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Pediatric related risk factors in acute and delayed chemotherapy-induced nausea and vomiting: multivariate analysis

Fatores de risco relacionados a náuseas e vômitos induzidos por quimioterapia aguda e tardia em pediatria: análise multivariada

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ABSTRACT

Objectives: This study aimed to characterize the clinical profile and the factors that predispose chemotherapy-induced nausea and vomiting (CINV) in the acute and delayed phases. **Methods:** A retrospective cohort study was conducted in a Brazilian hospital with pediatric patients under 18 years old receiving moderately or highly emetogenic chemotherapy. Thus, a descriptive analysis was performed to characterize this population, followed by univariate and multivariate analysis to evaluate the risk factors for CINV. In both phases, considering significant the variables with *p*-values <0.05. **Results:** The median age was 6 and 71% of the patients included used highly emetogenic protocols. Furthermore, 41% and 76% did not have vomit in the acute and delayed phase, respectively. Through logistic regression, it is noted that patients with bone tumors and sarcomas have higher CINV in the acute phase (OR 10.0, 95%IC 1.1-88.9, *p*=0.039), while patients who do not have complete control in the acute phase are more likely to have CINV in the delayed phase (OR 11.8, 95%IC 1.1-130.5, *p*=0.044). **Conclusion:** These results suggest that bone tumors and sarcomas are associated with an increase in CINV in the acute phase. In addition, control in the acute phase is associated with a complete response in the delayed phase.

Keywords: Vomiting; Chemotherapy; Pediatric; Oncology; Antiemetics.

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RESUMO

Objetivos: Este estudo teve como objetivo caracterizar o perfil clínico e os fatores que predispõem a náuseas e vômitos induzidos por quimioterapia (NVIQ) nas fases aguda e tardia. **Métodos:** Foi realizado um estudo de coorte retrospectivo em um hospital brasileiro com pacientes pediátricos menores de 18 anos recebendo quimioterapia moderada ou altamente emetogênica. Assim, foi realizada uma análise descritiva para caracterizar essa população, seguida de análise univariada e multivariada para avaliar os fatores de risco para NVIQ. Em ambas as fases, considerando significativas as variáveis com valores de p<0,05. **Resultados:** A mediana de idade foi de 6 anos e 71% dos pacientes incluídos usavam protocolos altamente emetogênicos. Além disso, 41% e 76% não apresentaram vômito na fase aguda e tardia, respectivamente. Por meio de regressão logística, nota-se que pacientes com tumores ósseos e sarcomas apresentam maior NVIQ na fase aguda (OR 10,0, IC95% 1,1-88,9, p=0,039), enquanto os pacientes que não possuem controle completo na fase aguda são maior probabilidade de ter CINV na fase tardia (OR 11,8, IC95% 1,1-130,5, p=0,044). **Conclusão:** Esses resultados sugerem que tumores ósseos e sarcomas estão associados a um aumento de NVIQ na fase aguda. Além disso, o controle na fase aguda está associado a uma resposta completa na fase tardia.

Descritores: Vômitos; Quimioterapia; Pediátrico; Oncologia; Antieméticos.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a common treatment-related side effect that can negatively impact quality of life and patient compliance.[1] These can be attributed to several factors, including the environment in which chemotherapy is administered, the emetogenicity of the chemotherapy, the dosage of emetogenic agents, and patient-related factors.[2] Some previous studies have already identified some risk factors for CINV in acute and delayed phase,[3-6] however the key aspect associated with the incidence of CINV consists in emetogenic potential of chemotherapy.

For complete prevention of these events, the use of triple therapy (5-hydroxytryptamine-3 [5-HT3] receptor antagonists, neurokinin-1 [NK1] receptor antagonists and corticosteroids - especially dexamethasone) for highly emetogenic chemotherapy (HEC) is recommended as an antiemetic prophylaxis, both for adults[7-9] and children[10,11] or dual therapy (5-HT3 receptor antagonists with dexamethasone or 5-HT3 antagonists with NK1 antagonists) for moderately emetogenic chemotherapy (MEC). However, many patients do not receive antiemetic regimens recommended by the guidelines,[12-16] therefore, they are more likely to suffer from CINV.

Despite the current antiemetic guidelines,[9,10] there are still unmet medical needs in the management of CINV, mainly for better control of nausea (particularly delayed nausea). In addition, the use of certain classes of drugs, especially NK1 antagonists, requires greater attention due to suboptimal use.

Thus, as CINV is an unpleasant adverse event and commonly reported in pediatrics, considering the shortage of studies for this population, aiming to minimize and/or avoid this event, this study aimed to describe the clinical profile of patients, analyze whether antiemetic prophylaxis used is consistent with international guidelines and to assess factors that significantly impact CINV in acute and delayed phases.

METHODS

Study population

This retrospective, single-center, cohort study was approved by the institutional review board (protocol No. CAAE 39799020.1.0000.5580). The study was drawn from patients with cancer treated with MEC or HEC by the oncology/hematology sector in the largest pediatric hospital in Brazil, between January 2018 to June 2020.

Inclusion criteria was patients under 18 years of age, treated with MEC and HEC chemotherapy. The selection of patients in group A (n=12) and B (n=60) was based in inclusion criteria and antiemetic prophylaxis. Antiemetic prophylaxis was considered as triple therapy for HEC (fosaprepitant, ondansetron and, if indicated, dexamethasone) and dual therapy for MEC (ondansetron, alizapride and, if indicated, dexamethasone). Exclusion criteria comprehend patients that were treated with minimal or low emetogenic chemotherapy and over 18 years old.

Data collection

All data were manually extracted from electronic health records, including baseline variables (initials of name, number of registers, sex and age), diagnosis, type of care (SUS or health insurance), chemotherapy regimen used in cycle, level of emetogenicity and antiemetic prophylaxis (checking indication, dose and schedule - global adequacy).

Outcomes

To evaluate factors considered to have a possible effect on the risk of experiencing acute and delayed nausea and vomiting, the following outcomes were considered: acute and delayed CINV.

Definitions

To evaluated the factors that predispose acute and delayed CINV, acute nausea and vomiting corresponds to the onset of these events within 24 hours after the end of the last chemotherapy administration in the block, while delayed nausea and vomiting begins at the end of the acute phase and may last for 96 hours. However, for blocks with multiple days, the acute phase ends 24 hours after the last dose on the last day and the delayed one starts with the end of the acute phase, lasting up to 96 hours.[17]

A complete response was considered when there were no emetic episodes and no use of rescue therapy, while the overall adequacy of antiemetic therapy was when indication, dose and schedule were appropriate.

Data analysis

Group A were matched 1:5 to group B using propensity score based on sex and age. Propensity score were estimated using logistic regression. CINV was the dependent variable, and all covariates listed in Table 1 were independent variables.

Table 1. Baseline characteristics of included patients.

Variable	Description	Group A (n=12)	Group B (n=60)	*p*-value
Sex	Male	10 (83%)	38 (63%)	0.314
Access to the service	Public	4 (33%)	33 (55%)	0.214
Age (Median years, IQR)		8 (5–11)	5 (3 – 9)	0.411
Diagnostic	Bone tumors and sarcomas	3 (25%)	12 (20%)	0.691
	Solid tumors	4 (33%)	8 (13%)	0.106
	Non-malignant hematological diseases	0	2 (3%)	1.000
	Malignant hematological diseases	5 (42%)	38 (65%)	0.204
Chemotherapy	Cisplatin + Doxorubicin	4 (33%)	2 (3%)	-
	Cisplatin + Etoposide	1 (8%)	4 (7%)	-
	Doxorubicin	0	5 (8%)	-
	Fludarabine + total body index	0	6 (10%)	-
	Ifosfamide + Etoposide	4 (33%)	2 (3%)	-
	Others	3 (25%)	41 (68%)	-
Emetogenic level	Highly emetogenic chemotherapy	10 (83%)	41 (68%)	0.489
	Moderately emetogenic chemotherapy	2 (17%)	19 (32%)	0.322
antiemetic prophylaxis	Ondansetron	0	23 (39%)	-
	Alizapride	0	1 (2%)	-
	Prednisolone	0	1 (2%)	-
	Ondansetron; Alizapride	0	20 (34%)	-
	Ondansetron; Corticosteroid	0	7 (7%)	-
	Ondansetron; Alizapride; Corticosteroid	0	8 (12%)	-
	Ondansetron; Alizapride; Fosaprepitant	4 (33%)	0	-
	Ondansetron; Alizapride; Corticosteroid; Fosaprepitant	5 (42%)	0	-
	Ondansetron; Corticosteroid; Fosaprepitant	3 (25%)	0	-
Adequacy of antiemetic prophylaxis	Overall adequacy (indication and duration)	5 (42%)	6 (10%)	0.015
	According to international protocols	7 (58%)	-	-
Duration of the chemotherapy blocks (days)		3 ± 1	3 ± 2	0.160
Acute phase	Without nausea	3 (37)%	24 (51%)	0.354
	No vomiting	7 (64%)	24 (41%)	0.751
Delayed phase	Without nausea	3 (75%)	27 (70%)	1.000
	No vomiting	4 (100%)	27 (76%)	0.106

After collecting the data, a descriptive analysis was performed, in which the categorical variables were expressed by means of absolute and relative frequencies (%) for each group. Otherwise, through the results of the Kolmogorov-Smirnov test, the numerical variables (age and days of chemotherapy) were represented as mean and standard deviation or median with interquartile interval (IQR 25%-75%), according to rejection or failing to reject the null hypothesis. Then, a comparison was conducted between the groups using the chi-square or Fischer test for categorical variables and t-test or Mann-Whitney test for numerical variables. Variables with a *p*-value <0.20 were included in the multivariate analysis by logistic regression. In the multivariate analysis, we considered the variables that presented a *p*-value <0.05 as statistically significant. Values were expressed as odds ratio (OR), in uni or multivariate analysis, by adopting a 95% confidence interval (CI). OR values greater than 1 indicate predisposition to nausea and emesis. The sensitivity analysis was carried out in the multivariate analysis.

All statistical analyzes were performed using the IBM® Statistical Package for the Social Sciences (SPSS®) Statistics 20.0 software (Chicago, Illinois, U.S.).

RESULTS

This cohort comprised 72 patients (Table 1). The majority patients were male (n=48/72) with acute B lymphoid leukemia (n=33/72). In the propensity score-matched, these and other covariates were well balanced. Three variables showed some imbalances, where patients had different diagnosis, chemotherapy blocks and emetic prophylaxis.

Regarding antiemetic prophylaxis, 83% and 68% of groups A and B, respectively, used HEC chemotherapy. In addition, for group B, the drug most used for prophylaxis was ondansetron, followed by the combination of ondansetron with alizapride.

Furthermore, 42% of group A and 10% of group B met the criterion of global adequacy with a significant difference between the groups (*p*=0.015). It was noted that 58% (n=7) of the patients in group A were in accordance with international protocols regarding its administration as prophylaxis, i.e., it was not administered as a rescue medication. Of these 7 patients, 83% did not have vomiting in the acute phase and of the 5 patients who administered fosaprepitant as a rescue drug, 60% vomited in the acute phase.

In the acute phase, 59% and 36% of the groups A and B (*p*>0.05), respectively, had vomiting, while in the delayed phase 0% and 24% of the group A and B, respectively, had vomiting (*p*>0.05).

The clinical outcomes observed in the cohort are represented in Table 2. Patients with bone tumors and sarcomas had a higher predisposition to CINV in the acute phase, both by univariate analysis, (OR, 8.2, 95%CI 1.0-66, 6, *p*=0.050) and the multivariate (OR 10.0, 95%CI 1.1-88.9, *p*=0.039). Whilst for CINV in the delayed phase analysis, it is noted that CINV in the acute phase is considered a risk factor for this outcome (OR 11.8, 95%CI 1.1-130.5, *p*=0.044).

DISCUSSION

The occurrence of CINV, in both phases, has a negative impact on quality of life.[18,19] Undertreatment of CINV, mainly in the acute phase, can increase the number of admissions and hospital costs.[20,21] In this study, we identified the clinical profile of patients and the factors associated with CINV control in the acute and/or delayed phase. Our results demonstrate that in the acute phase, patients with bone tumors and sarcoma tend to be at higher risk for CINV, whereas in the delayed phase, the factor related to CINV is the uncontrolled acute phase.

In pediatric patients, the risk factors are not totally similar to adults.[9] Due to these discrepancies, some studies have been carried out to clarify this causal relation, demonstrating that age (Holdsworth et al. (2006):[22] complete protection: 0-2 y: 77%, 3-5 y: 64%, 6-8 y: 66%, 9-11 y: 51%, 12-14 y: 54% and 15-17 y: 60%; Kishimoto et al. (2017):[23] ≤2 years: OR 0.25 [95%CI 0.10-0.63] *p*=0.0003),[22,23] combination of ondansetron with NK-1 antagonist in the acute phase (Dupuis et al. (2020):[17] RR 1.28 [95%CI 1.09-1.50], *p*=0.0023) and greater control of acute phase (Dupuis et al. (2020):[17] RR 0.89, [95%CI 0.84-0.94], *p*<0.0001; Holdsworth et al. (2006):[22] among 421 courses that were not protected in the acute phase, there was significantly lower complete protection in the delayed phase, n=155 courses; 36.8%, *p*<0.001) [17,22] are factors related to CINV. These results corroborate with the findings of the present study, where once the acute phase is controlled, lower is the chance of delayed CINV. With the control of the phases, consequently, there will be a reduction in the incidence of symptoms, including anticipatory CINV, associated with the next cycles. Thus, patients are more susceptible to continue the treatment, choosing to continue receiving it for several cycles.[24]

Similar to our study, some previous reports[23,25,26] have shown that the combination with fosaprepitant resulted in a significant improvement of the control of CINV in pediatric patients (Kishimoto et al. (2017):[23] OR 0.25, [95%CI 0.10-0.63], *p*<0.001; Willier et al. (2019):[26] acute CINV phase: 25.0% vs. 66.7%, *p*=0.0017; delayed CINV phase: 42.5% vs. 79.5%, *p*<0.0001; Radhakrishnan et al. (2019):[25] acute CINV phase: 86% vs. 60%, *p*<0.001; delayed phase: 79% vs. 51%, *p*<0.001; overall phase: 70% vs. 41%, *p*<0.001), both in the acute and in the delayed phase. Especially in the delayed phase, where the concentration of substance *p* tends to be predominant.[7,8,27,28]

Moreover, in the present study, bone tumor appears as a predisposing factor to having CINV in the acute phase. This can be explained, possibly, by the fact that the protocols used in these malignancies contain HEC, following the classification recommended by Pediatric Oncology Group of Ontario (POGO).[10,29] Contrarily, malignant hematological diseases have lower emetogenic protocols, corroborating the results of univariate and multivariate analysis, which demonstrated no association with CINV in the acute or delayed phase.

Table 2. Univariate and multivariate analysis to assess factors related to CINV in the acute and delayed phases.

Variables	Acute phase (n=72)						Delayed phase (n=33)					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*
Male	1.6	0.6-4.6	0.368				0.4	0.1-1.6	0.182	3.2	0.4-24.8	0.273
Public health system	1.1	0.4-3.0	0.876				2.3	0.6-9.6	0.242			
Emetogenic level	1.6	0.5-5.1	0.427	2.3	0.6-8.3	0.209	03	0.1-1.5	0.135	0.8	0.1-11.0	0.896
Fosaprepitant	0.9	0.2-3.2	0.819				0.4	0.0-3.6	0.379			
Ondansetron	0.8	0.3-2.2	0.594				0.4	0.1-1.7	0.208			
Ondansetron; Alizapride	1.0	0.3-3.2	0.949				0.8	0.2-4.2	0.825			
Ondansetron; Corticosteroid	0.6	0.1-2.7	0.462				0.1	0.0-1.2	0.066			
Ondansetron; Alizapride; Corticosteroid	3.4	0.4-29.6	0.265				0.6	0.1-4.7	0.609			
Ondansetron; Alizapride; Fosaprepitant	0.9	0.1-10.2	0.915				0.7	0.0-11.9	0.795			
Ondansetron; Alizapride; Corticosteroid; Fosaprepitant	1.8	0.2-17.3	0.600				0.7	0.0-11.9	0.795			
Ondansetron; Corticosteroid; Fosaprepitant	0.4	0.1-3.2	0.398				0.7	0.0-11.3	0.768			
Overall adequacy (indication and duration)	0.7	0.2-2.8	0.650				0.1	0.0-1.2	0.073	0.1	0.0-3.8	0.231
Bone tumors and sarcomas	8.2	1.0-66.6	0.050	10.0	1.1-88.9	0.039	3.6	0.3-44.8	0.314			
Solid tumors	0.4	0.1-1.3	0.118	0.7	0.2-2.8	0.636	0.3	0.0-2.6	0.255			
Non-malignant hematological diseases	0.9	0.1-10.2	0.915				0.8	0.1-9.7	0.855			
Malignant hematological diseases	0.7	0.2-1.8	0.448				2.0	0.5-8.8	0.335			
CINV in acute and delayed phase	-	-	-				0.2	0.0-1.4	0.110	11.8	1.1-130.5	0.044

The limitations of the study were: the study design (retrospective), with the possibility of information loss during the process; and the study conduction in a single center, not necessarily can be applicable to others. Moreover, nausea is a subjective outcome and difficult to be measured in pediatric patients.[30] Despite this potential bias, the consistency of the observations supports the need to improve the antiemetic prophylaxis in order to obtain an optimal management of the CINV.

Despite these limitations, the present study provides information relevant to the choice of antiemetic prophylaxis for each individual for the best control of CINV in acute and delayed phases, where the incorporation of triple or double therapy may be a good choice to avoid these unpleasant adverse effects, taking into account that patients with bone tumors and sarcomas as well as the difficult control of the acute phase are predisposing factors.

In general, to improve control at this phase and, hence, at a delayed phase, it is essential to combine the clinical profile of the service and the patient's clinic with adherence to international antiemetic prophylaxis protocols that include aprepitant or fosaprepitant, when possible and applicable. The strategy for the control of CINV is the prevention of symptoms, avoiding the use of rescue drugs. Also, understanding the predisposing factors will facilitate the adjustment of the therapeutic regimen for each pediatric patient, enabling maximum comfort and quality of life.

CONCLUSION

In general, cancer patients who did not use fosaprepitant had low control of nausea and vomiting in the acute phase. Furthermore, this study demonstrated that patients undergoing HEC chemotherapy blocks and diagnosis with bone tumors and sarcomas are more susceptible to CINV in acute phase, and that inadequate control in acute phase can result in CINV in the delayed phase.

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