Palonosetron versus ondansetron for prevention of chemotherapy-induced nausea and vomiting in paediatric patients with cancer receiving moderately or highly emetogenic chemotherapy.

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Abstract

BACKGROUND: Palonosetron has shown efficacy in the prevention of chemotherapy-induced nausea and vomiting in adults undergoing moderately or highly emetogenic chemotherapy. We assessed the efficacy and safety of palonosetron versus ondansetron in the prevention of chemotherapy-induced nausea and vomiting in paediatric patients.

METHODS: In this multicentre, multinational, double-blind, double-dummy, phase 3 study, paediatric patients aged between 0 and younger than 17 years, who were naive or non-naive to chemotherapy, and scheduled to undergo moderately or highly emetogenic chemotherapy for the treatment of malignant disease were
randomised centrally (1:1:1) to receive up to four cycles of 10 µg/kg or 20 µg/kg palonosetron on day 1, or three 150 µg/kg doses of ondansetron on day 1, scheduled 4 h apart, according to a static central permuted block randomisation scheme by an interactive web response system. Randomisation was stratified according to age and emetogenicity. Treatment allocation was masked to project team members involved in data collection and analysis, and members of the investigator's team. The primary endpoint was complete response (no vomiting, retching, or use of rescue drugs) during the acute phase (0–24 h post-chemotherapy) of the first on-study chemotherapy cycle, as assessed in the population of randomly assigned patients who received moderately or highly emetogenic chemotherapy and an active study drug. The primary efficacy objective was to show the non-inferiority of palonosetron versus ondansetron during the acute phase (0–24 h post-chemotherapy) of the first on-study chemotherapy cycle through comparison of the difference in the proportions of patients who achieved a complete response with palonosetron ($\pi_T$) minus ondansetron ($\pi_R$) versus a preset non-inferiority margin ($\delta -15\%$). To be considered as non-inferior to ondansetron, for at least one of the doses of palonosetron, the lower limit of the 97·5% CI for the weighted sum of the differences in complete response rates had to be superior to −15%. Safety was assessed, according to treatment received. This study is registered with ClinicalTrials.gov, number NCT01442376, and has been completed.

FINDINGS: Between Sept 12, 2011, and Oct 26, 2012, we randomly assigned 502 patients; 169 were assigned to receive 10 µg/kg palonosetron, 169 to receive 20 µg/kg palonosetron, and 164 to receive 3 × 150 µg/kg ondansetron, of whom 166, 165, and 162, respectively, were included in the efficacy analysis. In the acute phase, complete responses were recorded in 90 (54%) patients in the 10 µg/kg palonosetron group, 98 (59%) in the 20 µg/kg palonosetron group, and 95 (59%) in the ondansetron group. Non-inferiority versus ondansetron was shown for 20 µg/kg palonosetron in the acute phase (weighted sum of the differences in complete response rates 0.36% [97.5% CI −11.7 to 12.4]; p=0·0022). Non-
inferiority versus ondansetron was not shown for 10 μg/kg palonosetron in the acute phase (weighted sum of the differences in complete response rates −4.41% [97.5% CI −16.4 to 7.6]). In the first on-study treatment cycle, treatment-emergent adverse events were reported in 134 (80%) of 167 patients who received 10 μg/kg palonosetron, 113 (69%) of 163 who received 20 μg/kg palonosetron, and 134 (82%) of 164 who received ondansetron. The most common drug-related treatment-emergent adverse events were nervous system disorders, mainly headache, which occurred in three (2%) patients who received 10 μg/kg palonosetron, one (<1%) patient who received 20 μg/kg palonosetron, and two (1%) patients who received ondansetron. The incidence of serious adverse events in the first on-study treatment cycle was lower in the 20 μg/kg palonosetron group (43 [26%]) than in the 10 μg/kg palonosetron group (52 [31%]) and the ondansetron group (55 [34%]).

INTERPRETATION: Non-inferiority was shown for 20 μg/kg palonosetron during the acute phase of the first on-study chemotherapy cycle. 20 μg/kg palonosetron is now indicated by the European Medicines Agency and the US Food and Drug Administration for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients aged 1 month to younger than 17 years.

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