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REVIEW ARTICLE

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# Emesis induced by low or minimal emetic risk chemotherapy

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**Abstract** 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. The panel recognized the necessity of considering the introduction into clinical practice of new agents in these categories, particularly oral cytotoxic agents and targeted biological agents and also the possibility of over-treatment with antiemetics. There was consensus among panel members regarding the recommended treatment for patients receiving chemotherapy agents with low and minimal emetic risk. Patients without a history of nausea and vomiting for whom minimally emetic risk chemotherapy is prescribed should not routinely receive antiemetic prophylaxis. A single agent such as a low-dose corticosteroid is suggested for patients receiving agents of low emetic risk. If nausea and vomiting occurs during subsequent cycles of chemotherapy, prophylaxis with a single agent such as a substituted benzamide, a corticosteroid, or a phenothiazine should be administered. Only patients with persistent nausea and vomiting despite treatment with these recommended agents should receive a 5-HT3 receptor antagonist in the following cycles.

**Keywords** Low emetogenic chemotherapy · Minimal emetogenic chemotherapy

The lack of clinical trials performed in patients treated with low or minimally emetogenic chemotherapy has made it difficult until recently to identify those patients at risk of developing nausea and vomiting [1]. Although the ASCO Antiemetic Guidelines [3] for intermediate agents recommend that a corticosteroid be administered prophylactically, the recommendation received a low level of consensus from panel members as well as a Grade B/D recommendation. A review of the literature to date demonstrates that no relevant studies addressing this topic have been published since the last guidelines. A more recent review of this class of agents revealed that additional agents should be included in the table that outlines the emetogenic potential of both single intravenous and

single oral antineoplastic drugs. Although some of the agents listed may not be available internationally, it is important to include them overall.

An important issue to be considered is the introduction into clinical practice of new agents in this category, particularly oral cytotoxic agents and targeted biological agents, and the use of newer schedules with lower doses of emetogenic drugs (weekly taxanes) or their different combinations such as capecitabine plus weekly taxanes. The accurate assessment of the degree of nausea and/or vomiting with 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. It has been suggested that physicians and nurses through direct observation and follow-up of patient reports of nausea and vomiting episodes may provide perhaps the most reliable method of assessing overall emetogenicity of chemotherapy agents of low or minimal emetogenicity.

The extended use of oral agents given either on sequential days or on weekly schedules raises the problem of how to evaluate the emetic potential of such therapy, and how to define, if necessary, the optimal antiemetic treatment. The low emetic risk category for oral agents includes capecitabine and a few other representative drugs at this time. For these agents there is no evidence supporting the systematic use of antiemetic prophylaxis. Patients who receive oral chemotherapy agents within the minimal risk category should not receive prophylactic antiemetic treatment even if the chemotherapy agents are given for multiple days or weeks, following the recommendation of the previously described corresponding category of intravenous drugs. There is of course the possibility of the emergence of nausea and vomiting during protracted oral therapy. In this case an antiemetic treatment based on the administration of low-dose corticosteroids with or without metoclopramide should be considered.

An important problem in this category of low and minimal emetogenic drugs is the possibility of over-treatment with antiemetics. This has clearly been demonstrated by two consecutive drug utilization research trials by the Italian Group for Antiemetic Research (IGAR). In the first study evaluating 338 patients receiving chemotherapy, antiemetic prophylaxis was administered for acute emesis in 301 patients (89.1%), and for delayed emesis in 52 patients (15.4%). A 5-HT3 antagonist antiemetic was administered during the initial 24 h to approximately half of all patients [4]. In this trial 186 patients receiving 5-fluorouracil plus folinic acid for five consecutive days were observed. There were no differences found between those patients treated with antiemetics and those who received no treatment [5]. Even though the design of this trial did not include randomization, the observational data support the recommendation that this type of treatment which is categorized as chemotherapy with low emetic risk does not require, in principle, antiemetic prophylaxis. However, this will not be true for those patients who have previously experienced nausea and vomiting.

An even greater incidence of inappropriate prescribing of a 5-HT3 antagonist either alone or in combination for the prevention of acute emesis induced by chemotherapy with a low emetic risk was found in a subsequent IGAR drug utilization study involving 4477 patients, 509 of whom actually received low emetic risk chemotherapy. The proportion of inappropriate prescriptions was 65.7%, versus 47.7% in the previous study. This percentage was significantly reduced only when the treating centers were randomly visited by an expert and not through the dissemination of guidelines or the "audit and feedback" strategy [6].

Surprisingly, examples of over-treatment were also found in clinical practice in the treatment of delayed emesis of low emetogenic agents. While no prophylaxis should be given to these patients because they generally do not experience delayed emesis, a recent study has shown that among 215 such patients only 68.8% did not receive antiemetic treatment, and when treatment was administered it was 5-HT3 antagonist-based in 17.2% of the patients [2].

Considering the economic impact of this type of practice and the potential side effects of an unnecessary treatment, it is of paramount importance to define through well-designed randomized clinical trials whether treatment is necessary, and what antiemetic agents should be prescribed.

## Guideline recommendations

There was consensus among panel members regarding the recommended treatment for patients receiving chemotherapy agents with low and minimal emetic risk. Patients without a history of nausea and vomiting for whom minimal emetic risk chemotherapy is prescribed should not routinely receive antiemetic prophylaxis (Table 1). A single agent such as a low-dose corticosteroid is suggested for patients receiving agents of low emetic risk (Table 2).

**Table 1** Recommendation for low emetic risk chemotherapy agents

| |
|---|
| A single agent such as a low dose of a corticosteroid is suggested for patients receiving agents of low emetic risk |
| ASCO guideline: |
| Level of evidence: III, IV expert consensus |
| Grade of recommendation: D |
| MASCC guideline: |
| Level of consensus: moderate |
| Level of confidence: no confidence possible |

**Table 2** Recommendation for minimal emetic risk chemotherapy agents

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|---|
| No antiemetic treatment should be routinely administered before chemotherapy in patients without a history of nausea and vomiting |
| ASCO guideline: |
| Level of evidence: V expert consensus |
| Grade of recommendation: D |
| MASCC guideline: |
| Level of consensus: high |
| Level of confidence: no confidence possible |

In the event of the occurrence of nausea and vomiting during subsequent cycles of chemotherapy, prophylaxis with a single agent such as a substituted benzamide, a corticosteroid, or a phenothiazine should be administered. Only patients with persistent nausea and vomiting despite treatment with these recommended agents should receive a 5-HT3 receptor antagonist in the following cycles.

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