Netupitant and palonosetron (NEPA): a winning team in the race for the optimal treatment of chemotherapy-induced nausea and vomiting?

During the lifetime of many of healthcare professionals reading this article, the way in which chemotherapy induced nausea and vomiting (CINV) is approached and treated has transformed. The three papers reporting phase 2 and 3 dose-finding [1], efficacy and safety [1–3] studies of an oral fixed-dose combination (netupitant and palonosetron, NEPA) of a tachykinin NK₁ receptor [substance P (SP)] antagonist (NK₁ RA, netupitant, 300 mg) and a 5-hydroxytryptamine 3 receptor antagonist [5-HT₃ RA, palonosetron (PALO), 0.5 mg] are the latest clinical developments in the search for optimal anti-emetic therapy. This shift in approach to CINV is multifactorial: (i) a change in the attitude of healthcare professionals to nausea and vomiting, now viewed as something to be treated rather than tolerated by the patient; (ii) identification of risk factors initially: age, sex, alcohol consumption and emetic history, but screening for polymorphisms that may influence efficacy of 5-HT₃ RA (e.g. ABCBI, [4]) could be included; (iii) anti-emetic guidelines [5]; (iv) the introduction of the highly emetic cisplatin in the 1980s stimulated research into anti-emetics [6, 7]; (v) the recognition of anticipatory, acute and delayed phases of CINV [8] and insights into their differing mechanisms and pharmacology [9–11]; (vi) a shift in the way that identification of novel anti-emetics was approached by using models such as the ferret in which emesis was induced by cisplatin and which led to identification of the involvement of 5-HT₃ and NK₁ receptors [12]. Research into the involvement of 5-HT₃ and NK₁ receptors continues [13, 14].

Clinical significance

The papers make three advances of note: (i) a single oral dose of NEPA on day 1 with dexamethasone (DEX) on days 1–4 in patients receiving the first cycle of highly emetic chemotherapy (HEC)-based regimes blocked emesis in 98.5% of patients in the acute and 91.9% in the delayed phases with similar ‘no significant nausea’ values (98.5% and 90.4%, respectively) [1, Table 2]. Although NEPA is only given on day 1, the efficacy extends over the 120 h of study. In comparison with PALO (0.5 mg) alone, NEPA increased the acute and delayed no emesis rates by ~10% and the ‘no significant nausea’ rate by ~5% in the acute and ~10% in the delayed and overall phases [1, Table 2]. (ii) In moderately emetic chemotherapy (MEC), a single oral dose of NEPA and DEX on day 1 produced acute and delayed no emesis rates of 90.9% and 81.8% and no significant nausea of 87.3% and 76.9% [2, Table 2]. NEPA + DEX was superior to PALO + DEX with regard to acute and delayed emesis (including no rescue medication, [2, Figure 2]), but interestingly for ‘no significant nausea’ NEPA + DEX was only superior in the delayed phase [2, Table 2]. (iii) Maintenance of anti-emetic efficacy over repeated chemotherapy cycles is a challenge and the present study [3] investigated NEPA given on day 1 of each cycle with DEX on days 1–4 in HEC and only on day 1 in MEC. The complete response (no emesis and no rescue) rate for the overall responses (81%, 0–120 h) was maintained over six cycles; of the 309 patients evaluated in cycle 1, 75% completed four cycles and 40% six cycles [3, Figure 2]. The ‘no significant nausea’ rates ranged from 84% to 92%.

Scientific rationale

The inclusion of PALO as the 5-HT₃ receptor antagonist in NEPA is of particular interest. PALO differs from the earlier ‘setrons’ in having a longer plasma half-life (>40 h), inhibition of receptor function and higher binding affinity [14]; although these go some way to explaining the enhanced clinical efficacy, there is evidence that PALO has additional properties. Of particular relevance is 5-HT₃ R internalisation triggered by PALO binding, allosteric binding to the 5-HT₃ R and probably of most potential significance inhibition of intracellular ‘crosstalk’ between 5-HT₃ and NK₁ receptors [14–17]. The functional consequence of the latter is proposed to be that PALO and netupitant have a synergistic action to reduce the SP-mediated response [14]. Note that PALO is not an NK₁ RA. The contribution of the ‘crosstalk’ mechanism to the clinical efficacy of NEPA requires investigation. It may be possible to test the...
hypothesis in human volunteers by exploiting the involvement of 5-HT and SP in the axon-reflex cutaneous flare response that was used during the development of granisetron for duration of action studies.

**anti-emetic trial data gaps**

Data on emesis in patients who are not fully blocked are not usually reported, but could give important insights. It is unclear if patients who fail to meet the primary efficacy criteria (usually no emesis and no rescue) derive any benefit from the treatment and mechanistically such data would be invaluable in assessing the extent to which other mechanisms are involved especially if trends emerged in which rescue medications worked. However, without understanding the ‘failures’ (e.g. is their delayed emesis more driven by disrupted gut motility? [18]), identifying strategies to help this group will be difficult. Similar arguments apply to the assessment of nausea and particularly the use of ‘no significant nausea’ (visual analog scale <25 mm) as an efficacy end point. Assessment of nausea has hardly changed since the critical review by Morrow 30 years ago [19]—novel methods for objective assessment are needed. As nausea is recognised as the symptom of most concern to patients and is generally considered to be poorly treated and understood in contrast to vomiting [7, 8, 20], it would be helpful to have as much data as possible on actual scores in the ‘no significant nausea’ groups as well as ‘failures’ to see if they benefited from the treatment. The NEPA MEC study included an FLIE assessment [2, Figure 3] showing that although superior to PALO + DEX, in the NEPA + DEX arm while 90.1% of patients reported that vomiting had no impact on daily living the figure for the nausea domain was 71.5%. The clinical significance of ‘no significant nausea’ needs discussion.

If the present registration trial results are replicated in the ‘real’ clinical world, then the NEPA formulation appears to be an advance in terms of overall efficacy and simplicity of dosing regime with the maintenance of efficacy over multiple cycles of chemotherapy being particularly encouraging.

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**disclosure**

The authors have declared no conflicts of interest.

**references**


