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ORIGINAL ARTICLE

Impact of adjuvant lorazepam with granisetron on chemotherapy-induced nausea and vomiting in pediatric patients with acute lymphoblastic leukemia

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Abstract

Purpose Chemotherapy-induced nausea and vomiting (CINV) affects quality of life for patients with cancer undergoing chemotherapy. We aimed to assess the effect of lorazepam with granisetron on CINV in children with acute lymphoblastic leukemia (ALL).

Methods We reviewed the records of 71 consecutive patients with newly diagnosed ALL who received chemotherapy including vincristine, anthracycline, and systemic steroids between January 2011 and December 2016 in our hospital. The number of chemotherapy cycles reviewed was 164. All patients received granisetron as CINV prophylaxis.

Results Nausea was observed in 51/71 patients (72%) and 93/164 cycles (57%). Vomiting was observed in 47/71 patients (66%) and 79/164 cycles (48%). Age and gender distribution were not significantly different between patients who received lorazepam at the initiation of the chemotherapy cycle (LZP group, $n = 30$) and those who did not receive lorazepam (non-LZP group, $n = 134$). There were no significant differences in the incidence of CIN and CIV between the LZP group and non-LZP group (CIN, 67% vs. 57%, $P = 0.31$; CIV, 53% vs. 47%, $P = 0.98$). In multivariate logistic regression, female gender and older age (> 5 years) were significant risk factors for CIV (female, odds ratio (OR) 2.5, 95% confidence interval (CI) 1.3–5.0, $P = 0.007$; older age, OR 2.5, CI 1.3–4.8, $P = 0.008$).

Conclusions We found no beneficial effect of providing lorazepam as adjuvant antiemetic for prevention of CINV in children with ALL.

Keywords Lorazepam · Chemotherapy · Nausea · Vomiting · Antiemetics

Introduction

Nausea and vomiting are a common side effect of cancer chemotherapy [1], with a negative impact on patients' quality of life and ability to comply with therapy [1, 2]. A large number of medications have been proposed for chemotherapy-induced nausea and vomiting (CINV), including dexamethasone, tetrahydrocannabinol, levonantradol, benzodiazepines, medroxyprogesterone, nabilone, and propofol [3]. Despite advances in the prevention and management of CINV, it remains distressing for both adults [4] and children [5, 6].

Benzodiazepines are recommended for anticipatory CINV, and for refractory and breakthrough emesis [1], in several guidelines from Japan, Europe, and the USA [7–10]. Lorazepam is one of the intermediate-acting benzodiazepines and has been used as an antiemetic for CINV [11] before the availability of serotonin (5-HT_3) receptor antagonists. They are also recommended as an adjunctive therapy with granisetron [8, 9]. Current guidelines for children do not include benzodiazepines, partially because of limited evidence in this population [3, 6], and lack of observed benefit with lorazepam [12, 13]. Combined lorazepam and 5-HT_3 receptor antagonist for CINV in children displayed some effectiveness, but has not been rigorously evaluated [6, 14]. The aim of the

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present study was to assess the effect of lorazepam as adjuvant to 5-HT_3 receptor antagonist on CINV in children. We focused on acute lymphoblastic leukemia (ALL), the most common pediatric malignancy.

Methods

Study design

We conducted a retrospective chart review using inpatient medical records at Kobe Children's Hospital, a tertiary, pediatric medical center in Japan. The study was approved by the Institutional Review Board (IRB) of Kobe Children's Hospital.

Patients

We included 71 patients and 164 chemotherapy cycles (median age, 5 years; range, 1–19 years), newly diagnosed with ALL, who received chemotherapy including vincristine, anthracyclines (daunorubicin, doxorubicin, or pirarubicin), and systemic steroids (dexamethasone or prednisolone), at Kobe Children's Hospital, between January 1, 2011 and December 31, 2016. We determined if they received lorazepam through the hospital pharmacy database. All patients received granisetron. We excluded patients if they took lorazepam prior to administration of chemotherapy for anxiety, those with psychiatric disorders, cancer relapse, and central nerve system (CNS) lesions. We collected demographic profile data, medical information, and chemotherapy-related adverse events (CRAEs).

Definitions

We counted the days from the initiation of a chemotherapy cycle. The duration of a chemotherapy cycle began at the initial dose and ended with the start of the next chemotherapy cycle. Information on CIN, CIV, and CRAE were obtained from medical charts. CRAEs included constipation, diarrhea, headache, fatigue, abdominal pain, and rash. We defined nausea and vomiting as CINV within 7 days of the last day of a chemotherapy cycle, including both acute and delayed phases [15]. CINV may generally be divided into acute and delayed. The former [16, 17] is observed within 24 h of treatment and the latter [18, 19] occurs 24 h after the initiation of chemotherapy. The risk for emetogenic chemotherapy regimens was classified as high (highly emetogenic chemotherapy; HEC), moderate (moderately emetogenic chemotherapy; MEC), low, or minimally emetogenic, according to the current guidelines [2, 20].

Statistical analysis

Outcome measures were incidence and onset of CIN and CIV, and administration of antiemetics. The incidence of CIN and CIV was compared between children that received chemotherapy with lorazepam at the initiation of chemotherapy cycle (LZP group) and those that did not receive lorazepam (non-LZP group). Univariate analysis was performed using chi-square test and Fisher's exact test for qualitative variables. For quantitative variables, the non-parametric Mann-Whitney *U* test was used. Potential risk factors in the univariate analysis were included in a post hoc logistic regression model with CINV as dependent variable. The cut-off points for the variables were determined by the receiver operating characteristic curve analysis. A backward stepwise procedure was used to identify relevant factors in the model. We also conducted a subgroup analysis of age, gender, and cyclophosphamide use. If a *P* value was less than 0.05, the result was considered statistically significant. All statistical analyses were conducted using EZR on R (The R Foundation for Statistical Computing) [21].

Results

Patient demographics

Eligible were 37 males (52%) and 34 females (48%). Cycles with HEC were 99/164 (60%) and with MEC were 65/164 (40%). CIN was observed in 51/71 (72%) patients and 93/164 (57%) cycles. The median CIN onset was 3 (range 1–31) days after the initiation of chemotherapy. CIV was observed in 47/71 (66%) patients and 79/164 (48%) cycles. The median CIV onset was 3 days (range 1–24). The incidence of headache and abdominal pain as CRAEs was greatly higher in the chemotherapy cycles with CINV compared to cycles without CINV

Table 1 Association between CIN/CIV and adverse events

CRAEs, *n* (%)	CIN (*n* = 93)		*P* value [1]	CIV (*n* = 79)		*P* value [2]
Overall	87	(94)	0.398	76	(96)	0.070
Constipation	5	(5)	0.534	5	(6)	0.900
Diarrhea	6	(6)	1.0	4	(5)	1.0
Headache	26	(28)	0.003	23	(29)	0.005
Fatigue	82	(88)	0.291	69	(87)	0.291
Rash	1	(1)	0.086	5	(6)	0.107
Abdominal pain	51	(55)	0.048	46	(58)	0.012

CIN chemotherapy-induced nausea, *CIV* chemotherapy-induced vomiting, *CRAEs* chemotherapy related adverse events

[1] Comparison between CIN and without CIN, [2] Comparison between CIV and without CIV

(Table 1). The median age was significantly older in patients with CIN than without (7 years (range 1–16) vs. 4 years (1–19), $P < 0.001$). The number of females in the CIV group was significantly larger than in the non-CIV group (48/79 (61%) vs. 33/85 (39%), $P = 0.008$) (Table 2).

Comparisons between the LZP group and non-LZP group

Lorazepam was used in 19/71 patients (27%) and 30/164 cycles (18%). Age and gender distribution were not significantly different between the LZP group and non-LZP group. HEC was experienced significantly more in the LZP group (28/30 (93%)) than in the non-LZP group (71/134 (53%)) ($P < 0.001$). The incidence of CIN was 20/30 (67%) cycles of the LZP group and 73/134 (57%) cycles of the non-LZP group and that of CIV was 16/30 (53%) cycles in the LZP group and 69/134 (47%) cycles in the non-LZP group, which showed no significant difference in both incidences of CIN ($P = 0.311$) and CIV ($P = 0.984$). The onset of CIN and CIV were both the third day in the LZP group and the fourth day in the non-LZP group.

Multivariate logistic regression for CINV

In the multivariate logistic regression, older age (> 5 years) was a significant risk factor for CIN and CIV (CIN, OR 6.0, 95%CI 2.9–12, $P < 0.001$; CIV, OR 2.5, 95%CI 1.3–4.8, $P = 0.008$). Female gender showed high-risk for CIV (OR 2.5, 95%CI 0.2–0.8, $P = 0.007$). HEC, MEC, and the use of lorazepam were not significant factors.

Discussion

We found no benefit in using lorazepam as adjuvant therapy for prevention of CINV in children with ALL. This study was the first, to our knowledge, that assessed the benefit of adjuvant lorazepam with 5-HT_3 receptor antagonists on CINV in the pediatric population. We focused assessment in children with ALL that received a similar type of chemotherapy.

We report CIN and CIV in 72 and 66% of children respectively, a relatively high rate compared to previous reports. We report CINV in about 60% of our cohort, with a significant correlation between CINV and CRAEs. Previous studies reported CINV as bothersome for children, with as many as 60% reporting nausea or vomiting [22, 23], especially with high emetogenic chemotherapy and despite standard antiemetic prophylaxis (ondansetron/granisetron with dexamethasone) [17]. Anticipating CINV is an important principle in prevention and management of adverse effects in the "cancer continuum" [7, 17, 24] and novel additional antiemetic prophylactic therapies are needed.

This study identified two risk factors for CINV; female gender and older age. There were several reports about the association of female gender and younger age in adults and CINV [25, 26]. This study is in contrary to the finding that younger children were more likely to have CINV when given chemotherapy with ondansetron once daily alone or with

Table 2 Comparisons between CIN or CIV and non-CIN or non-CIV

Characteristic	CIN ($n = 93$)	Non-CIN ($n = 71$)	P value	CIV ($n = 79$)	Non-CIV ($n = 85$)	P value
Age (year), median (range)	7 (1–16)	4 (1–19)	< 0.001	6 (1–14)	4 (1–19)	0.098
Male/female, *n* (%)	42 (45)/51 (55)	41 (58)/30 (42)	0.118	31 (39)/48 (61)	52 (61)/33 (39)	0.008
Antiemetic, *n* (%)						
5-HT_3 receptor antagonist	93 (100)	71 (100)	–	79 (100)	85 (100)	–
Lorazepam	20 (22)	10 (14)	0.308	15 (19)	15 (18)	0.843
Other	5 (5)	3 (4)	1.0	4 (1)	4 (5)	1.0
Anticancer agent, *n* (%)						
Vincristine	93 (100)	71 (100)	–	79 (100)	85 (100)	–
Daunorubicin	42 (45)	29 (41)	0.635	40 (51)	31 (36)	0.094
Doxorubicin	1 (0)	3 (4)	0.317	1 (1)	3 (4)	0.621
Pirarubicin	50 (54)	39 (55)	1.0	38 (48)	51 (65)	0.170
L-Asparaginase	93 (100)	67 (94)	0.033	79 (100)	81(95)	0.148
Cyclophosphamide	54 (58)	45 (63)	0.522	40 (51)	59 (69)	0.022
Cytarabine	39 (42)	31 (44)	0.874	26 (33)	44 (52)	0.023
Dexamethasone	54 (58)	44 (62)	0.633	44 (56)	54 (64)	0.388
Prednisolone	51 (55)	36 (51)	0.638	49 (62)	38 (45)	0.039

CIN chemotherapy-induced nausea, *CIV* chemotherapy-induced vomiting

dexamethasone [23, 27]. These findings suggest that an optimal antiemetic regimen should be tailored individually according to the present risk factors. Further study would be needed to find out the effect of lorazepam among the patient subgroups.

Benzodiazepines have been used as adjunct therapy to decrease treatment-related anxiety and were recommended as preferred agents to treat and prevent anticipatory nausea and vomiting [7, 28, 29]. In one study among adults receiving cisplatin, clonazepam was associated with significant reduction in delayed vomiting [30]. In some small studies including adults before the emergence of 5-HT_3 receptor antagonists, lorazepam was considered valuable due to the ease of administration and amnesic and anxiolytic effects [31, 32]. Several studies evaluated a combination of lorazepam with 5-HT_3 receptor antagonist [33, 34]; the effect of the combination remains controversial. A randomized double-blind trial among 75 patients [34] reported no significant differences, similar to our study. A more recent study with 135 patients [33] reported that the addition of lorazepam to ondansetron and corticoids increased antiemetic control. Each chemotherapy was equivalent to HEC in the former study using cisplatin and MEC in the latter one using doxorubicin. It is possible that lorazepam was not effective for CINV in our study because of the higher incidence of patients in the LZP group that received HEC regimens than in the non-LZP group. The optimal indication of adjuvant lorazepam should be investigated with regard to the emetogenicity of chemotherapy.

This study has several limitations. We evaluated a hospital-based population and generalizability to community-based chemotherapy is challenging. Our sample size is relatively small, limiting the power of our finding. Furthermore, the severity of CIN was not evaluated and future use of a scoring system [35–37] will be of benefit. Similarly, a dose of lorazepam was not evaluated, to ensure consistency of treatment per protocol. Despite these limitations, the present study provides useful information on the use of lorazepam for prevention of CINV.

Conclusion

Lorazepam did not prevent CINV when administered with granisetron in children with ALL. CINV continues to be a common and distressing side effect in children with ALL. Novel methods are required to achieve adequate control of CINV and to improve the quality of life in children receiving chemotherapy more than ever.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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