Anti-emetic trials in oncology: What should be done next?

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SUMMARY

Weinstein *et al*. uphold our interest in this multinational, randomized, double-blind, parallel-group trial conducted in non-anthracycline and cyclophosphamide (AC) moderately emetogenic chemotherapy (MEC) group. It shows that the addition of fosaprepitant to the combination of ondansetron and dexamethasone provides superior control for chemotherapy-induced nausea and vomiting (CINV) mainly with respect to complete remission (CR) in the delayed phase.

The randomization was done in 1:1 manner to the single-dose fosaprepitant or control regimen via an interactive voice response system/interactive web response system. The patients in the fosaprepitant arm received intravenous fosaprepitant as a single 150 mg dose 30 minutes before initiation of MEC on day 1. On day 1, both arms received oral ondansetron and dexamethasone followed by oral ondansetron 8 hours after the first dose while on days 2 and 3, the patients in the control group received ondansetron every 12 hours, whereas those in the fosaprepitant group received a matching placebo. In terms of efficacy the primary end-point was the proportion of patients who achieved CR (no vomiting and no use of rescue medication) during the delayed phase (25–120 hours following initiation of the first MEC dose). Secondary efficacy end-points included the proportions of subjects achieving CR during the overall and acute phases (0–120 and 0–24 hours after MEC initiation, respectively) and the proportion of subjects without vomiting during the overall phase. A total of 1015 patients were randomized from October 2012 to November 2014. Both treatment arms were well balanced with respect to the types of chemotherapy regimens used, single-day regimens (71.3% and 69.9%) for fosaprepitant and control regimens, respectively.

CR in the delayed phase (the primary end-point) was significantly higher in the fosaprepitant versus the control regimen (treatment difference 10.4%; $p<0.001$). The fosaprepitant regimen was also superior in terms of CR during the overall phase of treatment (difference 10.2%; $p<0.001$) but not for CR in the acute phase of treatment (difference 2.3%; $p=0.184$). Fosaprepitant was also superior to the control arm in terms of no vomiting in the overall phase of treatment (difference 9.8%; $p<0.001$). In view of good tolerability of fosaprepitant and superior outcomes, the authors concluded that fosaprepitant should be used in MEC regimen in the prophylactic anti-emetic combination.

COMMENT

We underscore some relevant points for incorporation in future trials of anti-emetic agents. First, the control arm here seems to be inadequate as palonosetron is evidently a more efficacious 5HT3 antagonist for delayed vomiting compared with ondansetron, and so recommended as the preferable drug in MEC as per the anti-emetic guidelines and various reports.[1–3] It is not clear whether the same benefit of fosaprepitant would have accrued if it had been combined with a palonosetron-containing anti-emetic regimen as palonosetron has better effect on delayed emesis than ondansetron. In other words, it is possible that fosaprepitant might be making

up for the inferior anti-emetic regimen especially with respect to delayed vomiting.

Second, anti-emetic trials often do not stratify patients based on their risk factors. Such studies should stratify and analyse patients according to known risk groups such as age, gender, history of alcoholism, motion sickness, etc.[4] For newer drugs such as NK1 antagonists it would help to identify the appropriate subgroup of patients. Besides, absolute reduction in delayed vomiting by 10% implies that the number needed-to-treat (NNT) is 10 with fosaprepitant. Thus, over-treatment in 9 patients will benefit 1 patient. Knowing the appropriate subgroup will optimize the use of newer anti-emetics, thereby reducing cost as well as toxicity.

Third, the anti-emetic regimens used for the treatment of acute emesis should be the same in both arms as the carry over effect of drugs such as phenothiazines can confound results in the evaluation of delayed emesis. It is not known whether the rescue medications used during the acute phase were equivalent in the two arms as these medications are likely to confound the results of the effect of fosaprepitant on delayed emesis.

Moreover, this treatment might not prove cost-effective in a developing country such as India where cheaper drugs such as olanzapine should be explored. We need an efficacious and cost-effective anti-emetic agent, and for optimum results we should stratify the patients based on both chemotherapy and risk factors.

REFERENCES

1 Basch E, Hesketh PJ, Kris MG, Kris MG, Feyer PC, Somerfield MR, *et al.* Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline update. *J Oncol Pract* 2011;**7:**395–8.

2 Jin Y, Sun W, Gu D, Yang J, Xu Z, Chen J. Comparative efficacy and safety of palonosetron with the first 5-HT3 receptor antagonists for the chemotherapy-induced nausea and vomiting: A meta-analysis. *Eur J Cancer Care (Engl)* 2013;**22:**41–50.

3 Schwartzberg L, Barbour SY, Morrow GR, Ballinari G, Thorn MD, Cox D. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). *Support Care Cancer* 2014;**22:**469–77.

4 Sekine I, Segawa Y, Kubota K, Saeki T. Risk factors of chemotherapy-induced nausea and vomiting: index for personalized antiemetic prophylaxis. *Cancer Sci* 2013;**104:** 711–17.

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