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Palonosetron

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Palonosetron is a new serotonin 5-HT_3 receptor antagonist with a binding affinity at least 30 times higher than that of the other, conventional 'setrons' (such as ondansetron, granisetron and dolasetron) and with a much longer plasma half-life (mean 40 hours). The clinical development programme of this molecule included:

- a North American study[1] comparing palonosetron versus dolasetron in patients receiving moderately emetogenic chemotherapy (MEC), such as cyclophosphamide and anthracyclines. Concomitant corticosteroids were permitted at the investigator's discretion, but were administered to only 5% of patients. This trial demonstrated that single intravenous doses of palonosetron 0.25 or 0.75mg were as effective as dolasetron in preventing acute chemotherapy-induced nausea and vomiting (CINV) and superior in preventing delayed CINV after administration of MEC;
- a European study[2] comparing palonosetron versus ondansetron 32mg, again in patients treated with MEC. In this study, as in the previous one, patients could be naive or non-naive to chemotherapy, but concomitant corticosteroids were not allowed. The results indicated that a single intravenous dose of palonosetron 0.25mg was superior to a single ondansetron 32mg dose for the prevention of both acute and delayed CINV;
- a North American/European trial[3] evaluating palonosetron versus ondansetron 32mg in the prevention of CINV in patients receiving highly emetogenic chemotherapy (HEC), such as cisplatin, dacarbazine or high-dose cyclophosphamide. Corticosteroids were left to clinician's choice and were administered to two-thirds of patients. Palonosetron was superior to ondansetron in the prevention of acute CINV;
- a combined analysis[4] that demonstrated that palonosetron maintains its activity over multiple courses of chemotherapy, including HEC.

All these studies were well conducted, but important methodological drawbacks can be observed in the design. These were due to the registrative nature of these trials and to regulatory requirements that do not adhere to the current guidelines. In particular:

- in most cases, no corticosteroids (e.g. dexamethasone) were given in the first 24 hours;
- no corticosteroids or metoclopramide or 5-HT_3 antagonists were administered in the 24- to 120-hour period after chemotherapy to prevent delayed emesis;
- a large number of patients were non-naive to chemotherapy.

Palonosetron is now registered in the US and is awaiting approval in Europe for the prevention of acute CINV due to MEC and HEC, and of delayed CINV due to MEC. It is conceivable that approval of the drug will allow the design of subsequent independent trials that are based on current guidelines. ▲

References

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