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CHEMOTHERAPY

NEPA—a single oral dose providing effective prevention of chemotherapy-induced nausea and vomiting

Nausea and vomiting are two of the most common adverse effects of many cancer treatments and are especially associated with chemotherapy. The risk of chemotherapy-induced nausea and vomiting (CINV) varies based on the type of treatment received and on several external factors. Some chemotherapy regimens, such as cisplatin, are highly emetogenic (HEC) with an high incidence of CINV (>90%), whereas others are moderately emetogenic (MEC) with a 30–90% incidence of nausea and vomiting.

CINV has a multifactorial origin, involving several neurotransmitters and receptors. Antiemetic guidelines recommend the use of combination regimens—over several days—to prevent and control CINV; however, adherence to such guidelines is suboptimal and many patients remain undertreated.

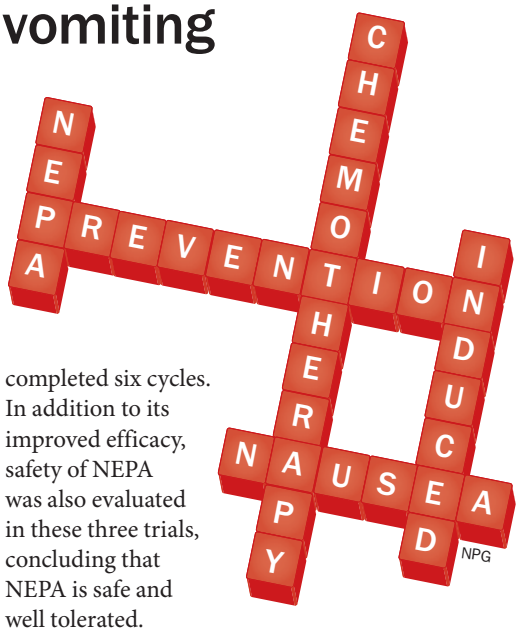
Three studies published in the *Annals of Oncology* have now demonstrated that a single oral dose of the NEPA combination regimen is effective and safe in preventing CINV, providing an improved method to control such adverse effect and to possibly obtain higher adherence to the guidelines and to the chemotherapy regimens.

The NEPA regimen is a novel oral fixed-dose combination of netupitant (a highly selective neurokinin-1 receptor antagonist), and palonosetron (PALO, a 5-hydroxytryptamine type 3 receptor antagonist) that can deliver guideline treatments in a convenient single dose.

In the first study, Paul Hesketh and colleagues performed a multicentre, randomized, double blind phase II study that accrued 694 patients, to establish the optimal fixed-dose of NEPA, and tested three different concentrations of netupitant (100, 200 or 300 mg) in combination with 0.50 mg of oral PALO and dexamethasone (DEX). As Hesketh emphasizes, "the objective was to demonstrate superior CINV prevention with the NEPA dose combinations over oral PALO (and DEX)," in a HEC cisplatin setting. All three doses tested showed superior complete response during the overall phase (0–120 h post-treatment) and delayed phase (25–120 h post-treatment). However, only the $NEPA_{300}$ dose showed superiority compared with PALO in the acute phase (within 24 h of chemotherapy) and for all the secondary efficacy end points (no emesis, no significant nausea and complete protection). Hesketh highlights that "on the basis of these results, the $NEPA_{300}$ oral fixed-dose combination was selected for continued development."

In the second study, Matti Aapro and colleagues randomized 1,455 chemotherapy-naive patients to receive the optimal $NEPA_{300}$ oral dose or a single oral dose of PALO in an anthracycline-based (AC) MEC setting. In this phase III trial, $NEPA_{300}$ was superior to PALO during all phases post-chemotherapy for the primary efficacy end point of complete response and also during the delayed and overall phases for the secondary end points of no emesis, no significant nausea and complete protection. Aapro says that "these efficacy benefits translated into a clinical benefit, as a greater proportion of NEPA-treated patients reported no impact on daily routine due to their nausea or vomiting." He continues, "the consistent superiority of NEPA over PALO across all end points during the delayed phase is a particularly important finding, as the delayed phase has remained a challenge in most clinical settings."

Finally, in the third study, Richard Gralla and colleagues randomly assigned 413 patients receiving multiple cycles of HEC or MEC to receive $NEPA_{300}$ or PALO (plus aprepitant). In this phase III trial, the researchers demonstrated that $NEPA_{300}$ is highly effective in preventing CINV and that this combination retains its efficacy over multiple cycles of chemotherapy. Notably, 75% of patients completed at least four cycles of chemotherapy and 40% completed six cycles. In addition to its improved efficacy, safety of NEPA was also evaluated in these three trials, concluding that NEPA is safe and well tolerated.



Gralla emphasizes "our study is one of the most extensive antiemetic studies showing such a degree of cardiac safety" and continues, "the NEPA combination is a very simple all oral single-dose regimen to aid adherence to antiemetic prevention, and achieves this in some of the most difficult and frequent emetic settings." All the authors agree that further trials will have to assess the efficacy of NEPA in minimizing the more challenging nausea symptom, in higher-risk patients and in other treatments such as radiotherapy.

Alessia Errico

Original articles Gralla, R. J. *et al*. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. *Ann. Oncol.* doi:10.1093/annonc/mdu096 | Hesketh, P. J. *et al*. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. *Ann. Oncol.* doi:10.1093/annonc/mdu110 | Aapro, M. A. *et al*. Randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann. Oncol.* doi:10.1093/annonc/mdu101