderately or highly emetogenic chemotherapy or trials of delayed emesis after high-dose cisplatin (see text)	High	High

Appropriate candidates for phase I trials are normal volunteers or cancer patients who have failed prior conventional antiemetic treatments. In this type of trial efficacy parameters are important, but clearly secondary to toxicity assessments. After successful completion of phase I trials, phase II trials should be completed to confirm antiemetic efficacy and define minimally fully effective doses. Appropriate study populations for phase II trials are patients failing conventional treatment. If substantial efficacy is noted in initial studies, then appropriate additional populations for study include chemotherapy-naive patients receiving moderately to highly emetogenic chemotherapy.

Phase III trials should be initiated only after completion of phase I/II trials. A pre-randomization stratification for important prognostic variables such as gender and ethanol consumption should be required unless a large sample population of patients is enrolled in the study and the impact of prognostic factors is analyzed by a multifactorial analysis at the end of the study. A randomized, parallel double-blind study is the preferred design for comparative trials. The comparator arm should always contain the current best available treatment. If efficacy results of phase II trials are sufficiently compelling, then the new agent can be compared as a single agent against the best available therapy. An acceptable alternative design is to combine the new agent with the current best standard and compare it with the current best standard combined with placebo.

Treatment with antiemetic placebos alone is no longer acceptable with chemotherapies known to induce emesis in most patients. This includes the evaluation of acute emesis with moderate to highly emetogenic chemotherapy and delayed emesis in patients receiv-

ing high-dose cisplatin (≥ 100 mg/m^2). Use of placebos in delayed emesis following lower dose cisplatin and non-cisplatin-based chemotherapy remains controversial and should be further evaluated. In either of the latter instances, if a placebo treatment is employed there should be zero tolerance for the development of any breakthrough emesis or nausea, with immediate rescue of patients developing symptoms.

A key element in new agent and new regimen evaluation is a careful assessment of the side effect profile. This includes objectively measurable side effects, such as changes in vital signs, blood chemistries, electrocardiograms or physical examinations, which are typically scored using the NCI common criteria. In addition, subjectively measurable side effects, such headache, akathisia, sedation, and diarrhea, should also be assessed. Typically these effects are measured by their presence or absence and then with a categorical rating by the patient (mild, moderate or severe effects). An ongoing challenge in the evaluation of the side effects of new agents is separating the adverse effects of the antiemetics from those of the chemotherapy, symptoms of the malignancy, intercurrent illnesses or concomitant medications.

Defining chemotherapy emetogenicity

Defining the emetogenicity of chemotherapy agents is of value for at least two important reasons. Such a classification can be used as a framework for defining antiemetic treatment guidelines. Secondly, it can provide a means for clinical investigators to attain a more precise definition of the emetogenic challenge that is being employed in an antiemetic trial. A useful schema would provide enough information to be utilized for both of these purposes. At present there is no commonly accepted schema for classifying the emetogenicity of cancer chemotherapy agents or combinations. A number of schemas have been proposed in which chemotherapy agents have been divided among three to five emetogenic levels [1, 4, 23, 24, 30]. The literature has been a very limited source of useful information in the development of these schemas, given the imprecise, inconsistent and extremely limited ways in which information on emesis and nausea has been recorded in most therapeutic trials. Most schemas have not differentiated between the various types of emesis, such as acute, delayed and anticipatory, and few have accounted for im-

Table 3 Consensus recommendations on defining emetogenicity of chemotherapy

Recommendations	Level of consensus	Confidence level
1. Emetic potential and pattern of emesis should be rigorously assessed during clinical development of new agents	High	High
2. Comprehensive schema for classifying chemotherapy emetogenicity incorporating all important treatment and patient related prognostic variable not currently available	High	High
3. Descriptive classification based upon clinical database of homogeneously treated patients should be established	High	Moderate
4. Working schema for use in defining emetogenicity for antiemetic trials and for development of treatment guidelines proposed (see Table 4)	Moderate	Low

Table 4 Approximate emetogenic potential of single chemotherapy agents

Degree of emetogenicity	Agents
High	Cisplatin ≥ 50 mg/m^2 Mechlorethamine Streptozocin Cyclophosphamide >1500 mg/m^2 Carmustine >250 mg/m^2 Dacarbazine
Moderate to high	Cisplatin <50 mg/m^2 Cytarabine >1 gm/m^2 Carboplatin Ifosfamide Carmustine ≤ 250 mg/m^2 Hexamethylmelamine (p.o.) Cyclophosphamide ≤ 1500 mg/m^2 Anthracyclines Topotecan Irinotecan Procarbazine (p.o.) Methotrexate >250 mg/m^2 Cyclophosphamide (p.o.) Mitoxantrone
Low to moderate	Taxoids Etoposide Methotrexate >50 mg/m^2 <250 mg/m^2 Mitomycin Gemcitabine Fluorouracil <1000 mg/m^2
Low	Bleomycin Busulfan Chlorambucil (p.o.) 2-Chlorodeoxyadenosine Fludarabine Hydroxyurea Methotrexate ≤ 50 mg/m^2 L-phenylalanine mustard (p.o.) 6-Thioguanine (p.o.) Vinblastine Vincristine Vinorelbine

portant treatment- and patient-related variables, such as chemotherapy dose, rate and route of administration, gender, age, and history of ethanol consumption [7, 18].

Recently Hesketh et al. proposed a classification system for acute emesis that accounts for chemotherapy dose and standardizes the rate and route of chemotherapy administration [19]. Chemotherapy agents were divided into five levels according to the expected frequency of emesis in the absence of effective antiemetic prophylaxis. Given the paucity of objective data in the literature, however, this schema, like others proposed earlier, reflects primarily the opinions of the authors and is thus potentially open to some of the criticisms that have been directed at prior schemas.

Hesketh et al. also proposed an algorithm to define the acute emetogenicity of chemotherapy combinations [19]. It was partially validated by analyzing a database of patients treated with placebos on clinical trials with ondansetron [2, 5, 6, 10]. The primary limitation of this algorithm is the relatively homogeneous nature of the patient sample on which it was validated (primarily women with breast cancer receiving cyclophosphamide-based chemotherapy). Its potential applicability in more heterogeneous populations receiving non-cyclophosphamide-based regimens remains to be determined.

At present, no single schema addresses all of the important issues that must be taken into account in defining a definitive emetogenic classification system, and further work should be carried out on this important issue (Table 3). One potential area in which new information can be obtained relates to the emetogenic potential of new cytotoxic agents. During the initial evaluation process of a new cytotoxic agent there is a unique opportunity to obtain definitive information on the emetogenic potential and pattern of emesis in the absence of routine antiemetic treatment. Such information should be routinely recorded during new drug development.

Another potential approach to defining chemotherapy emetogenicity would be to analyze large databases in which information on emesis has been prospectively recorded and antiemetic prophylaxis was uniform. Such an analysis could provide information on relative emetogenicity and potentially permit gender and other important prognostic variables to be accounted for as well.

Despite the limitations of all the emetogenic classifications schemas proposed to date, there is still a need to agree upon a working schema than can be employed for treatment recommendations and for defining the emetogenic challenge in clinical trials. For this purpose, a modification of the schema of Hesketh et al. is proposed (Table 4). Chemotherapy agents are listed in order of decreasing emetogenicity with division across four broad emetogenic groups: high, moderate–high, low–moderate, and low.

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