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Aprepitant and control of emesis induced by five-day chemotherapy

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Addition of aprepitant, an NK-1 receptor antagonist, to dexamethasone and a 5-HT3 receptor antagonist contributes substantially to emetic control in patients receiving five-day cisplatin-containing chemotherapy, a new trial shows. Some needs in antiemetic therapy remain unmet, including control of emesis with multiple-day chemotherapy and control of nausea.

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The past few decades have seen remarkable progress in antiemetic control of patients receiving highly and moderately emetic chemotherapy. Well-designed trials supported by thorough neuropharmacological research have led to the development of convenient antiemetic regimens that target relevant neurotransmitters.[1] These trials have enabled safe administration of chemotherapy in an outpatient clinical setting for most patients. An almost-universal use of effective antiemetic regimens has helped to preserve the quality of life of patients while they receive chemotherapy and has had concomitant financial benefits through a reduction in the number of hospitalisations and urgent care visits. A study by Albany and colleagues[2] now brings a new dimension to the prevention of chemotherapy-induced emesis. The researchers demonstrate that addition of NK-1 receptor antagonist aprepitant to dexamethasone and a 5-HT3 receptor antagonist improves antiemetic control in patients receiving five-day cisplatin-containing chemotherapy. The trial provides new information with important implications for evidence-based guidelines for antiemetic treatment, and the results highlight areas where well-designed studies are required to improve treatment strategies in many oncology settings.

In this double-blind phase III crossover study, patients with germ-cell tumours receiving two cycles of five-day cisplatin-based chemotherapy were randomly assigned to aprepitant (125 mg on day 3 and 80 mg once a day on days 4–7) or placebo; both arms also received dexamethasone (20 mg daily on days 1 and 2 during acute emesis phase, and 4–8 mg twice a day on days 6–8 during the delayed emesis phase) and a 5-HT3 receptor antagonist (once a day on days 1–5) on first cycle and were crossed over to the other treatment arm on the second cycle. Addition of aprepitant (three-drug treatment arm) resulted in substantially better prevention of

vomiting on each day of chemotherapy, in both the delayed emesis setting (days 6–8) and acute emesis setting (days 1–5), compared with the control (two-drug arm). Patients expressed preference for receiving aprepitant in this double-blinded crossover design. Additionally, no difference was observed in adverse effects between the three-drug aprepitant-containing arm and the two-drug control arm. The fact that a 42% complete emetic control is achieved with aprepitant add-on over five days of chemotherapy versus 13% in the control arm provides sufficient evidence to call for an update of the evidence-based guideline recommendations for antiemetic treatment in patients receiving multiple-day chemotherapy.

The findings of Albany et al.[2] not only expand our knowledge of how to treat emesis in patients receiving multiple days of chemotherapy, but also illustrate that in many common chemotherapy settings antiemetic control is not sufficient. We still need better approaches to prevent chemotherapy-induced nausea and limited information is currently available for anti-emesis treatment in many common oncology settings including chemotherapy given with radiotherapy. Furthermore, the study reveals that optimal schedules have not been defined for use of corticosteroids as antiemetic drugs or for the dosing and scheduling of NK-1 receptor antagonists.

Addition of aprepitant resulted in ... better prevention of vomiting on each day of chemotherapy

As the authors also acknowledge, the study has several limitations. An inherent problem in prevention of emesis induced by multiple days of chemotherapy is that several emetic phases (acute emesis, delayed emesis, and even anticipatory emesis) potentially coexist on the subsequent treatment days. This problem is observed in the dexamethasone dosing schedule. For treating acute emesis, dexamethasone is given only on the first two days of chemotherapy to avoid potential adverse effects with longer treatment. The results indicate that patients experience increased nausea and vomiting after the first two days. Albany and colleagues are rightly concerned about adverse effects associated with dexamethasone treatment when given daily for multiple days, but these potential side-effects with short courses of steroid treatment should be weighed against the benefit of control of emesis. Several trials have indicated a carry-over effect of delayed emesis control even when dexamethasone is stopped after the first day of chemotherapy.[3,4] However, whether this carryover effect would hold in multiple-day chemotherapy regimens is not clear.

Another limitation of the Albany et al.[2] trial is that aprepitant treatment is not given until day 3 of chemotherapy. Earlier studies indicated that treatment with an NK-1 receptor antagonist on the first day of chemotherapy has beneficial effects on emetic control on the subsequent days[5] and that higher single doses of an NK-1 receptor antagonist might provide long-term emetic control.[6] Therefore, initiation of aprepitant treatment on the first day of chemotherapy could lead to better control of both acute and delayed emesis, and perhaps of nausea.

In the Albany et al.[2] study, participants received 5-HT3 receptor antagonists other than palonosetron as part of the antiemetic regimen. Randomised trials have demonstrated better emetic control with palonosetron when used as monotherapy[7] or in combination with dexamethasone,[8] compared with older 5-HT3 receptor antagonists, such as ondansetron and granisetron. Indeed, a phase II trial, conducted by two of the researchers involved in the Albany et al. study, using palonosetron in a multiple-day intermittent administration schedule (on days 1, 3 and 5),[9] demonstrated that palonosetron plus dexamethasone treatment might improve control of emesis in patients with testicular cancer receiving multiple-day cisplatin-based chemotherapy, and might allow an every-other-day dosing schedule with this agent. These data are supported by results

Key points

- Oral aprepitant added to dexamethasone and a 5-HT3 receptor antagonist regimen improves five-day complete emetic control in patients with germ-cell tumours receiving cisplatin-containing chemotherapy
- Aprepitant-containing three-drug combination therapy has no additional side-effects compared with the two-drug (dexamethasone and a 5-HT3 receptor antagonist) regimen
- More research on drug scheduling and dosing of the aprepitant-containing three-drug combination regimen might lead to enhanced emetic control
- The new trial highlights several issues in antiemetic therapy that need further research, such as the requirement for improved control of nausea in many emetic chemotherapy settings.

of other studies using palonosetron.[7,8]

Unfortunately, although aprepitant addition treatment in the present study results in meaningful improvement in control of emesis, the majority of patients in the three-drug treatment arm still experienced vomiting. Even more surprisingly, only 13% of patients in the control arm were free of vomiting. These results demonstrate that aprepitant should be used in antiemetic regimens, and that studies are urgently needed to investigate whether other aprepitant and dexamethasone treatment schedules could improve emetic control.

The findings of this trial have additional implications. The control of nausea is only marginally improved with the aprepitant-containing regimen, and on several days nausea is not well controlled. This problem also exists with single-day chemotherapy, especially in the delayed emesis setting, and with different types of chemotherapy.[4,6,8] Given that the control of nausea lags behind the control of vomiting, future studies should focus on controlling nausea as the primary endpoint in major trials.

Even considering the remarkable progress in controlling emesis, it should be noted that few trials have been performed in chemotherapy settings other than in those with single-day chemotherapy administration. More antiemetic trials are needed in many chemotherapy settings, including those in paediatric oncology, those using oral chemotherapy or new molecularly targeted agents, those in patients previously treated with chemotherapy, and those using concomitant chemotherapy plus radiotherapy. These studies should also include multiple-day treatment settings.

The Albany et al.[2] study is a useful contribution to the knowledge of antiemetic treatment. It provides evidence for a new approach for controlling emesis in multiple-day chemotherapy and highlights many unmet needs in the complete control of emesis for all patients on each cycle of chemotherapy. ■

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Competing interests
The author declares associations with the following companies: Eisai, Helsinn and Merck. Please see the original article online for full details of the relationships

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