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Measurement of success: parameters of efficacy

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Before discussing the different parameters of anti-emetic trials it is necessary to underline the importance of adequate study design; i.e. double-blind, stratification for known prognostic factors such as gender, age, alcohol intake, previous experience with chemotherapy, emetic potential of the cytotoxic agents used and patient susceptibility to motion sickness. A major imbalance between two arms of a trial with regard to these factors might jeopardise the outcome of the study, despite careful assessment of efficacy. The ideal anti-emetic study comprises a parallel design and two 'identical' groups—i.e. the patients are naive, receiving the same chemotherapy, the numbers of each gender are similar and they are matched for alcohol intake. In practice this is often difficult to obtain. The cross-over design circumvents this problem, however, it has other disadvantages - as discussed elsewhere in this supplement.

Parameters of efficacy for the acute phase

It is rather obvious that the ultimate goal of antiemetic treatment should be the total protection from chemotherapy-induced nausea and vomiting, during all courses of treatment and with drugs devoid of adverse events. If, however, this complete protection is not achieved, what level of control should then be considered acceptable by the patient, and is scientifically measurable? Presently control is assessed by vomiting, as an objective endpoint, and nausea, as a subjective endpoint. Although there is often a positive correlation between the two, complete control should be defined as the absence of both phenomena, and should be mentioned in reporting antiemetic efficacy.

The cut-off point between major and minor control varies between two and six emetic episodes in 24 h. This is an arbitrary definition, however, it is generally accepted at the moment. However, from the patient's point-of-view, are 6 emetic episodes in rather a short period of time, without accompanying signs of nausea, a completely different experience from 0–1 emetic episodes and a prolonged period of mild-moderate nausea?

The overall level of efficacy of an anti-emetic can only be evaluated by the patient and should be recorded as well as the objective measures – number of emetic episodes; retches; the time point of occurrence. Nausea can be assessed by either a visual analogue scale or a categorical scale–none, mild, moderate, severe. The duration of nausea is often not independently recorded.

It is clear that the 'interviewer' has an impact on the outcome of subjective study endpoints and interviewing should, therefore, be carried out preferably by a trained nurse and, in the ideal situation, by the same nurse on every occasion. Interval assessments, e.g. every 8 h, should be avoided in view of the bias which can be introduced when nausea and/or vomiting are discussed with the patient.

Side effects should be recorded with a checklist to guide the interviewer and the patient. An underestimation of side effects can be expected when an open approach like 'Did you experience any adverse events?' is used. The possible disadvantages of an overestimation of adverse events is, from my point of view, only a minor problem.

Information regarding appetite, actual food and liquid consumption and general well being is relevant but complicates the study. It gives more tools to describe a failure or a success, but does not add independent hard data.

Parameters of efficacy for the delayed phase

There are strong arguments in favour of considering the delayed phase sequelae as a distinct and separate phase of chemotherapy-induced nausea and vomiting. The classical pattern of delayed symptoms is that the peak incidence of nausea and vomiting occurs 48–72 h after the start of chemotherapy, rarely lasting longer than 3 to 4 days. If no complete protection is obtained during this period, what is then a relevant endpoint? The absence of days with more than two emetic episodes and no days with moderate or severe nausea? Cumulative assessment over the whole period?

Secondly, only indirect measurements are possible because efficacy and side effects are only reported by the patient—by means of a diary card in combination with daily telephone interviews, or one interview immediately after the observation period. Relevant observations are the frequency of vomiting and retching and the actual times of occurrence. Nausea should be assessed with either a graded scale or a visual analogue scale, also the time of onset and duration should be recorded. Information regarding appetite and food intake might provide some background information, but are not essential items to describe efficacy.

Assessment during multiple day chemotherapy

The same parameters as mentioned earlier should be recorded and preferably be presented as a day-to-day analysis to describe the pattern of failure. This type of presentation enables the description of a complicated situation with, on one hand, the effects of a daily acute event and, on the other hand, the gradual impact of a delayed signal.

General remarks

Patient preference can only be regarded when a cross over design is used and has been put forward as an overall estimate of efficacy. Although preference should not be disregarded, it is a subjective parameter and is influenced by several factors such as side-effects, for example sedation or extrapyramidal reactions and also efficacy. Furthermore, when medication with amnesic properties is given it is clear that this has a major impact on a patient's judgement.

Conclusion

The key items of efficacy assessment are the number of emetic episodes and graded information regarding nausea. Information should be obtained by independent observation or self-reporting in combination with a standardised interview. For out-patient assessment a daily telephone interview might improve these data.

When reporting on antiemetic studies adequate raw data should be given enabling comparisons between studies to be made, irrespective of differences in the definition of a response.