Published in final edited form as:

J Pediatr Oncol Nurs. 2014 ; 31(5): 277–283. doi:10.1177/1043454214531090.

Aprepitant Reduces Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients with Brain Tumors

Kelly Duggin, BSN, RN¹, Kelly Tickle, MSN, APN, PCNS-BC, CWON¹, Gina Norman, MSN, APN, PCNS-BC¹, Jie Yang, PhD², Chong Wang, MS³, Shane J. Cross, PharmD, BCPS⁴, Amar Gajjar, MD⁵, and Belinda Mandrell, PhD, RN⁶

¹Divisions of Patient Care Services, Nursing, St. Jude Children's Research Hospital, Memphis, TN

²Department of Preventive Medicine, Stony Brook University, New York

³Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

⁴Department of Pharmaceutical Services, St. Jude Children's Research Hospital, Memphis, TN

⁵Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

⁶Division of Nursing Research, St. Jude Children's Research Hospital, Memphis, TN

Abstract

Purpose—Chemotherapy-induced nausea and vomiting (CINV) are common and distressing side effects in patients with brain tumors and may be associated with radiation and the administration of highly emetogenic chemotherapy (HEC). Pediatric antiemetic guidelines recommend administration of a 5-hydroxytryptamine-3 (5HT₃) receptor antagonists and the addition of aprepitant, a neurokinin 1 (NK₁) antagonist with corticosteroids for the treatment of HEC. However, challenges persist in treating CINV in patients with brain tumors as corticosteroids are contraindicated due to potential impairment of the blood brain barrier permeability. Our objective was to determine whether a 5HT₃ receptor antagonist and the addition of aprepitant, a neurokinin 1 (NK₁) antagonist without a corticosteroid, were effective in reducing HEC vomiting in pediatric brain tumors.

Methods—A retrospective review found that 18 patients with a history of high-grade vomiting during radiation were prescribed a 5HT₃ receptor antagonist and aprepitant without a corticosteroid during their first course of HEC. To determine the efficacy of aprepitant without a corticosteroid, each recipient was matched with two controls that did not received aprepitant.

Results—During HEC, controls without aprepitant were more likely to have grade 2 or higher vomiting than the aprepitant recipients ($p = 0.03$; odds ratio = 4.15; 95% confidence interval [1.59, 10.82]), after controlling for radiation-associated vomiting toxicity.

Corresponding author: Belinda Mandrell, Division of Nursing Research, MS 738, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105.

Conflict of Interest Statement

All Authors disclose no affiliations or other areas of real or perceived conflict of interest that they consider to be relevant and important with any organization that to any author's knowledge has a direct interest, particularly a financial interest, in the subject matter discussed.

Discussion—Significantly less vomiting was identified in children receiving HEC and prescribed a 5HT₃ receptor antagonist and aprepitant. Findings suggest that the addition of a NK₁ antagonist may be beneficial to emetic control in this highly vulnerable population.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) are two of the most distressing side effects reported by oncology patients (Holdsworth, 2006; Sun, 2005). Patients may report one or all three types of CINV: *Acute CINV* occurs during chemotherapy or within 24 hours of administration; *delayed CINV* occurs 24 hours after completion of chemotherapy; and *anticipatory CINV* occurs before chemotherapy administration and is an acquired learned response to persons or experiences (Hawkins & Grunberg, 2009). Although considerable progress has been made toward improving CINV with administration of 5-hydroxytryptamine-3 (5HT₃) receptor antagonists, there continue to be therapeutic challenges particularly in the control of delayed CINV. Despite antiemetic regimens, 30% of patients continue to experience acute CINV, and 40% to 80% experience delayed CINV after administration of moderately emetogenic chemotherapy (MEC) to highly emetogenic chemotherapy (HEC) (Hickok J.T., 2003). The challenge in alleviating CINV in those with persistent symptoms led to the development of specific antagonists against neuroreceptor neurokinin 1 (NK₁), aprepitant and fosaprepitant.

Serotonin and substance P are the key neurotransmitters involved in the emetic response. Acute CINV is mediated by serotonin via the peripheral pathway within the gastrointestinal tract. After chemotherapy is administered, serotonin is released and binds to 5HT₃ receptors, sending signals to the chemoreceptor vomiting center within the medulla. The 5HT₃ receptors antagonists, ondansetron and granisetron are highly effective in treating the peripheral pathway activation of acute CINV.

Delayed CINV is mediated by substance P, which binds to NK₁ receptors within the vomiting center. The activation of substance P and binding to NK₁ receptors occurs approximately 16 hours after chemotherapy administration. Aprepitant, which targets the central pathway of CINV, was approved for prevention of CINV in adults receiving HEC in 2003 and in adults receiving MEC in 2006 (Merck & Co., 2011). Therefore, optimal control of CINV may require targeting both the peripheral with a 5HT₃ receptor antagonist and central pathways with a NK₁ receptor (Grunberg, 1993; P. J. Hesketh, Van Belle, S., Aapro, M., Tattersall, F.D., Naylor, R.J. Hargreaves, R., & Horgan, K.J., 2003; NCCN, 2012a).

Aprepitant is an oral formulation, with the pro-drug fosaprepitant available as an intravenous preparation. Current antiemetic practice guidelines from the Society of Clinical Oncology (Basch et al., 2011) recommend the three-drug combination of an NK₁ antagonist, a 5-HT₃ receptor antagonist, and dexamethasone for adults receiving HEC. For MEC, the recommendations suggest a two-drug combination of palonosetron (or other 5-HT₃ receptor antagonist) and dexamethasone, with limited evidence supporting the addition of aprepitant. Recently, a guideline for the prevention of acute CINV in pediatric cancer patients was published and supported by the Multinational Association for Supportive Care in Cancer (MASCC) (Dupuis et al., 2013). The guideline recommends the use of a 5-HT₃ receptor

antagonist, corticosteroid plus aprepitant for children (12 years and older) receiving HEC. For children in whom corticosteroids are contraindicated, the guidelines recommended the use of a 5-HT₃ receptor antagonist, plus chlorpromazine (thorazine) or nabilone (Cesamet). Corticosteroids are contraindicated or strongly discouraged during administration of radiation and chemotherapy treatment of brain tumors due to a potential impairment of the blood brain permeability (Ostergaard et al., 1999) reducing the chemotherapy delivery to the tumor site and the cytotoxic effects of therapy (Rieger, Durka, Streffer, Dichgans, & Weller, 1999; Weller, Schmidt, Roth, & Dichgans, 1997),

Treatment of brain tumors requires multimodal therapy, including surgery, cranial radiation, and chemotherapy. The literature is lacking in describing the incidence and distress of vomiting among pediatric cancer patients during cancer therapy (Holdsworth, 2006; Robinson & Carr, 2007). Within the adult literature, approximately 50–80% of patients undergoing radiotherapy will experience nausea and/or vomiting with occurrence dependent upon the radiation site (Feyer, Stewart, & Titlbach, 1998). A cross-sectional study explored nausea and vomiting according to radiation site and found 48% of adults experienced nausea and vomiting during radiotherapy to regions of the head/neck/brain (Enblom, Bergius Axelsson, Steineck, Hammar, & Borjeson, 2009). Adult and pediatric cancer patients who experience vomiting during cranial radiation are typically prescribed a 5-HT₃ receptor antagonist as an antiemetic rescue. However, a subset of patients may continue to have poorly controlled nausea and vomiting (Feyer et al., 2011). This poorly controlled nausea and vomiting during radiation may place the patient at an increased risk of anticipatory nausea and vomiting with subsequent therapy (P. J. Hesketh, 1999; NCCN, 2012a; Sun, 2005). The current study was undertaken in children and young adults with brain tumors to determine their experience of vomiting during radiotherapy and to compare the efficacy a 5-HT₃ receptor antagonist and aprepitant without corticosteroids in controlling chemotherapy induced vomiting (CIV) during their first course of HEC.

Method

The study was approved by the Institutional Review Board. A retrospective review of clinical charts and the institutional pharmacy database identified all patients on the medulloblastoma protocol who had been prescribed aprepitant during their first course of HEC from 09/09/2003 to 12/3/2010. The protocol included patients not only treated for medulloblastoma, but those with cranial atypical teratoid rhabdoid tumor and primitive neuroectodermal tumor. During this time aprepitant had been prescribed at the discretion of the medical staff as a non-formulary antiemetic to children and young adults, weighing 40 kilograms.

Demographics were extracted from the chart review of aprepitant recipients including: diagnosis, age, gender, weight, and disease-risk (average versus high risk). Each aprepitant recipient was matched by diagnosis, age, gender, weight (< 40kg) and disease-risk with two controls, patients treated for a brain tumor who had not received aprepitant during their first course of HEC. If a recipient could not be matched to a control on all four variables, we matched that patient on age and risk. Table 1 and 2 depict the demographic and numerical demographics of the 52 patients included in the study.

The medulloblastoma treatment protocol included 6 weeks of daily cranial radiation, the dose of which was determined by disease risk, average risk or high risk. Average-risk disease was classified as local tumor without invasion beyond the posterior fossa, residual tumor $<1.5 \text{ cm}^2$, and no CNS or extraneural metastasis. High-risk disease was classified as metastatic disease within the neuraxis and residual tumor $>1.5 \text{ cm}^2$. Patients classified as average risk disease ($n=39$) received 55.8 Gy to the primary site and 23.4 Gy to the craniospinal axis, while those classified as high risk disease ($n=13$) received 55.8 Gy ($\pm$ boost) and 36–39.6 Gy to the craniospinal axis. Risk was an important variable to control between the aprepitant recipients and controls, with patients at higher risk having more extensive disease and higher doses of cranial radiation which might contribute to a higher grade of vomiting. Cranial radiation was followed by 6 weeks rest, after which 4 monthly courses of chemotherapy were administered and included cisplatin (75 mg/m^2) and vincristine (1 mg/m^2) on Day -4 (day 1 of chemotherapy) and cyclophosphamide (2000 mg/m^2) on Days -3 and -2 (day 2 and 3 of chemotherapy). After a day of rest on Day -1 , all patients received an autologous stem cell rescue on Day 0.

As per the pediatric classification guideline, HEC agents in the chemotherapy regimen included cisplatin and cyclophosphamide 1000 mg/m^2 (Dupuis et al., 2013; Dupuis et al., 2011). Both aprepitant recipients and control patients received scheduled ondansetron every 8 hours from admission until discharge. If the patient had breakthrough vomiting before the next scheduled dose of ondansetron, lorazepam $\pm$ diphenhydramine or promethazine were administered. Granisetron was administered every 12 hours in place of ondansetron, if the patient developed refractory or uncontrollable vomiting. Due to potential impairment of the blood brain barrier, corticosteroids were not prescribed during radiation or chemotherapy administration to the aprepitant recipients or controls.

Procedure of Toxicity Grading

The vomiting toxicity during cranial radiation and the first course of HEC were reviewed and rated by a blinded study nurse. If available, the number of vomiting episodes was recorded for each day within the 6 weeks of cranial radiation. The radiation therapy documentation noted the presence of nausea and vomiting within the previous 24 hours; however, with the patients treated as outpatients the documentation did not always include the total number of vomiting episodes. Therefore, we recorded the number of daily vomiting episodes over the 6 weeks that the patient received radiation. Vomiting for less than 3 weeks during radiation was graded as “no or mild vomiting” and vomiting documented for more than 3 weeks during radiation was graded as “severe vomiting”. The number of CIV episodes within each 24 hours of hospitalization was calculated for each patient and graded from the nursing documentation. All vomiting episodes were graded (0–3) according to the Common Toxicity Criteria for Adverse Events v3.0 (CTCAE) (Health, 2006). There were no vomiting episodes of grade 4 or 5. The graded radiation vomiting episodes (“no or mild” vs. “severe”) and CIV episodes (grade 0–3) were then compared to the data base maintained by the research study coordinator. If a discrepancy between vomiting episodes was noted, the nurse and study coordinator reviewed the medical record for consensus. Aprepitant is a known inhibitor of CYP3A4 (Sanchez, 2004) and all medical records were reviewed for any adverse effects attributed to aprepitant. To investigate the potential increased risk of adverse

effects of cyclophosphamide and vincristine when given with aprepitant, the neuropathy CTCAE data and the number of days to reach an absolute neutrophil count of 1000 cells/ μ L after chemotherapy were reviewed.

Statistical Analysis

The demographic differences between the aprepitant recipients and controls who did not receive aprepitant were compared using Fisher's exact or Chi-square test with exact p-values for categorical variables and Wilcoxon's rank sum for continuous variables. Univariate Generalized Estimating Equations (GEE) regression models (Liang, 1986) were applied to examine the association between grade 2 or higher vomiting during the first course of HEC among aprepitant recipients versus control patients and potential risk factors including gender, average versus high risk disease, age at first course of chemotherapy, and grade of vomiting during radiation therapy. Inpatient correlation was modeled by an unstructured dependence matrix. A multivariable GEE model was used to compare the difference in grade 2 or higher CIV between aprepitant recipients versus controls, after controlling for the number of weeks of vomiting during radiation therapy. SAS version 9.2 (SAS Institute, Cary, NC) was used for the statistical analyses.

Results

Fifty-two patients were included in the analysis. Eighteen aprepitant recipients were identified with an age range of 11–20 years, with 14 of the recipients less than 18 years of age. Thirty-four controls who did not receive aprepitant were identified with an age range of 10–21 years, with 28 of the controls less than 18 years of age. Two of the aprepitant recipients could only be matched to one control each. Eighteen patients received aprepitant as per the discretion of the medical team for 3 consecutive days, beginning with 125 mg PO on Day –4 of chemotherapy and 80 mg PO on Day –3 and Day –2. There was no difference between the groups according to gender, disease risk, or age at first course of HEC. Patients who received aprepitant with their first course of HEC course were more likely to have experienced more than 3 weeks of vomiting during radiation therapy than controls ($p=0.01$).

The univariate model included diagnosis, gender, risk, age, weight, weeks of radiation vomiting, and group (aprepitant recipient versus no aprepitant). The no aprepitant control had grade 2 or higher CIV when compared to the aprepitant recipients ($p=0.01$; odds ratio= 3.52, with 95% confidence interval [1.47, 8.42]). The final multivariate GEE model included group (aprepitant recipient versus no aprepitant) and weeks of vomiting during radiation as an explanatory variable. Patients who did not receive aprepitant were significantly more likely to have grade 2 or higher vomiting during the first course of HEC than were the aprepitant recipients ($p=0.03$; odds ratio= 4.15, with 95% confidence interval [1.59, 10.82]), after controlling for radiation-associated vomiting toxicity. On the day after HEC completion, 44% of the controls had delayed vomiting of grade 2 and 3, compared to 16% of the aprepitant recipients. There were no documented neuropathic toxicities reported from the time of chemotherapy completion to count recovery, and the mean absolute neutrophil count recovery for both groups was 18 days, with a range of 15 to 21 days for aprepitant recipients and 14 to 28 days for the controls.

Discussion

Chemotherapy induced vomiting is one of the most complex and exhausting challenges for patients and their caregivers, hindering one's quality of life, interrupting activities and interactions with others, resulting in fatigue, anorexia, and sleep disturbance. Frequent vomiting also prevents the patient from performing typical activities of daily living and decreases medication compliance (Reddy, Gralla, & Hesketh, 2006). In the oncology literature, the evidence-based data of occurrences among children and young adults is limited. A study of 35 children found 83% reported nausea and 41% reported vomiting during chemotherapy, with symptoms persisting 48 hours after chemotherapy administration (Hockenberry et al., 2010). This prompted study of CINV before, during and after a course of MEC or HEC among 40 pediatric oncology patients, rating nausea and vomiting by the patient, caregiver and nurse. Nausea and vomiting were reported throughout the course of therapy, with delayed CINV occurring most frequently (Rodgers et al., 2012). Therefore, alleviation of CIV during HEC may require targeting both the peripheral and central pathways involved in the vomiting mechanism (Grunberg, 1993; P. J. Hesketh, Van Belle, S., Aapro, M., Tattersall, F.D., Naylor, R.J. Hargreaves, R., & Horgan, K.J., 2003; NCCN, 2012a).

Along with occurrences, risk factors associated with chemotherapy administration are less known among children and adolescents. Age has been found to be a risk factor for CINV, with the younger child at greatest risk (Holdsworth, 2006; Kris et al., 2006). Risk factors within the adult literature are defined as female gender, having a history of grade 2 or higher nausea and vomiting with previous chemotherapy, repeated doses of HEC, and radiation-associated high-grade nausea and vomiting (P. J. Hesketh, 1999; NCCN, 2012a; Sun, 2005). Taking these risk characteristics into consideration, patients receiving HEC for treatment of a brain tumor with a history of radiation-associated vomiting may be at particular risk for anticipatory CIV.

This review was prompted after bone marrow transplant nurses clinically noted less episodes of vomiting among patients receiving aprepitant with their first course of HEC. A retrospective comparison found that patients who received aprepitant and a scheduled 5HT₃ receptor antagonist during their first course of HEC were more likely to have experienced 3 or more weeks of vomiting during radiation therapy, and this history of prolonged vomiting during radiation most likely prompted the clinician to add aprepitant to the chemotherapy antiemetic regimen. Despite the history of prolonged radiation-associated vomiting and heightened risk for CIV, the aprepitant recipients had significantly lower-grade CIV during administration of HEC than did the controls, as noted by the unit nurses. We had no reported adverse events related to the administration of aprepitant, nor found any associated neuropathy or delay in absolute neutrophil count recovery. Our findings indicate that patients at risk for CIV during HEC may benefit in administration of aprepitant with a 5-HT₃ receptor antagonist without administration of a concurrent corticosteroid.

A major limitation of this retrospective review is our small sample size and the lack of patient reported outcomes. Thus, the presence or severity of nausea was not able to be assessed. The retrospective nature of the study prevented us from obtaining pharmacokinetic

or clinical assessments during administration of aprepitant and quantifying CIV in real time. Therefore, we had to rely on chart review and Common Toxicity Criteria, as documented by the study team. Another limitation is the statistical model did not include the use of breakthrough or rescue antiemetics as potential confounders. Lastly, we had to rely on medical chart review to infer why these patients were prescribed aprepitant at the discretion of the medical staff.

Summary

There is limited literature documenting the incidence of CINV among pediatric cancer patients (Holdsworth, 2006; Robinson & Carr, 2007) and we found only adult studies describing the incidence of nausea and vomiting during radiation (Enblom et al., 2009; Feyer et al., 2011). The few noted pediatric studies suggest the need in treating HEC induced nausea and vomiting with agents that target both the acute and delayed mechanisms of CINV (Baggott et al., 2010; Hockenberry et al., 2010; Rodgers et al., 2012). In summary, our retrospective study observed brain tumor patients prescribed therapy targeting the peripheral and central vomiting pathways even without a corticosteroid to be more effective in controlling vomiting than a 5HT₃ receptor antagonist alone. Proactive interventions as outlined in the recently published pediatric antiemetic guidelines (Dupuis et al., 2013) may improve symptom control, the patient's quality of life and impact the nursing staff and healthcare system by decreasing patient acuity and healthcare costs. Although the evidence for aprepitant use among children and young adults is limited, the tolerability and efficacy of aprepitant suggest that the adult dose is clinically effective for children (Gore, 2009). Endorsement and strong recommendation for the use of aprepitant in children 12 years of age receiving HEC by the Multinational Association for Supportive Care in Cancer should encourage prospective studies to strengthen the evidence-based data and lessen the identified research gaps (Dupuis et al., 2013).

Acknowledgments

This study was supported in part by a Cancer Center Support grant (CA 21765) from the National Cancer Institute and by the American Lebanese Syrian Associated Charities (ALSAC). To Jami Gattuso and Nancy West, Division of Nursing Research and Leigh Ann Christy, Clinical Research Associate. To Pam Dotson, MBA, RN, Senior Vice President of Patient Care Services and Chief Nursing Officer, for her advocacy of evidence-based practice in improving the quality of life for our patients and families. To Angela McArthur PhD, ELS for manuscript editing.

References

- Baggott C, Dodd M, Kennedy C, Marina N, Matthay KK, Cooper BA, Miaskowski C. Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy. *J Pediatr Oncol Nurs.* 2010; 27(6):307–315.10.1177/1043454210377619 [PubMed: 20739586]
- Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, Lyman GH. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2011; 29(31):4189–4198. JCO.2010.34.4614 [pii]. 10.1200/JCO.2010.34.4614 [PubMed: 21947834]
- Dupuis LL, Boodhan S, Holdsworth M, Robinson PD, Hain R, Portwine C, Sung L. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. *Pediatr Blood Cancer.* 2013; 60(7):1073–1082.10.1002/pbc.24508 [PubMed: 23512831]

- Dupuis LL, Boodhan S, Sung L, Portwine C, Hain R, McCarthy P, Holdsworth M. Guideline for the classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients. *Pediatr Blood Cancer*. 2011; 57(2):191–198.10.1002/pbc.23114 [PubMed: 21465637]
- Enblom A, Bergius Axelsson B, Steineck G, Hammar M, Borjeson S. One third of patients with radiotherapy-induced nausea consider their antiemetic treatment insufficient. *Support Care Cancer*. 2009; 17(1):23–32.10.1007/s00520-008-0445-x [PubMed: 18528717]
- Feyer PC, Maranzano E, Molassiotis A, Roila F, Clark-Snow RA, Jordan K. Mascc/Esomo. Radiotherapy-induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: update 2009. *Support Care Cancer*. 2011; 19(Suppl 1):S5–14.10.1007/s00520-010-0950-6 [PubMed: 20697746]
- Feyer PC, Stewart AL, Titlbach OJ. Aetiology and prevention of emesis induced by radiotherapy. *Support Care Cancer*. 1998; 6(3):253–260. [PubMed: 9629879]
- Gore L, Chawla S, Petrilli A, Hemenway M, Schissel D, Chua V, Carides AD, Taylor A, DeVandry S, Valentine J, Evans JK, Oxenius B. for the Adolescent Aprepitant in Cancer Study Group. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. *Pediatric Blood Cancer*. 2009; 52:242–247.10.1002/pbc.21811 [PubMed: 18985740]
- Grunberg SM, Hesketh PJ. Control of chemotherapy-induced emesis. *New England Journal of Medicine*. 1993; 329:1790–1796. [PubMed: 8232489]
- Hawkins R, Grunberg S. Chemotherapy-induced nausea and vomiting: challenges and opportunities for improved patient outcomes. *Clin J Oncol Nurs*. 2009; 13(1):54–64. V85551005V7V7216 [pii]. 10.1188/09.CJON.54-64 [PubMed: 19193549]
- Health, U.S. National Institutes of. Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria (CTC). National Cancer Institute; 2006. Retrieved from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf
- Hesketh PJ. Defining the emetogenicity of cancer chemotherapy regimens: Relevance to clinical practice. *Oncologist*. 1999; 4(3):191–196. [PubMed: 10394587]
- Hesketh PJ, Van Belle S, Aapro M, Tattersall FD, Naylor RJ, Hargreaves R, Horgan KJ. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *European Journal of Cancer*. 2003; 39:1074–1080.
- Hickok JT, Roscoe JA, Morrow GR, et al. Nausea and emesis remain significant problems of chemotherapy despite prophylaxis with 5-hydroxytryptamine-3 antiemetics: A University of Rochester James P. Wilmot Cancer Center Community Clinical Program Study of 360 cancer patients treated in the community. *Cancer*. 2003; 97:6.
- Hockenberry MJ, Hooke MC, Gregurich M, McCarthy K, Sambuco G, Krull K. Symptom clusters in children and adolescents receiving cisplatin, doxorubicin, or ifosfamide. *Oncol Nurs Forum*. 2010; 37(1):E16–27.10.1188/10.ONF.E16-E27 [PubMed: 20044328]
- Holdsworth MT, Raisch DW, Frost J. Acute and delayed nausea and emesis control in pediatric oncology patients. *Cancer*. 2006; 106:931–940. [PubMed: 16404740]
- Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Grunberg SM. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol*. 2006; 24(18):2932–2947. JCO.2006.06.9591 [pii]. 10.1200/JCO.2006.06.9591 [PubMed: 16717289]
- Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986; 73:13–22.
- Merck & Co., Inc. Emend (fosa-prepitant dimeglumine) for injection. 2011. from http://www.merck.com/product/usa/picirculars/e/emend_iv/emend_iv_pi.pdf
- NCCN, National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Antiemesis. 2012a. from http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf
- Ostergaard L, Hochberg FH, Rabinov JD, Sorensen AG, Lev M, Kim L, Rosen BR. Early changes measured by magnetic resonance imaging in cerebral blood flow, blood volume, and blood-brain barrier permeability following dexamethasone treatment in patients with brain tumors. *J Neurosurg*. 1999; 90(2):300–305.10.3171/jns.1999.90.2.0300 [PubMed: 9950501]

- Reddy GK, Gralla RJ, Hesketh PJ. Novel neurokinin-1 antagonists as antiemetics for the treatment of chemotherapy-induced emesis. *Support Cancer Ther.* 2006; 3(3):140–142. 52J867U05320TN13 [pii]. 10.3816/SCT.2006.n.011 [PubMed: 18632487]
- Rieger J, Durka S, Streffer J, Dichgans J, Weller M. Gemcitabine cytotoxicity of human malignant glioma cells: modulation by antioxidants, BCL-2 and dexamethasone. *Eur J Pharmacol.* 1999; 365(2–3):301–308. [PubMed: 9988115]
- Robinson DL, Carr BA. Delayed vomiting in children with cancer after receiving moderately high or highly emetogenic chemotherapy. *J Pediatr Oncol Nurs.* 2007; 24(2):70–80. 10.1177/1043454206298840 [PubMed: 17332421]
- Rodgers C, Kollar D, Taylor O, Bryant R, Crockett K, Gregurich MA, Hockenberry M. Nausea and vomiting perspectives among children receiving moderate to highly emetogenic chemotherapy treatment. *Cancer Nurs.* 2012; 35(3):203–210. 10.1097/NCC.0b013e3182281493 [PubMed: 21915041]
- Sanchez RI, Wang RW, Newton DJ, et al. Cytochrome P450 is the major enzyme involved in the metabolism of the substance P receptor antagonist aprepitant. *Drug Metab Dispos.* 2004; 32:1287–1292. [PubMed: 15304427]
- Sun CC, Bodurka DC, Weaver CB, Rasu R, Wolf JK, Bevers MW, Smith JA, Wharton JT, Rubenstein EB. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. *Support Care Cancer.* 2005; 13:219–227. [PubMed: 15538640]
- Weller M, Schmidt C, Roth W, Dichgans J. Chemotherapy of human malignant glioma: prevention of efficacy by dexamethasone? *Neurology.* 1997; 48(6):1704–1709. [PubMed: 9191791]

Table 1

Categorical demographics of 52 pediatric patients with CNS tumors

	Group and Number of Patients (%)			
Category	Total 52 (100)	Controls 34 (65.4)	Aprepitant recipients 18 (34.6)	P-value
Diagnosis				
ATRT	2 (3.85)	2 (5.88)	0 (0)	0.42
MB	41 (78.85)	25 (73.53)	16 (88.89)	
PNET	9 (17.31)	7 (20.59)	2 (11.11)	
Sex				
Female	20 (38.46)	10 (29.41)	10 (55.56)	0.08
Male	32 (61.54)	24 (70.59)	8 (44.44)	
Disease risk				
Average	39 (75)	27 (79.41)	12 (66.67)	0.33
High	13 (25)	7 (20.59)	6 (33.33)	

Abbreviations: ATRT, atypical rhabdoid tumor; MB, medulloblastoma; PNET, primitive neuroectodermal tumor

Table 2

Numerical demographics of 52 pediatric patients with CNS tumors

Group and Variable	Minimum	Median	Maximum	Mean	SD	P-value
<i>Controls (n=34)</i>						
Age at first course (y)	10.84	13.09	21.89	14.23	3.17	0.07
Weight (kg)	30.2	48.5	118.2	56.46	22.05	0.48
Height (cm)	134.3	159.2	196.8	160.59	14.42	0.16
BMI (kg/m ²)	14.08	19.44	37.22	21.36	5.94	0.93
<i>Aprepitant recipients (n=18)</i>						
Age at first course (y)	11.12	14.94	20.7	15.74	3.15	–
Weight (kg)	39	51.25	128.7	60.88	25.26	–
Height (cm)	151.2	164.25	189.6	166.34	12.42	–
BMI (kg/m ²)	15.08	19.26	38.85	21.38	6.03	–

Abbreviations: BMI, body mass index; SD, standard deviation