original contribution

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A Randomized, Multicenter, Open-Label Comparison of the Antiemetic Efficacy of Dolasetron Versus Ondansetron for the Prevention of Nausea and Vomiting During High-Dose Myeloablative Chemotherapy

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Abstract

This study assessed the efficacy and safety of dolasetron compared with ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy followed by peripheral blood stem cell support. Twenty centers randomized 197 patients to receive dolasetron 100 mg intravenously (I.V.) followed 8-12 hours later by a single oral dose of dolasetron 100 mg or ondansetron 32 mg I.V., followed 8-12 hours later by a single oral dose of ondansetron 8 mg during high-dose chemotherapy (HDC) regimens for breast cancer (n = 96; 48.7%), non-Hodgkin's lymphoma (n = 83; 42.1%), or Hodgkin's disease (n = 18; 9.1%). All patients received a daily I.V. bolus of dexamethasone 10 mg with study antiemetic agents and a continuous infusion of diphenhydramine, lorazepam, and dexamethasone (ie, BAD pump) throughout the course of the study, with patient-controlled on-demand bolus doses as needed. After completing a daily diary of emetic episodes and rescue medication use, 164 of 197 patients were evaluable. Total plus complete responses (no emesis, no nausea, no rescue) over the entire study period were achieved in 45.7% and 46.9% of patients on the dolasetron and ondansetron arms, respectively. Dolasetron and ondansetron were well-tolerated. This study demonstrates that dolasetron and ondansetron are equally safe and effective in the prevention of nausea and vomiting associated with HDC ($P = 0.955$).

Introduction

The therapeutic options for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) have dramatically changed since the 1980s.[1] The introduction of $5HT_3$ receptor antagonists has revolutionized the prevention and treatment of CINV, and the use of these agents has been

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recognized as the standard of care since 1991.[2] Despite this therapeutic advance, CINV associated with high-dose chemotherapy (HDC) continues to be problematic as a result of high doses of combination chemotherapy delivered over multiple days, as well as emetogenic supportive care agents (prophylactic antibiotics and antifungal agents).

The American Society of Clinical Oncology, American Society of Health System Pharmacists, and the Multinational Association of Supportive Care in Cancer have published evidence-based antiemetic guidelines for the use of $5HT_3$ receptor antagonists for the prevention and treatment of nausea and vomiting associated with highly and moderately emetogenic chemotherapy.[2-5] These guidelines firmly suggest that $5HT_3$ receptor antagonists be used in conjunction with dexamethasone as the standard of care in most patient populations. As a result of a lack of published clinical data, patients receiving HDC are not included in existing guidelines and pose a unique challenge to clinicians.

The 2 major patterns of emesis in HDC—acute and delayed—overlap, which makes successful prophylaxis of nausea and vomiting over an entire treatment course very difficult. In a prospective evaluation of antiemetic outcomes following HDC with peripheral blood stem cell support (PBSC) support, Ballen et al reported outcomes over a 7-day period in 82 patients.[6] Ninety-five percent of patients had nausea and 80% had ≥ 1 emetic episode over the study period; the percentage of patients with emesis peaked on day 5, with 44% of patients experiencing emesis. Thus, it appears that the majority of patients treated with HDC experience incomplete control of emesis, and nausea and vomiting progressively worsen with each passing day. These results contrast with the successful prophylaxis of acute emesis with $5HT_3$ receptor antagonists in standard chemotherapy regimens in which complete responses (CRs) have been documented in the majority of patients at high risk.[7-11]

Dolasetron is a highly selective $5HT_3$ receptor antagonist with documented antiemetic efficacy for highly and moderately emetogenic chemotherapy.[7,10-13] In a randomized, double-blind study comparing the efficacy of ondansetron (32 mg intravenously [I.V.]) and dolasetron (1.8 mg/kg and 2.4 mg/kg I.V.) in 609 patients receiving their first course of cisplatin, there were no significant differences among the 3 treatment groups in terms of efficacy and safety.[14] A double-blind randomized comparison of the antiemetic efficacy of single I.V. doses of dolasetron or granisetron in patients receiving high-dose cisplatin demonstrated that there were no statistical differences between dolasetron- and granisetron-treated patients in regards to CR, CR plus major response, time to first emetic episode, and/or nausea severity.[13] Of 474 patients evaluable for efficacy, CR was achieved in 54%, 47%, and 48% of patients treated with dolasetron 1.8 mg/kg, 2.4 mg/kg, and granisetron 3 mg, respectively. Both these studies confirm the efficacy of dolasetron in highly emetogenic chemotherapy, including high-dose cisplatin.

These head-to-head data clearly show the efficacy of dolasetron in highly emetogenic chemotherapy and its equivalence to ondansetron and granisetron, and the current study adds to this body of literature and compares the efficacy and safety of dolasetron and ondansetron in more difficult-to-treat patients receiving HDC for breast cancer, non-Hodgkin's lymphoma (NHL), or Hodgkin's disease (HD).

Patients and Methods

Between May 1997 and March 2001, 197 patients were randomly assigned to receive dolasetron or ondansetron during myeloablative HDC regimens followed by PBSC support. Patients were stratified according to chemotherapy protocol and were eligible for randomization if they were ≥ 18 years of age; had a confirmed diagnosis of epithelial carcinoma of the breast, NHL, or HD; and had a performance status ≤ 2 on the Eastern Cooperative Oncology Group performance scale.

Beginning with the first dose of chemotherapy and continuing until 24 hours after the last chemotherapy dose, each patient completed a daily diary recording the time and number of emetic episodes. To assess their nausea, patients completed a visual analogue scale (VAS) twice daily during the course of the study.

Treatment Centers

Patients were treated in one of 20 participating community-based cancer centers in the United States by oncologists affiliated with the US Oncology Research network (see appendix). Study procedures such as HDC or PBSC transplantation were conducted according to an approved treatment protocol. The majority of patients were treated on an outpatient basis.

Study Design

This randomized, multicenter, open-label study compared 2 different $5HT_3$ receptor antagonists, dolasetron and ondansetron, for the prevention of nausea and vomiting during and immediately after HDC or PBSC transplantation. Patients assigned to arm 1 received a single I.V. dose of dolasetron 100 mg administered 30-60 minutes before HDC followed by a single oral dose of dolasetron 100 mg administered 8-12 hours afterward on each day of therapy. Patients in arm 2 were treated with a single I.V. dose of ondansetron 32 mg administered 30-60 minutes before HDC followed by a single oral dose of ondansetron 8 mg administered 8-12 hours afterward on each day of therapy. Antiemetic therapy and patient documentation of emetic episodes with use of rescue medication(s) began before the start of chemotherapy and continued daily until 24 hours after the last dose of chemotherapy.