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REVIEW ARTICLE

Delayed emesis: moderately emetogenic chemotherapy

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Abstract Data on the incidence and efficacy of antiemetic prophylaxis against delayed emesis induced by moderately emetogenic chemotherapy are scanty. An overview of the literature has been done that showed the efficacy of dexamethasone in two of three randomized trials. Its optimal dose and duration of administration has not been defined. Only one of four randomized studies showed a statistically significant efficacy of 5-HT_3 antagonists. Finally, only weak evidence has been published on the efficacy of dopamine receptor antagonists.

Keywords Delayed emesis · Moderately emetogenic chemotherapy · Dexamethasone · 5-HT_3 antagonist

Introduction

Data on the incidence of delayed emesis in patients treated with moderately emetogenic chemotherapy are scanty. In a large study by the Italian Group for Antiemetic Research, evaluating patients who received cyclophosphamide, doxorubicin, epirubicin, and/or carboplatin without receiving any antiemetic prophylaxis beyond day 1, the incidence of moderate–severe vomiting and nausea in the delayed phase was 20% and 25%, respectively [13].

In contrast, a substantially higher frequency of delayed onset emesis and nausea was observed in a recent survey of 68 patients who received their first cycle of moderately emetogenic chemotherapy [10]. A 5-HT_3 antagonist was administered in 100% of patients, and a corticosteroid was administered in 84% of patients in the first 24 h. Delayed nausea and vomiting were reported in 57% and 41% of patients. Differences in the reported incidence of delayed emesis and nausea are likely due to differences in patient and treatment characteristics.

Current practice guidelines for prophylaxis of delayed emesis

The current MASCC, ASCO, ASHP, and ESMO practice guidelines for prophylaxis of delayed emesis following moderately emetogenic chemotherapy are contained in Table 1 [1, 2, 6, 8]. The recommendations range from routine use of combinations of corticosteroids, 5-HT_3 antagonists, and dopamine receptor antagonists to use of these agents only when the physician feels that the risk is high enough to warrant prophylaxis. This diversity of recommendations reflects the limited amount of high quality of evidence (a problem acknowledged in these guidelines) and the lack of a precise definition of those groups that are at substantial risk of delayed nausea and emesis.

Literature search strategy

A Medline search was conducted of English-language articles using the search terms "delayed," "emesis," and "randomized" or "randomised." Abstracts were reviewed, and articles were excluded if they possessed any of the following characteristics: review articles, nonrandomized design, cause for emesis other than chemotherapy, inclusion of patients receiving cisplatin or multiple-day chemotherapy, or high-dose chemotherapy administered prior to a transplant. An additional study was discarded because it used a crossover design over multiple cycles and did not include a statement of sample size [3].

Overview of literature

Two major types of randomized trials describing delayed emesis exist: those in which the antiemetic therapies only differ beyond day 1 and those in which there is a difference starting at day 1. The latter studies are problematic to interpret when there is a difference in the control of emesis in the acute phase because the strongest prognostic factor for delayed emesis is the occurrence of nausea or emesis in the acute phase [16]. None of the studies reviewed carried out a statistical analysis that adjusted for the differences in antiemetic control in the acute phase. Thus, studies in which antiemetic efficacy differs between the randomized groups in the acute phase can describe the frequency with which nausea and vomiting occur in the delayed phase but cannot distinguish between a specific effect in the delayed phase and an effect due to better antiemetic control in the first 24 h.

Corticosteroids

Three studies have evaluated the role of dexamethasone administration beyond day 1. The Italian Group for Antiemetic Research evaluated the role of dexamethasone alone or combined with ondansetron on days 2–5 [15]; 618 patients who had no emesis and either no or mild nausea in the first 24 h were randomized to placebo, dexamethasone, or dexamethasone plus ondansetron. Dexamethasone was statistically significantly superior to placebo in terms of the percentage of patients free of delayed vomiting or moderate-to-severe nausea (87.4% versus 76.8%; $p<0.02$).

A nonblinded study was conducted by Koo and Ang in which all patients received granisetron and dexamethasone on day 1 [19]. Patients were randomized to receive dexamethasone 4 mg bid or no further antiemetic therapy from day 2–5. In the group that received dexamethasone beyond day 1, there was a statistically significant increase in the proportion of patients free of emesis (57% versus 33%; $p=0.05$).

Inoue et al. enrolled 68 patients receiving irinotecan plus dexamethasone and granisetron on day 1 into a study comparing dexamethasone 8 mg po daily with placebo on

Table 1 Previous consensus guideline recommendations

Group	Comment	Options
MASCC [1]	When incidence is high enough to warrant prophylaxis. Continue for 72 h minimum	Dexamethasone alone 5-HT_3 receptor alone Combination of above
ASCO [8]	Routine for high risk, not recommended for intermediate risk e.g., irinotecan, taxanes	Corticosteroid alone Corticosteroid plus metoclopramide Corticosteroid plus 5-HT_3 antagonist
ASHP [2]	Routine	5-HT_3 antagonist plus dexamethasone
ESMO [6]	Routine	Corticosteroid plus a 5-HT_3 antagonist Corticosteroid plus a dopamine antagonist

days 2–4 [12]. The proportion of patients without delayed emesis was minimally higher in the group that received dexamethasone in the delayed phase (82.9% versus 78.8%; *p*=not significant). The sample size was insufficient to rule out a clinically important difference.

In summary, two randomized trials have shown that administration of dexamethasone 4 mg bid on days 2–5 reduces the likelihood of delayed-onset emesis.

5-HT_3 receptor antagonists

Four studies have addressed the role of administering a 5-HT_3 RA beyond day 1 [15, 18, 20, 21], one of which administered a different 5-HT_3 receptor antagonist on day 1 [21]. The latter reference was included because the control of acute emesis was virtually identical between the two 5-HT_3 receptor antagonists on day 1.

Kaizer et al. conducted a three-arm study in 302 patients. One comparison (*n*=252) was oral ondansetron for 4 days versus placebo beyond day 1 with all patients receiving ondansetron and dexamethasone on day 1 [18]. The group of patients that received ondansetron beyond day 1 had a complete response rate that was 17.5% higher than the group receiving placebo (one-sided *p* value =0.012). The magnitude of the benefit may have been overestimated because at 24 h, when the antiemetics were identical, there was already a 7.7% difference between the placebo and the ondansetron group in favor of the latter (D. Warr personal communication).

The Italian Group for Antiemetic Research conducted a double blind study comparing dexamethasone versus dexamethasone plus ondansetron from days 2–5. All patients received ondansetron and dexamethasone on day 1 [15]. The primary endpoint was the percentage of patients who experienced neither emesis nor moderate-to-severe nausea. In those patients who did not experience vomiting or moderate-to-severe nausea on day 1, a combination of dexamethasone and ondansetron beyond day 1 was numerically superior to dexamethasone alone (91.9% versus 87.4%; *p* value not significant), and the ondansetron group experienced more constipation. In patients who experienced vomiting or moderate-to-severe nausea on day 1 despite dexamethasone and ondansetron, ondansetron plus dexamethasone was again numerically but not statistically significantly superior to dexamethasone alone (40.9% versus 23.3%). The sample size (*n*=87) limited the ability to detect clinically important differences in the latter subgroup.

In a moderate-sized study (*n*=407), Pater et al. compared placebo to either ondansetron or dolasetron on days 2–7 [20]. Continued administration of a 5-HT_3 receptor antagonist was associated with a modest, statistically nonsignificant improvement in the complete response rate (47% versus 41%; *p* value =0.24). There was a small but statistically significant improvement in mean nausea score with the administration of a 5-HT_3 receptor antagonist beyond day 1 (*p* value =0.015, one sided) but significantly more constipation.

Stewart et al. compared the administration of intravenous granisetron on day 1 versus administration of intravenous ondansetron followed by oral ondansetron on multiple days in a placebo-controlled three-arm study (*n*=333 for the comparison of continued ondansetron beyond 24 h) [21]. As one would expect, IV ondansetron followed by oral ondansetron and a single dose of IV granisetron produced virtually identical results in the first 24 h with respect to no vomiting (78% versus 81%) and no nausea (51% versus 54%) respectively. Thus, the results beyond day 1 may be used to evaluate whether or not the administration of a 5-HT_3 receptor antagonist beyond the acute phase improves antiemetic results. The continued administration of ondansetron on day 2–5 did not provide any statistically significant advantage over placebo in the percentage of patients with no emesis over the entire study duration (58% for ondansetron versus 54% for placebo), but there was a statistically significant difference in nausea severity in favor of the ondansetron group (no nausea in 33% versus 25%; *p*=0.009).

In summary, all four studies showed a trend for better control of vomiting in the patients who received a 5-HT_3 receptor antagonist but only one showed a statistically significant difference. This would be consistent with a modest benefit.

Dopamine receptor antagonists

Herrstedt et al. have shown that metopimazine 30 mg qid increases the antiemetic efficacy of ondansetron in both the acute and delayed phases of emesis in patients who received intravenous CMF chemotherapy (*p*=0.006) [11]. In this study, the administration of the dopamine receptor antagonist began on day 1 and was associated with improvement in the acute-phase results. Thus, differences in the control of delayed emesis may be due to effects in the acute phase, and one cannot draw conclusions about the value of administration beyond day 1.

Although proof of principle that metopimazine has antiemetic efficacy that is additive to ondansetron, this study did not administer dexamethasone on day 1 and so the standard therapy did not conform to the practice guidelines in Table 1. An additional limitation is that this drug has very limited availability throughout the world.

A study excluded from the formal review by virtue of the inclusion of a minority (23%) of patients who received cisplatin chemotherapy supported the possible value of dopamine receptor antagonists in patients who received moderately emetogenic chemotherapy [7]. Esseboom et al. found that domperidone 20 mg tid improved antiemetic control in the delayed phase compared to placebo after ondansetron plus or minus dexamethasone

was administered on day 1($p<0.001$). This difference appeared to be almost exclusively due to differences observed in the breast cancer (noncisplatin) population. A highly unusual finding was the absence of any nausea or vomiting in the first 24 h of this study in any of the 60 evaluable patients.

In summary, these studies provide weak evidence that the addition of a dopamine receptor antagonist may improve the control of delayed onset nausea.

Palonosetron

Palonosetron is a 5-HT_3 receptor antagonist that has a long half-life and avid receptor binding. Two studies in patients with moderately emetogenic chemotherapy demonstrated efficacy with a single intravenous dose of palonosetron 0.25 mg that was superior to single intravenous administration of dolasetron or ondansetron in both the acute and delayed phase [5, 9]. In neither study were corticosteroids used. Somewhat surprisingly, a higher dose of palonosetron was less effective than a lower dose although still numerically superior to the 5-HT_3 receptor antagonist.

In the absence of day 1 dexamethasone, single-dose palonosetron 0.25 mg is superior to other 5-HT_3 receptor antagonists. However, superior efficacy in the setting of dexamethasone as recommended by the consensus guidelines [1, 2, 6, 8] has not been demonstrated. As with studies of other agents, it is likely that superiority in the initial 24 h explains much of the superiority observed in the delayed phase.

NK_1 receptor antagonists

No studies have been reported in which this novel antiemetic class was used for moderately emetogenic chemotherapy.

Discussion

The incidence of delayed onset emesis despite a 5-HT_3 receptor antagonist and dexamethasone on day 1 varies considerably amongst studies. Since a major determinant of the frequency of delayed onset nausea and vomiting is the occurrence of acute onset emesis, emphasis should be placed upon the control of emesis in the first 24 h. There is, however, also evidence from randomized trials that dexamethasone, 5-HT_3 receptor antagonists and possibly dopamine receptor antagonists contribute to the control of delayed onset emesis. Although the randomized trials used dexamethasone, this drug is not available as an oral formulation in some countries or is available only as a formulation of 0.5 or 0.75 mg. It is probable that prednisone 25 mg bid would provide equivalent benefit.

A significant problem is that antiemetic guidelines may not be widely implemented. A study of Italian prescribing practices carried out in 1996 in 33 oncological centers found that only 33% of patients who received antiemetic therapy for moderately emetogenic chemotherapy received prophylactic therapy for delayed-onset emesis [14]. An intervention of a visit by an expert in antiemetic therapy failed to influence the proportion of patients who received a prescription for prophylactic therapy [17]. A subsequent large study showed a substantial improvement in the proportion of patients who received prophylactic therapy (70%), and 52.4% received antiemetics that conformed to the recommended prophylaxis. Thus, a substantial gap remains between guidelines and actual practice [4].

Conclusions

Patients who receive moderately emetogenic chemotherapy known to be associated with a significant incidence of delayed nausea and vomiting should receive antiemetic prophylaxis for delayed emesis:

- MASCC level of confidence: high; level of consensus: high
- ASCO level of evidence: I; grade of recommendation: A

Oral dexamethasone is the preferred treatment:

- MASCC level of confidence: high; level of consensus: high
- ASCO level of evidence: II; grade of recommendation: A

5-HT_3 receptor antagonists may be used as an alternative:

- MASCC level of confidence: moderate; level of consensus: moderate
- ASCO level of evidence: II; grade of recommendation: B

A grade/recommendation is not given for dopamine receptor antagonists and palonosetron because a contribution to the delayed phase that is independent of the acute phase has not been demonstrated. The optimal duration and dose of dexamethasone have not been defined. Further studies are required to clarify the role of palonosetron and the role more widely available dopamine receptor antagonists, such as metoclopramide, prochlorperazine, or domperidone.

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