Aprepitant Effective in Preventing Chemotherapy-Induced Nausea and Vomiting in Children

BACKGROUND: Chemotherapy-induced nausea and vomiting (CINV) is a common complication of many cancer treatments in adults and in children. The oral neurokinin-1 (NK1) receptor antagonist aprepitant (Emend) is an effective option for CINV prevention in adult patients who receive emetogenic chemotherapy. However, its safety and efficacy in pediatric patients have not been investigated before, despite the high incidence of CINV events in this patient population. Furthermore, current clinical guidelines have no age-related recommendations for the prevention of CINV in children undergoing moderate or highly emetogenic chemotherapy. A recent study investigated the efficacy and safety of oral aprepitant in pediatric patients with cancer who receive highly emetogenic chemotherapy.

METHODS: This multicenter, randomized, placebo-controlled phase 3 study included 307 patients with cancer aged 6 months to 17 years who received emetogenic chemotherapy between September 2011 and August 2013 in 49 sites in 24 countries. The patients were randomized in a 1:1 manner, based on age and the type of chemotherapy to be used, to aprepitant plus ondansetron (Zofran) or to placebo plus ondansetron, with or without dexamethasone. The study used 2 doses of aprepitant based on the patient’s age—6 months to <12 years and 12 years to 17 years. The patients in the aprepitant group received aprepitant plus ondansetron on day 1 of chemotherapy, followed by aprepitant alone on days 2 and 3; the control group received placebo plus ondansetron on the first day of chemotherapy, followed by placebo alone on days 2 and 3. Episodes of vomiting and retching and the use of rescue medications were recorded up to 120 hours after the initiation of chemotherapy. The primary efficacy end point was the proportion of patients achieving a complete response (ie, no CINV events or the use of a rescue medication) during the delayed phase, 25 to 120 hours, after the initiation of emetogenic chemotherapy.

RESULTS: Overall, 51% of the patients receiving aprepitant and 26% of the patients receiving placebo achieved a complete response in the delayed phase (P < .001). The median time to the first vomiting episode was 96.3 hours in the aprepitant group compared with 27.5 hours in the control group. After 98 hours, 68% of patients in the aprepitant group and 52% of patients in the control group were free of rescue medication use. The most common grade 3 or 4 adverse events were febrile neutropenia (15% with aprepitant vs 14% with placebo), anemia (9% vs 17%, respectively), and reduced neutrophils (7% vs 11%, respectively). In addition, 2 patients in the aprepitant group discontinued therapy because of a serious adverse event. No treatment-related deaths were reported.

This study shows that a 3-day regimen of oral aprepitant, in conjunction with ondansetron, with or without the addition of dexamethasone, provides significant benefits for pediatric patients who receive highly emetogenic chemotherapy. Aprepitant was approved by the US Food and Drug Administration for the treatment of this patient population on August 28, 2015.


COMMENTARY BY ROBERT J. IGNOFFO

This is an important study for pediatric oncologists and their patients; it is the first large, phase 3 study assessing the role of a neurokinin-1 (NK1) receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting (CINV). A 2-or 3-combination therapy using a 5-hydroxytryptamine 3 receptor antagonist plus dexamethasone with or without an NK-1 antagonist is considered the standard of care for adult patients receiving moderately or highly emetogenic chemotherapy, but no large studies have been performed in the pediatric setting. However, because of its adverse effects on bone growth, the use of dexamethasone is not preferred in the pediatric patient population. Owing to the wide variation in antiemetic regimens, only 28% of the
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>300 patients received dexamethasone as part of their antiemetic regimen.

The benefit of aprepitant over ondansetron with or without dexamethasone was improved complete overall response, along with improved prevention of acute and delayed emesis. Furthermore, the addition of aprepitant did not cause any other significant adverse effects. It appears that aprepitant in oral and injectable forms is safe in pediatric patients, even those aged <11 years. These results may provide pediatric oncologists with an effective strategy for managing CINV in this patient population.

Another observation is that the lead authors of this study are affiliated with the manufacturer of the study drug, which may indicate a bias toward the drug. However, because of the international nature of the study group, bias may be a less significant issue in this study.

Bevacizumab for Advanced Lung Cancer Does Not Increase Risk for Hospitalization or Unexpected Toxicity

BACKGROUND: Although chemotherapy consisting of the combination of carboplatin (Paraplatin), paclitaxel (Taxol), and bevacizumab (Avastin; CPB) has been used since 2006 for the treatment of patients with non–small-cell lung cancer (NSCLC), few studies have assessed toxicity and hospitalizations associated with the use of bevacizumab in a community setting. However, studies show that 60% of net medical costs for patients with lung cancer are related to hospitalization, and 72% of community-based patients with advanced NSCLC require at least 1 hospitalization after chemotherapy, making research in regard to hospitalization after chemotherapy prevalent. To understand the effects of bevacizumab, a new retrospective analysis focused on toxicity and hospitalization within 180 days of receiving CPB compared with those receiving carboplatin plus paclitaxel.

METHODS: The primary data source was the Cancer Research Network’s Virtual Data Warehouse, which contains patient data taken from electronic health records as well as administrative and claims databases. The study included 1109 patients from the Virtual Data Warehouse’s Virtual Tumor Registry who had stage IIIB to stage IV nonsquamous NSCLC and were diagnosed between January 2005 and December 2010. All the participants received first-line carboplatin plus paclitaxel (82%) or CPB (18%). The patients were monitored from the initiation of chemotherapy until death, health plan termination, or 180 days, whichever came first. Follow-up continued until December 31, 2011.

RESULTS: Approximately 57% of patients receiving CPB and approximately 53% of patients receiving carboplatin plus paclitaxel had evidence of any toxicity event. The patients receiving CPB were more likely to have hemorrhage, proteinuria, and gastrointestinal perforation.

Furthermore, 34% of patients receiving carboplatin plus paclitaxel and 19% of patients receiving CPB had at least 1 hospitalization. Specifically, 310 patients receiving carboplatin plus paclitaxel had 438 hospitalizations for a total of 2360 days, with 6% of those hospital stays resulting in death. Only 38 patients receiving CPB had hospital stays (total, 62 hospitalizations) for a total of 282 days, with 3% resulting in death. Although not aligned with the toxicity findings, this study found that patients receiving CPB as first-line chemotherapy had a significantly lower risk for hospitalization and length of hospital stay in the first 180 days after treatment. This information should provide reassurance to oncologists that the use of bevacizumab for advanced NSCLC is not associated with any increased risks for hospitalization or unexpected toxicity.


COMMENTARY BY ROBERT J. IGNOFFO

This important study reports some unexpected and counterintuitive findings. Adding bevacizumab to carboplatin plus paclitaxel (CP) chemotherapy was expected to increase the number and severity of hospitalizations compared with CP chemotherapy alone, but this was not the case. Although the expected toxicities of hemorrhagic events—including gastrointestinal perforation and proteinuria—were significantly more common with the addition of bevacizumab than CP chemotherapy alone, the hospitalization rate for CP chemotherapy with bevacizumab was approximately 50% lower than that of CP chemotherapy alone. Furthermore, these results were consistent regardless of sex and age. The authors speculate that the decreased hospitalization rate attributed to the addition of bevacizumab may actually be a result of better disease control, or that the control group was hospitalized for more progressive disease.

The results of this study suggest that although the
Daratumumab, an Anti-CD38 Monoclonal Antibody, Effective Treatment Option for Patients with Relapsed and/or Refractory Multiple Myeloma

BACKGROUND: Although the currently available therapies improve outcomes for patients with multiple myeloma, their prognosis is poor if the disease relapses or is refractory to proteasome inhibitors and immunomodulatory drugs.

Daratumumab is a monoclonal antibody that induces the killing of CD38-expressing tumor cells, a substantial target in the treatment of myeloma. As a result of daratumumab’s successful performance in preclinical studies, a new phase 1/2 study investigated the use of daratumumab in patients with relapsed and/or refractory multiple myeloma.

METHODS: The study included adult patients with myeloma whose disease relapsed after or was refractory to 2 or more different previous therapies, with 64% of patients having disease refractory to lenalidomide (Revlimid) and bortezomib (Velcade). All patients were enrolled in the study between March 2008 and January 2015. The study was an open-label, multicenter trial that was conducted in 2 parts. In the dose-escalation phase, 32 patients received daratumumab at doses of 0.005 mg/kg to 24 mg/kg of body weight. In the dose-expansion phase, 72 patients received either 8 mg/kg of daratumumab (30 patients) or 16 mg/kg (42 patients), with the doses being administered on different schedules. The patients received therapy until disease progression or until unmanageable toxic events occurred. The end points included safety, pharmacokinetics, objective response, time to disease progression, and progression-free survival.

RESULTS: The results show that daratumumab has an acceptable safety profile, with infusion-related reactions of grade 1 or 2, including bronchospasm, headache, dyspnea, and fever. No patient discontinued treatment as a result of an infusion-related reaction. Moreover, daratumumab induced favorable clinical responses in both parts of the study. In the dose-escalation phase, 33% of patients had a partial response to doses ranging from 4 mg/kg to 24 mg/kg. In the dose-expansion phase, the response rate for patients receiving 8 mg/kg of daratumumab was 10% compared with 36% for patients receiving a dose of 16 mg/kg, with 69% of patients who had a response remaining progression-free at 12 months.

In addition, of the patients who received 16 mg/kg of daratumumab, 46% saw a 50% reduction in the level of M protein or free light chains. Daratumumab has shown to be an effective single-agent treatment option for patients with difficult-to-treat multiple myeloma. The drug’s target of CD38 and its mechanism of action make this treatment superior to currently available therapies.

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In November 2015, the US Food and Drug Administration (FDA) granted accelerated approval to daratumumab (Darzalex; Janssen Biotech, Inc, Horsham, PA) for use in patients with advanced multiple myeloma who had received ≥3 prior treatments, including a proteasome inhibitor (ie, alone or in combination with an immunotherapeutic agent).

Toxicities were evaluated in 156 patients who received the proposed dose and schedule of daratumumab. Adverse reactions that occurred in ≥20% of patients were infusion reactions, fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection. Although the toxicity profile for daratumumab was deemed acceptable, precautions are needed to prevent severe infusion-related reactions. Specifically, 1 hour prior to a daratumumab infusion, patients should receive intravenous methylprednisolone plus an antipyretic (acetaminophen) and an antihistamine (diphenhydramine). Postinfusion, additional corticosteroids should be given later on day 1, followed by another dose orally on day 2. Precautions are needed for patients with respiratory disorders who may require bronchodilator therapy, or an inhaled corticosteroid to prevent respiratory compromise. In addition, antiviral therapy to prevent herpes zoster virus should be initiated and continued 3 months after discontinuation of daratumumab.

Daratumumab has the potential to be a major advancement for patients with advanced multiple myeloma, but further comparative studies are needed to prove its value. As a condition of the FDA accelerated approval, Janssen Biotech, Inc, must sponsor a large, phase 3 trial demonstrating the superiority of daratumumab over standard care.

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addition of expensive new compounds to standard chemotherapy may be costly, cost benefits may be realized as a result of improved response rates and decreased hospitalizations. The authors also suggest that real-world studies are needed to assess the true benefits of expensive new agents when they are added to standard chemotherapy.