original reports

Olanzapine for Prevention of Vomiting in Children and Adolescents Receiving Highly Emetogenic Chemotherapy: Investigator-Initiated, Randomized, Open-Label Trial

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abstract

PURPOSE Chemotherapy-induced nausea and vomiting (CINV) is a significant toxicity of chemotherapy. Olanzapine is recommended in adult patients for the prevention of CINV but has not been prospectively investigated in children.

METHODS This investigator-initiated, randomized, open-label trial evaluated olanzapine in children (ages 5-18 years) scheduled to receive the first cycle of highly emetogenic chemotherapy (HEC). All participants received aprepitant, ondansetron, and dexamethasone during and 2 days after chemotherapy. Participants in the study group additionally received oral olanzapine 0.14 mg/kg/day (rounded to the nearest 2.5 mg; maximum, 10 mg) during the chemotherapy block and 3 days postchemotherapy. The primary objective was to compare complete response (CR) rates (no vomiting and no rescue medication) between the groups in the acute, delayed, and overall periods. Nausea comparison and safety evaluation were secondary and additional objectives, respectively. The collection of outcomes and adverse events was performed daily until the completion of the overall period.

RESULTS A total of 240 patients underwent randomization. We performed a modified intention-to-treat analysis on 231 patients (116 in the control group and 115 in the study group). A higher proportion of patients in the olanzapine group achieved CR in the acute period (78% *v* 59%; $P = .001$), delayed period (74% *v* 47%; $P < .001$) and overall period (64% *v* 38%; $P < .001$) than in the control group. The proportion of patients with no nausea was significantly higher in the olanzapine group in the acute period (74% *v* 52%; $P < .001$), delayed period (74% *v* 47%; $P < .001$), and overall period (64% *v* 37%; $P < .001$). Grade 1/2 somnolence was greater in the olanzapine group (35% *v* 11%; $P < .001$). There was no grade 3/4 somnolence reported.

CONCLUSION Olanzapine significantly improved CR rates for vomiting in children receiving the first cycle of HEC.

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a common and distressing toxicity of cancer chemotherapy in children, which hampers the quality of life (QOL).[1-3] The Pediatric Oncology Group of Ontario (POGO) has reported guidelines for the emetogenic classification of antineoplastic agents, prevention, and treatment of breakthrough and refractory CINV in children. The Children's Oncology Group and several other institutions have endorsed these guidelines.[4]

The current recommendations of the POGO for the prevention of CINV in pediatric patients receiving highly emetogenic chemotherapy (HEC) include a combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist, and a corticosteroid.[5] Recently, a second-generation atypical antipsychotic agent, olanzapine, has been explored for the management of CINV. The Food and Drug Administration approved the drug for schizophrenia and bipolar I disorder treatment in adolescents ages 13-17 years.[6] Olanzapine blocks multiple neurotransmitter receptors, including the dopaminergic receptors; 5-HT2a, 5-HT2c, 5-HT3, and 5-HT6 serotonergic receptors; and alpha-1 adrenergic, muscarinic, and histaminic receptors. The antiemetic potential of this agent was attributed to the blockade of the D2, 5-HT2c, and 5-HT3 receptors.[7]

Several randomized trials established the efficacy of olanzapine in the prevention of CINV in adult patients.[8-10] Drowsiness (34.4%) and constipation (28.7%) were the most commonly reported adverse effects in adults.[11] The safety of olanzapine in children has been established by Flank et al.[12,13] Olanzapine is currently recommended for the treatment of breakthrough and refractory CINV in children.[14] However, it is not recommended for the prevention of CINV in children because of the lack of efficacy data. We designed this randomized trial based on the hypothesis that olanzapine

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Chemotherapy-induced nausea and vomiting are two of the most common and worst-feared toxicities of cancer chemotherapy. Over the last decade, antiemetic regimens have improved in adult patients, but only a few trials have studied pediatric patients. Olanzapine, a second-generation atypical antipsychotic agent, has been approved for adult patients to prevent CINV. We have olanzapine for the prevention of CINV in children. To our knowledge, this is the first randomized, phase III olanzapine trial to date.

Knowledge Generated

Olanzapine significantly improved vomiting and nausea control rates in children when administered along with ondansetron, dexamethasone, and aprepitant. Olanzapine was well tolerated.

Relevance

Many pediatric protocols are highly emetogenic and have reduced control rates with existing antiemetic regimens. The use of olanzapine, along with another antiemetic regimen, can improve complete response rates for vomiting in children, minimizing chemotherapy-related complications.

is effective in the prevention of CINV when concurrently administered with a standard antiemetic regimen in children (ages 5-18 years) receiving the first cycle of HEC.

METHODS

Trial Design

This open-label, parallel-group, randomized controlled trial was conducted at a tertiary care hospital in New Delhi, India, from July 2017 to July 2019. The institutional ethics committee approved the study. Consent was obtained from the parent or guardian of all patients, and assent was obtained from all children > 6 years of age. The trial was conducted per the Indian Council of Medical Research and Good Clinical Practice guidelines. The trial was registered with ClinicalTrials.gov (NCT 03219710).

Definitions

Nausea was defined as a subjective experience of impending emesis. Vomiting was defined as expulsion of stomach contents through the mouth. A minimum interval of 5 minutes had to exist between each episode of vomiting. Chemotherapy block was defined as the number of days of chemotherapy administered in continuity during the first cycle. Nausea and vomiting that occurred after the initiation of chemotherapy, during chemotherapy, and up to 24 hours after completion of the chemotherapy block was defined as acute CINV. Delayed CINV referred to nausea and vomiting that occurred 24-120 hours after completion of the chemotherapy block. Nausea and vomiting that occurred after initiation of chemotherapy, during chemotherapy, and for 120 hours postchemotherapy block was categorized as overall CINV. Assessment of nausea and vomiting was performed during the first cycle of chemotherapy only. Rescue medication was defined as drugs administered in addition to standard medications to control nausea or vomiting.

Eligibility Criteria

Chemotherapy-naïve pediatric patients between 5 and 18 years of age with a confirmed diagnosis of cancer, weighing 15-65 kg (upper limit of weight was removed subsequently), scheduled to receive the first cycle of HEC per the POGO classification,[15] and with Eastern Cooperative Oncology Group performance status of 0, 1, or 2 were included in this study. Furthermore, only children who were able to swallow the medication and children or guardians who could understand and speak either English or Hindi were included. Children who had vomited in the previous 24 hours, received olanzapine in the previous 14 days, or received any other antipsychotic drugs within the previous 30 days and those with a history of hypersensitivity to olanzapine were excluded from the study. Additional exclusion criteria are summarized in the Data Supplement.

Randomization and Masking

Patients who met the inclusion criteria were assigned to either the study group or control group by simple randomization with concealed allocation using a computer-generated random number table using SPSS v.11 (SPSS, Chicago, IL). Because this was an open-label trial, children or guardians, as well as investigators responsible for randomization (D.D.) and drug administration (A.S.P.), were aware of the assigned group. To minimize bias, the investigators involved in randomization and drug administration did not participate in collecting primary outcome data and analyses of the results.

Study Intervention

Study participants in both groups received a combination of ondansetron, dexamethasone, and aprepitant. The dose of dexamethasone administered was 3 mg/m^2 every 8 hours and that of ondansetron was 0.15 mg/kg every 8 hours during the days of chemotherapy and for 2 subsequent

days. The dose before chemotherapy was administered intravenously, and subsequent doses were administered orally. The dosage of aprepitant was based on the weight of the patient. Patients weighing 15-40 kg were prescribed an 80-mg capsule of aprepitant orally on days 1-3. Patients weighing > 40 kg were prescribed a 125-mg capsule on day 1 and 80 mg on days 2 and 3. Patients in both weight categories received aprepitant for 3 days only, irrespective of the number of days of the chemotherapy block. In addition to this antiemetic regimen, participants in the study group received an oral dose of an olanzapine tablet at 0.14 mg/kg/dose once daily (rounded to nearest 2.5 mg; maximum, 10 mg) during the chemotherapy block and additionally for 3 days after completion of the block (Data Supplement). The rescue medication used was intravenous or oral metoclopramide.

Procedures and Data Collection

Demographic and baseline clinical parameters were recorded 1 day before chemotherapy administration. Patients admitted to the inpatient ward for the treatment were discharged after completion of the chemotherapy block and were observed as outpatients for the rest of the study period. Patients who underwent the treatment in an outpatient daycare facility were admitted daily for administration of the drugs until completion of the chemotherapy block. During the chemotherapy block, the investigator (A.S.P.) administered olanzapine 1 hour before the treatment. The parent or guardian administered olanzapine on subsequent days. Outcome data were collected on a case record form from the day of the start of chemotherapy until 120 hours after the last dose by the investigators (R.D.N. and S.B), who were blinded to the study group allocation. During chemotherapy, designated investigators recorded the outcome and toxicity data in person, and patients or guardians were subsequently telephoned daily until completion of the overall period to record the outcome parameters. A diary (Data Supplement) was provided to each patient or guardian to document the number of episodes of vomiting, nausea, and toxicities experienced, and the diary was collected at the end of the overall period. Toxicities that were prospectively documented by telephone and listed in the diary included abdominal pain, constipation, mucositis, somnolence, diarrhea, decreased food intake, headache, myalgia, increased appetite, fatigue, and extrapyramidal adverse effects. Data provided in the diary and those documented over the telephone were compared, and in case of discrepancy, the higher grade of toxicity was considered. After completion of the overall period, recording of the data on toxicity was based on spontaneous reporting by the patient or guardian until the next chemotherapy cycle (Fig 1).

The weight of the patient was measured at 3 time points: baseline, the end of the overall period, and before the second cycle of chemotherapy. The National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) was used to assess and grade vomiting and other adverse events. The Edmonton Symptom Assessment Scale (ESAS)[16] was used to grade nausea. The ESAS is a numeric rating scale, with scores ranging from 0 to 10. A score of 0 indicates no nausea, and 10 denotes severe nausea. Scores of 1-3, 4-7, and 8-10 were graded as mild, moderate, and severe nausea, respectively.

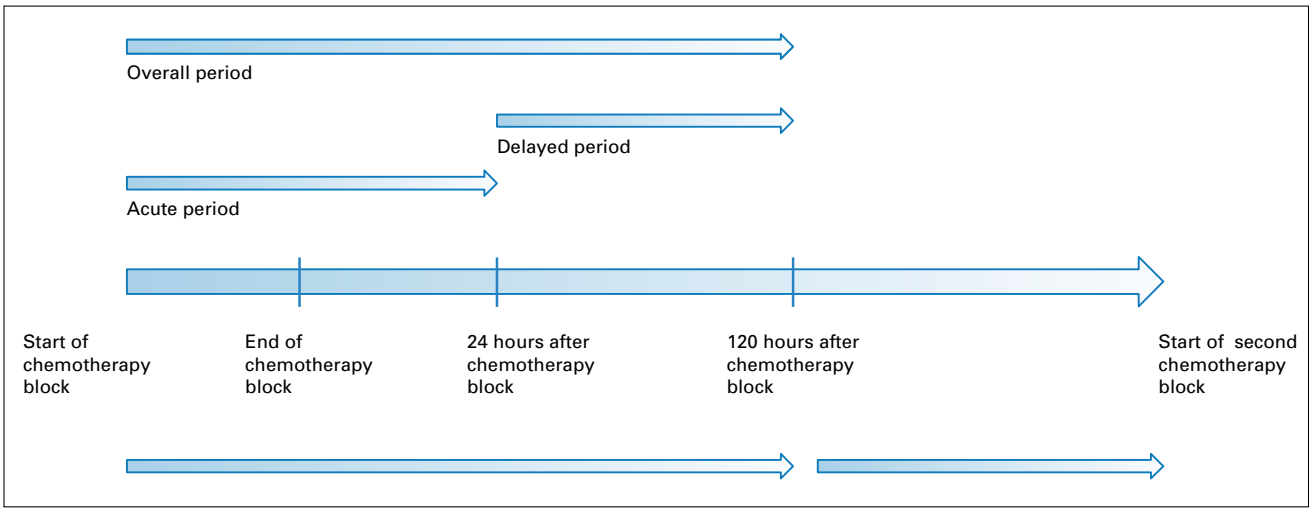

FIG 1. Timeline and procedure of data collection. Baseline and demographic details were collected before chemotherapy administration. During the chemotherapy block administration, outcome and toxicity data were collected in person on a case record form. After completion of the chemotherapy block, the patient/guardian was telephoned every day to collect data. Patients/guardians were asked to document the outcome measure in the diary provided to them. At the end of the overall period, the diary was collected and compared with the data collected over the telephone. Toxicity data after the overall period were collected on spontaneous reporting of the patient/guardian. Weight was measured at baseline, at the end of overall period, and at the end of study period.

Outcomes

The primary objective of the study was to compare the number of patients with complete response (CR) in the acute, delayed, and overall assessment periods. A child was considered to have CR when there was no episode of vomiting and no use of rescue medication (administered to patients with severe nausea [ESAS score ≥ 8] and/or > 2 vomiting episodes) during the respective periods. The secondary objective was to compare the number of patients who did not experience any nausea (ie, only an ESAS of 0) in the three assessment periods. An additional objective was the safety evaluation of the intervention.

Statistical Analyses

A study from our center that assessed aprepitant for the prevention of CINV reported CR rates of 48%, 34%, and 22% in the acute, delayed, and overall periods, respectively.[17] In accordance with the trial in adult patients,[10] a 20% absolute increase in CR rates with olanzapine was assumed, with a type I error of 5% and 80% power. Based on this assumption, the estimated sample size was 105, 106, and 94 patients in each group in the three respective assessment periods. The target sample size required was 116, 117, and 104 patients in each group in the respective periods, considering a 10% attrition/loss-to-follow-up rate. Therefore, we considered a sample of 120 patients per group to address the primary outcome in the three assessment periods. Sample size calculations were based on a two-sided test and the χ^2 test with continuity correction.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants. Modified intention-to-treat was performed for efficacy analysis, that is, patients who had received chemotherapy, taken at least one dose of the antiemetic regimen, and had one or more post-treatment outcome measurements.

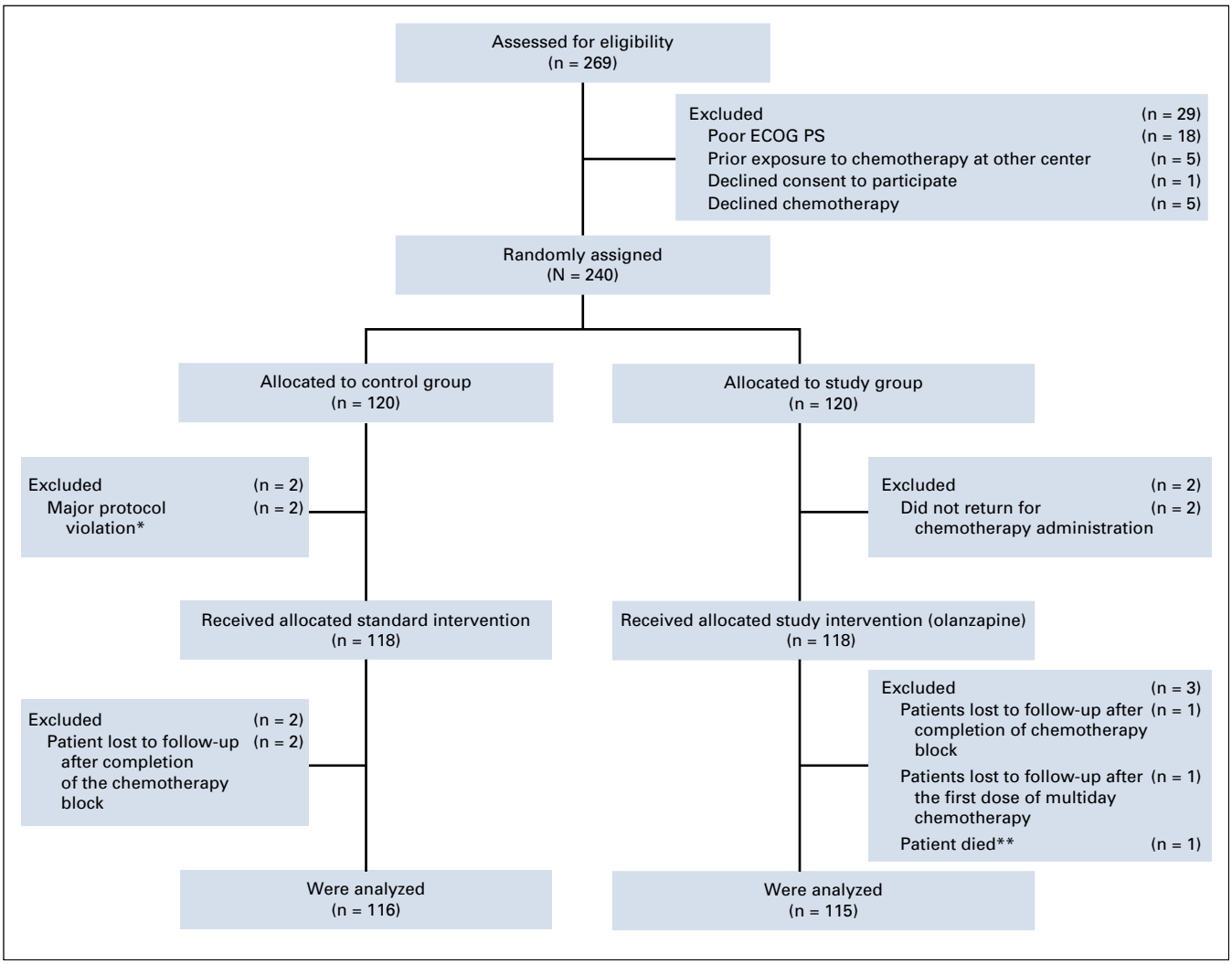

FIG 2. CONSORT diagram. (*) Major protocol violation: Two patients were incorrectly randomly assigned because their weight was > 65 kg (initial upper limit of inclusion). (**) Patient died at home on day 2 of enrollment after chemotherapy. The reason for death was not known. ECOG PS, Eastern Cooperative Oncology Group performance score.

Comparison between categorical variables was performed using the χ^2 test or Fisher's exact test and between continuous variables using the *t* test or Wilcoxon test. A paired *t* test was used to calculate the mean change in weight of the patients from baseline. The level of significance was set at .05. Primary and secondary objectives were compared between the control and study groups, presenting the values as both absolute and relative differences with 95% CIs. We performed an exploratory analysis to identify subgroups that did not benefit from the addition of olanzapine (Data Supplement). All analyses were performed using Stata software version 15.1 (STATA, College Station, TX).

RESULTS

A total of 269 patients ages 5-18 years scheduled to receive HEC were screened for eligibility. Inclusion criteria were met by 240 patients, who were randomly assigned into study and control groups. Nine patients were excluded (five of whom were excluded because of lack of data); therefore, 231 patients were considered eligible for the efficacy analysis (115 in the olanzapine group and 116 in the control group), as presented in the CONSORT diagram (Fig 2).

More male patients than female patients were present in both groups. Clinical and demographic characteristics were balanced between the groups, except that patients receiving multiday chemotherapy regimens were significantly higher in the study group (Table 1; Data Supplement). A total of 238 patients received the study medication (ondansetron, dexamethasone, aprepitant [control group] plus olanzapine [study group]). Ninety-four percent of patients complied with and adhered to the study protocol. Seven patients (3%) missed either one or two doses of the antiemetic medications (Data Supplement). The mean olanzapine dose (± standard deviation [SD]) used in the current trial was 0.13 ± 0.02 mg/kg/dose. The mean and

TABLE 1. Demographic and Baseline Clinical Parameters

Parameter	Control Group (n = 120)	Study Group (n = 120)	*P*
Median age (range), years	11 (5-18)	12.5 (5-18)	.21
Sex			
Male	91 (76)	83 (69)	.25
Female	29 (24)	37 (31)	
Mean weight ± SD (kg)	32.3 ± 14.9	33.8 ± 13.2	.41
Mean body mass index ± SD (kg/m^2)	16 ± 3.2	16.1 ± 2.7	.89
Diagnosis			
Primitive neuroectodermal tumor	40 (33)	29 (24)	.79
Hodgkin lymphoma	33 (27)	29 (24)	
Osteosarcoma	17 (14)	24 (20)	
Rhabdomyosarcoma	10 (8)	8 (7)	
Other[a]	20 (18)	30 (25)	
ECOG performance status			
0-1	75 (63)	75 (63)	.60
2	45 (37)	45 (37)	
Chemotherapy regimens administered	(n = 120)	(n = 118)[b]	
Vincristine-doxorubicin-cyclophosphamide	40 (33)	29 (25)	.51
Doxorubicin-bleomycin-vinblastine-dacarbazine	33 (27)	29 (25)	
Cisplatin-doxorubicin	17 (14)	25 (21)	
Vincristine-actinomycin D-cyclophosphamide	10 (8)	8 (7)	
Other regimens[c]	20 (18)	27 (22)	
Duration of chemotherapy block	(n = 120)	(n = 118)[b]	
Single day	88 (73)	72 (61)	.043
Multiday	32 (27)	46 (39)	

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

[a]Other listed in the Data Supplement.

[b]Two patients did not receive chemotherapy at our center.

[c]Other chemotherapy regimens listed in the Data Supplement.

median duration of olanzapine treatment was 4.77 ± 1.13 days and 4 days, respectively, (range, 2-8 days).

Outcomes

The CR rates between the groups in the acute, delayed, and overall periods were 78% versus 59% ($P = .001$), 74% versus 47% ($P < .001$), and 64% versus 38% ($P < .001$), respectively, in favor of the olanzapine group (Table 2; Data Supplement). The proportion of patients who did not experience nausea was significantly higher in the olanzapine group than in the control group during the acute (74% *v* 52%; $P < .001$), delayed (74% *v* 47%; $P < .001$), and overall (64% *v* 37%; $P < .001$) periods (Table 3; Data Supplement). The proportion of patients who received rescue medication was 13% in the study group versus 21% in the control group ($P = .12$).

Adverse Events

A total of 233 patients were available for toxicity analysis. Adverse events of all grades reported in > 10% of the study participants included abdominal pain (32%), fatigue (28%), constipation (24%), mucositis (24%), somnolence (23%), diarrhea (17%), decreased food intake (16%), and headache (12%; Table 4). Somnolence was reported more frequently among patients in the olanzapine group than those in the control group (35% *v* 11%; $P < .001$). In the olanzapine group, 31 patients (27%) experienced grade 1 somnolence, nine (8%) had grade 2 somnolence, and none reported grade 3/4 somnolence. In the control group, 13 patients (11%) had grade 1 somnolence with no grade 2/3/4 presentation. There was no report of discontinuation of olanzapine because of somnolence. The frequency and distribution of other adverse effects were similar between the groups. Six patients experienced grade 3 or 4 adverse events and were similar between the groups.

Two deaths were reported. One patient in the study group died at home on the second day after chemotherapy, and the exact cause of death could not be ascertained. Notably, this child received a single dose of 2.5 mg olanzapine (0.1 mg/kg/dose). The other patient, who belonged to the control group, died as a result of neutropenic enterocolitis.

The mean (SD) baseline weight of patients was comparable between the control and study groups (32.3 ± 14.9 *v* 33.8 ± 13.2 kg; $P = .41$). The mean change in weight of the patients at the end of the overall period was +0.07 ± 0.65 kg in the control group and −0.05 ± 0.7 kg in the olanzapine group ($P = .27$). The mean change in weight before the second cycle of chemotherapy, compared with baseline, was +0.11 ± 0.86 kg in the control group and +0.06 ± 0.76 kg in the olanzapine group ($P = .46$).

DISCUSSION

This large randomized, open-label, phase III trial showed that the addition of olanzapine to aprepitant, dexamethasone, and ondansetron resulted in superior control of CINV in chemotherapy-naïve pediatric patients. The absolute increase in the CR rate with the addition of olanzapine was 19% (95% CI, 7.9% to 31.4%) in the acute period, 27% (95% CI, 15.2% to 39.5%) in the delayed period, and 26% (95% CI, 13.1% to 38.0%) in the overall period. Likewise, a significant reduction in nausea was observed among patients in the olanzapine group compared with the control group in the three periods: acute, 22% (95% CI, 34.3% to 10.0%); delayed, 27% (95% CI, 38.6% to 14.4%); and overall, 27% (95% CI, 39.6% to 14.8%). A similar benefit of olanzapine was reported in a previous study in chemotherapy-naïve adult patients receiving HEC.[18]

Although a significant proportion of patients in the olanzapine group experienced somnolence compared with the control group, there were no grade 3 or 4 adverse effects. A meta-analysis of trials in the adult population reported an

TABLE 2. Comparison of CR Rates for Chemotherapy-Induced Vomiting Between the Groups

Parameter	Control Group (n = 116)	Study Group (n = 115)	Total (N = 231)	*P*	OR[a]	95% CI
Acute period						
CR	68 (59)	90 (78)	158 (68)	.001	2.54	1.43 to 4.52
No CR	48 (41)	25 (22)	70 (32)			
Delayed period						
CR	54 (47)	85 (74)	139 (60)	< .001	3.25	1.87 to 5.66
No CR	62 (53)	30 (26)	92 (40)			
Overall period						
CR	44 (38)	73 (64)	117 (51)	< .001	2.84	1.67 to 4.85
No CR	72 (62)	42 (36)	114 (49)			

NOTE. Data are No. (%) unless otherwise indicated.
Abbreviations: CR, complete response; OR, odds ratio.
[a]OR > 1 means the odds of CR were greater in the olanzapine group.

TABLE 3. Comparison of Chemotherapy-Induced Nausea Between the Groups

Parameter	Control Group (n = 116)	Study Group (n = 115)	Total (N = 231)	*P*	OR[a]	95% CI
Acute period						
No nausea	60 (52)	85 (74)	145 (63)	< .001	2.64	1.52 to 4.60
Nausea	56 (48)	30 (26)	86 (37)			
Delayed period						
No nausea	55 (47)	85 (74)	140 (61)	< .001	3.14	1.81 to 5.46
Nausea	61 (53)	30 (26)	91 (39)			
Overall period						
No nausea	43 (37)	74 (64)	117 (51)	< .001	3.06	1.79 to 5.24
Nausea	73 (63)	41 (36)	114 (49)			

Abbreviation: OR, odds ratio.
[a]OR > 1 means the odds of "no nausea" is greater in the olanzapine group.

absolute increase of 8.2% (95% CI, 1.9% to 18.8%) in the risk of somnolence with olanzapine compared with placebo.[19] A recent feasibility study by Flank et al[20] reported that 40% of the included children experienced somnolence with an olanzapine dose of 0.14 mg/kg, similar dosing to the current trial. Considering the benefits of olanzapine observed in this trial, increased occurrence of grade 1 and 2 somnolence should not be a barrier to prescribing the drug. Olanzapine at a dose of 5 mg/day has been shown to be effective in preventing CINV in adult patients with a lower incidence of somnolence.[21] Based on 5 mg in adult dosing, an initial dose of 0.1 mg/kg of olanzapine was suggested by Flank et al[20] by using the allometric scaling method.

Weight gain is one of the common metabolic abnormalities associated with long-term use of olanzapine in children.[22] However, weight gain was not reported when the drug was used for control of CINV.[13] In the current trial, no significant change in weight of the patients was observed, eliminating the need for monitoring the waist circumference, which is otherwise recommended during long-term administration of olanzapine.[23] QTc prolongation is another complication that some authors feared when a combination of olanzapine and serotonin receptor antagonists was used.[24] However, such a complication has not been reported in pediatric patients.[13] Therefore, it may not be necessary to obtain a baseline ECG. Furthermore, the ASCO guidelines recommend olanzapine in adults for the prevention of CINV without baseline ECG monitoring.[25]

In the current trial, all the subgroups benefited from the addition of olanzapine, except for female patients (Data Supplement). In adult patients, female sex is a well-known risk factor for increased CINV.[26] However, female sex is not

TABLE 4. Comparison of All Grade and Grade 3/4 Toxicities Between the Groups

	Any Grade Toxicity				Grade 3 or 4 Toxicity			
Parameter	Control Group (n = 118)	Study Group (n = 115)	Total (N = 233)	*P*	Control Group (n = 118)	Study Group (n = 115)	Total (N = 233)	*P*
Abdominal pain	42 (36)	32 (28)	74 (32)	.20	1 (1)	2 (2)	3 (1)	.23[a]
Fatigue	40 (34)	25 (22)	65 (28)	.039	0	0	0	0
Constipation	26 (22)	29 (25)	55 (24)	.56	0	0	0	0
Mucositis	31 (26)	24 (21)	55 (24)	.33	1 (1)	0 (0)	1 (0.4)	.70[a]
Somnolence	13 (11)	40 (35)	53 (23)	< .001	0	0	0	0
Diarrhea	17 (14)	22 (19)	39 (17)	.33	0 (0)	2 (2)	2 (1)	.47[a]
Decreased food intake	21 (18)	16 (14)	37 (16)	.42	0	0	0	0
Headache	16 (14)	11 (10)	27 (12)	.34	0	0	0	0
Myalgia	9 (8)	6 (5)	15 (6)	.45	0	0	0	0
Increased appetite	3 (3)	2 (2)	5 (2)	1.0	0	0	0	0
Extrapyramidal symptoms[b]	0	0	0	0	0	0	0	0

NOTE. Data are No. (%).
[a]*P* value calculated by Fisher's exact test.
[b]Extrapyramidal symptoms include abnormal movements, tremors, dystonia, and stiffness.

associated with poor chemotherapy-induced vomiting (CIV) control in pediatric patients.[27] On pooled analysis of both arms in our trial data, CR rates were similar in both sexes (Data Supplement).

The merits of the current study are that, to our knowledge, it is the first randomized, adequately powered, phase III trial evaluating the efficacy of olanzapine in pediatric patients for the prevention of CINV. A standard antiemetic regimen was used for comparison in this trial, and commonly used pediatric single-day and multiday HEC protocols were evaluated.

Limitations of the current study are that we assessed nausea using the ESAS, which was previously used at our institute.[17,28] The ESAS is generally used in the adult population; thus, the use of pediatric-specific nausea assessment tools such as the Pediatric Nausea Assessment Tool would have been more appropriate for our cohort.[29] The dose of aprepitant used in our trial was different from that recommended in the current POGO guidelines.[5] Our trial's dosing of aprepitant was adopted because of the nonavailability of the syrup formulation in our country. A similar dosing strategy was reported to be effective in the prevention of CINV without additional toxicity.[17,30,31] Although we considered the older version of the antineoplastic agents' emetogenic classification by the POGO,[15] all the regimens used in our trial were highly emetogenic per the current classification.[32]

Olanzapine significantly improved the control of CIV during the acute, delayed, and overall periods in children and adolescents ages 5-18 years receiving the first cycle of HEC, with a tolerable safety profile. Future trials comparing olanzapine with aprepitant may merit investigation. Olanzapine dose-optimizing studies to decrease somnolence without compromising benefit may also merit investigation. QOL was not assessed in the current trial, and future trials may investigate QOL prospectively.

AFFILIATIONS

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PRIOR PRESENTATION

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SUPPORT

Intas Biopharmaceuticals, Ahmedabad, India, provided the study drug olanzapine free of cost. However, the company was not involved in designing the study, data collection, analysis, writing the manuscript, or process of paper submission.

CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.00871.

AUTHOR CONTRIBUTIONS

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Provision of study materials or patients: Ramavath D. Naik, Ashwati S. Pillai
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Data analysis and interpretation: Ramavath D. Naik, Sreenivas Vishnubhatla, Vishwajeet Singh, Sameer Bakhshi
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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