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Research

Retrospective Evaluation of Chemotherapy Induced Nausea and Vomiting in Pediatric Oncology Patients

Pediatrik Onkoloji Hastalarında Kemoterapiye Bağlı Bulantı ve Kusmanın Retrospektif Değerlendirilmesi

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ABSTRACT

Objective: Nausea and vomiting are among the most common and distressing side effects caused by chemotherapy. This study aimed to evaluate the effectiveness of the antiemetic protocol used in our center and to explore possible improvements.

Methods: In this study, the medical records of patients aged between 1 month and 18 years who were diagnosed with solid tumors and lymphomas and who received chemotherapy and radiotherapy in our clinic were retrospectively reviewed.

Results: Of the patients included in the study, 60.9% (n=53) were male, and 39.1% (n=34) were female. Among the 151 chemotherapy cycles administered, acute and delayed vomiting were observed in 26.5% and 18% of cycles, respectively. Refractory and anticipatory vomiting occurred in 6% and 18% of cases, respectively. Refractory vomiting was detected in adolescents, in the germ cell tumor group, and during the initial chemotherapy cycles. The lowest incidence of acute vomiting (0%-20%) occurred in patients who engaged in play activities or watched television or videos during treatment. In 70.2% of the chemotherapy cycles, granisetron was administered alone, while aprepitant was added in 23.2%.

Conclusion: Chemotherapy-associated vomiting is a frequent and undesirable side effect in pediatric patients. The relationship between nausea and vomiting and factors such as parental smoking, educational background, and activities during chemotherapy administration warrants further investigation.

Keywords: Nausea-vomiting, chemotherapy, childhood

ÖZ

Amaç: Bulantı-kusma kemoterapinin en sık neden olduğu, rahatsız edici yan etkilerdir. Bu çalışmada merkezimizdeki antiemetik protokolün etkinliğinin değerlendirilmesi ve antiemetik protokolün iyileştirilmesi amaçlandı.

Gereç ve Yöntem: Bu çalışmada kliniğimizde tedavi gören solid tümör ve lenfoma tanısı ile kemoterapi ve radyoterapi alan, 1 ay-18 yaş arasında olan hastaların dosyaları retrospektif olarak incelendi.

Bulgular: Çalışmaya alınan hastaların %60,9'u (n=53) erkek ve %39,1'i (n=34) kadındı. Hastalara verilen 151 kürün %26,5'inde akut kusma, %18'inde geç kusma görüldü. Dirençli kusma oranı %6, beklenti kusması oranı %18 idi. Dirençli kusma ergenlerde, germ hücreli tümör grubunda ve ilk kemoterapi kürlerinde saptandı. En yüksek akut kusma tek kemoterapötik ilaç alanlarda gözlendi. En düşük düzeyde akut kusma kür sırasında oyun oynayan, televizyon ve video izleyen hastalarda (%0 ile %20) gözlendi. Kürlerin %70,2'sinde granisetron tek başına verildi, %23,2'sinde aprepitant eklendi.

Sonuç: Kemoterapi ile ilişkili kusma çocukluk çağında sık görülen ve istenmeyen bir yan etkidir. Ebeveyn sigara içiciliği, eğitimi ve kemoterapi alırken yapılan aktivitelerle bulantı-kusma arasındaki ilişki irdelenebilir.

Anahtar Kelimeler: Bulantı-kusma, kemoterapi, çocukluk çağı

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INTRODUCTION

Nausea and vomiting are among the most common side effects of chemotherapy (1). They significantly impair the patient's quality of life and may lead to metabolic disturbances, malnutrition, and reduced physical and mental performance. Prolonged hospitalizations and delays in subsequent chemotherapy cycles are other undesirable consequences (2). Ultimately, nausea and vomiting can hinder the optimal delivery of treatment. In addition, chronic nausea and vomiting related to the disease or treatment may occur in patients with advanced-stage cancer or in those undergoing radiotherapy (3).

Nausea and vomiting caused by chemotherapy can be acute, delayed, anticipatory, or refractory. Acute vomiting refers to vomiting that occurs within the first 24 hours of chemotherapy. Delayed vomiting refers to vomiting that occurs between 24 hours and 5 days. Anticipatory vomiting occurs after prior chemotherapy and before treatment in subsequent cycles. Refractory vomiting refers to episodes of vomiting that persist despite antiemetic protocols. The frequency and severity of nausea and vomiting in patients receiving chemotherapy or radiotherapy can be influenced by numerous factors, including the dose and combination of chemotherapy agents; the radiotherapy target areas (such as total body, abdomen, or brain); and individual patient factors, such as age, sex, and comorbidities (4).

The availability of antiemetic drugs for children is limited. Over time, the administration of higher doses and more frequent dosing of chemotherapeutic agents, as well as the inclusion of newly developed anticancer drugs in treatment protocols, necessitates a re-evaluation of the adequacy of current antiemetic regimens. This study aimed to investigate the factors influencing chemotherapy-induced nausea and vomiting.

METHODS

Patients aged 1 month to 18 years who were diagnosed with solid tumors and lymphomas and who received chemotherapy and radiotherapy at our clinic between October 1, 2021, and July 21, 2022, were included in this study. Patients over 18 years of age and those diagnosed with leukemia were excluded. Data from 151 chemotherapy cycles administered to 87 eligible patients were retrospectively reviewed. Ethical approval was obtained from the Bursa Uludağ University Faculty of Medicine, Clinical Research Ethics Committee (approval no: 2021-13/7, date: 22.09.2021).

Patients' age, sex, oncological diagnoses, chemotherapeutic agents used in their protocols, date of the first chemotherapy session, dates of chemotherapy cycles considered for evaluation, and antiemetic medications used were recorded. If applicable, surgical history and radiotherapy status, including sites and doses, were evaluated. The presence of acute, delayed, anticipatory, and refractory vomiting was identified through medical records. The patients' social activities during chemotherapy [such as reading books, playing games on the phone, engaging in playdough, puzzles, or coloring, and watching television (TV) or videos] were documented. Patient activities were prospectively observed and recorded during the thesis period; however, the current study was designed as a retrospective analysis based on the review of these pre-existing records. The caregivers' educational background and the smoking status of both caregivers and patients were also assessed.

A standard form was created for each patient included in the study. The emetogenic potential of chemotherapy protocols was evaluated based on the literature (5,6). Based on the number of vomiting episodes in the medical records and data on appetite and nutritional intake, the severity of acute and delayed nausea/vomiting was determined (7). In our clinic, 5-hydroxytryptamine 3 (5-HT_3) receptor antagonists and dexamethasone or aprepitant are used as antiemetics in patients undergoing highly emetogenic chemotherapy. A 5-HT_3 receptor antagonist is used in patients receiving moderately emetogenic or low-emetogenic chemotherapy. Patients who continued to experience vomiting despite these treatments were assessed for their additional treatment needs.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics 22.0 software. Categorical variables were presented as frequencies (n) and percentages (%). Pearson's chi-square tests were used to compare oncological diagnoses, age, sex, chemotherapeutic agents, and number of drugs. The significance level was set at $p<0.05$.

RESULTS

Of the patients included in the study, 60.9% (n=53) were male and 39.1% (n=34) were female. The mean age at diagnosis was 9.08±5.43 years (range: 0.58-17.9 years). Among the patients, 32.2% (n=28) were younger than 5 years of age, 23% (n=20) were 5-9 years of age, 26.6% (n=23) were 10-14 years of age, and 18.4% (n=16) were 15 years of age or older.

When evaluated by diagnosis, the most common diagnoses were central nervous system tumors (19.5%; n=17), followed by malignant bone tumors (18.4%; n=16), germ cell tumors (13.8%; n=12), and non-Hodgkin lymphoma (11.5%; n=10) (Figure 1).

With respect to treatment modalities, 82.8% (n=72) of patients received chemotherapy, and 17.2% (n=15) received radiotherapy. Across the entire patient cohort, 12.6% (n=19) were undergoing their first chemotherapy cycle, while 87.4% (n=132) had previously received chemotherapy. According to the emetogenic risk of the chemotherapeutic agents administered, 95.4% (n=144) of chemotherapy cycles were classified as highly emetogenic, 3.3% (n=5) as moderately emetogenic, and 1.3% (n=2) as minimally emetogenic. Table 1 presents the patients' demographic characteristics and treatments received.

Acute vomiting was observed in 26.5% (n=40) of chemotherapy cycles. Among these cases, 20.8% (n=19) were observed in males and 35% (n=21) in females (p=0.062). Among participants older than 15 years, acute vomiting was present in 39.3% (n=13) (p=0.069). Delayed vomiting occurred in 18% (n=27) of chemotherapy cycles. Of these, 55.5% (n=15) and 44.4% (n=12) were observed in male and female patients, respectively (p=0.666). With respect to age, 12.1% (n=4) were older than 15 years (p=0.337).

Refractory vomiting was noted in 6.0% (n=9) of cycles. In all cases, the patients were aged 13.5 years or older. The male-to-female ratio was 8:1. Among those receiving their first chemotherapy cycle, the incidence of refractory vomiting was 15.5%, compared with 4.5% among those receiving subsequent cycles; this difference was not statistically significant (p=0.087). The distribution of patients by vomiting type is presented in Table 2.

When examining rates of acute and delayed vomiting by tumor type, 45% (n=18) of patients with acute vomiting had malignant bone tumors, while 18.6% (n=5) of patients with delayed vomiting had Wilms tumors. Patients with malignant bone tumors were the most likely to experience persistent vomiting despite receiving an antiemetic protocol appropriate for their diagnosis and required additional doses of granisetron. The use of aprepitant was most frequently required for malignant bone tumors and germ cell tumors (Figure 2 and Table 2).

Regarding additional therapies, 25 cycles (16.5%) included radiotherapy targeting the cranium, craniospinal axis, abdomen, pelvis, or thorax, administered non-concurrently with chemotherapy. Intrathecal therapy was administered over nine cycles. Additional doses of granisetron were required in 66.6% of cycles with intrathecal therapy and 33.4% of those without. This difference was statistically significant (p=0.004).

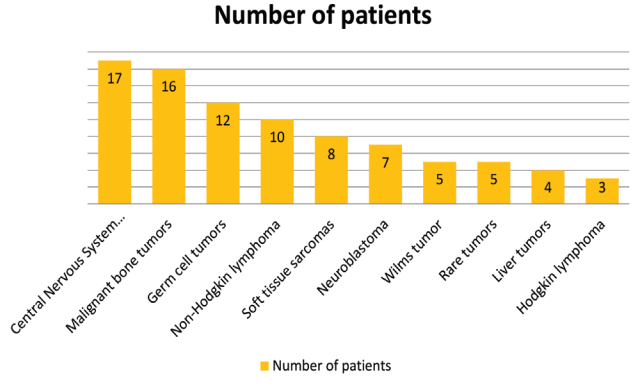

Figure 1. Distribution of patients by oncological diagnosis

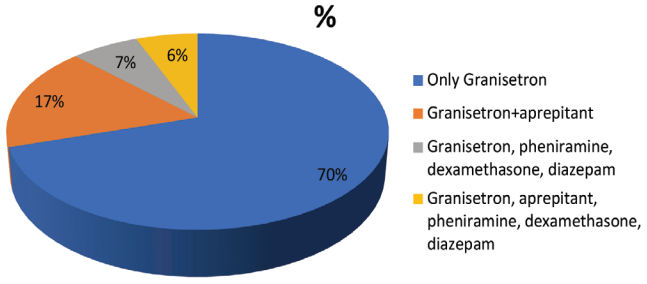

Figure 2. Antiemetic drugs used in patients

Table 1. Demographic data and treatments received by patients

Data	Number of patients	Percentage of patients (%)
Sex		
Female	34	39.1%
Male	53	60.9%
Age (years)		
<5	28	32.2%
5-9	20	23%
10-14	23	26.4%
>15	16	18.4%
Distribution of chemotherapy cycles by emetogenicity	**Number of cycles**	**Percentage of cycles (%)**
Low emetogenicity	2	1.3%
Moderate emetogenicity	5	3.3%
High emetogenicity	144	95.4%
Distribution by anticipatory vomiting		
With anticipatory vomiting	27	18%
Without anticipatory vomiting	124	82%
Distribution by acute vomiting		
With acute vomiting	40	26.5%
Without acute vomiting	111	73.5%
Distribution by delayed vomiting		
With delayed vomiting	27	18%
Without delayed vomiting	124	82%
Distribution by refractory vomiting		
With refractory vomiting	9	6%
Without refractory vomiting	142	94%

Table 2. Patients' tumor types and vomiting rates

Tumor type	Acute vomiting present n=40 (%)	Acute vomiting absent n=111 (%)	Delayed vomiting present n=27 (%)	Delayed vomiting absent n=124 (%)
Non-Hodgkin lymphoma	2 (5)	18 (16.2)	2 (7.4)	18 (14.5)
Hodgkin lymphoma	2 (5)	1 (0.9)	2 (7.4)	1 (0.8)
Neuroblastoma	0 (0)	9 (8.1)	2 (7.4)	7 (5.6)
CNS tumors	4 (10)	24 (21.6)	3 (11.1)	25 (20.2)
Soft tissue sarcoma	4 (10)	9 (8.1)	2 (7.4)	11 (8.9)
Malignant bone tumors	18 (45)	21 (18.9)	4 (14.8)	35 (28.2)
Liver tumors	1 (2.5)	5 (4.5)	1 (3.7)	4 (6.4)
Wilms tumor	5 (12.5)	5 (4.5)	5 (18.6)	5 (4)
Germ cell tumors	3 (7.5)	13 (11.7)	3 (11.1)	13 (10.5)
Rare tumors	1 (2.5)	5 (4.5)	3 (11.1)	3 (2.5)
Total	40 (100)	111 (100)	27 (100)	124 (100)

CNS: Central nervous system

Surgery was performed in 125 of the 151 chemotherapy cycles. An additional dose of granisetron was required in 32 of these cycles (25.6%), while it was not required in 93 cycles (74.4%). There was no significant association between surgery and the need for additional granisetron (p=0.819).

Patients' activities during chemotherapy were also assessed. Patients engaged in play during 68.8% (n=104) of cycles. Readings were observed in 30 cycles (19.8% of cycles). The incidence of acute vomiting during play and while watching TV or videos ranged from 0% to 20%, indicating a low frequency.

Among caregivers, 17% (n=14) were illiterate; 15% (n=13) had completed primary education; 30% (n=26) had completed middle school; 30% (n=26) had completed high school; and 8% (n=8) had completed university degrees. No association was found between caregiver education and the presence of early or delayed vomiting.

Caregiver smoking was reported in 23% (n=20), and patient smoking was reported in 2.3% (n=2). Among the 40 cycles with acute vomiting, 17.5% (n=7) had a smoking caregiver (p=0.387). Among the 27 cycles with delayed vomiting, 22.2% (n=6) involved a smoking caregiver, indicating a statistically significant association (p=0.017).

DISCUSSION

Adverse effects of treatment in pediatric oncology patients significantly compromise treatment adherence. Nausea and vomiting are the most common acute side effects (1). Very few randomized clinical trials have investigated antiemetic protocols in pediatric cancer patients. Moreover, both parents and healthcare professionals may underestimate nausea and vomiting when patients with cancer experience other serious medical problems. In particular, recognizing the severity of symptoms in delayed nausea and vomiting remains a challenge (8). At our center, data on pediatric patients with cancer receiving chemotherapy, including the effectiveness of the antiemetic protocol, were evaluated. Based on the results of this study, we aimed to improve control of patients' nausea and vomiting.

Nausea and vomiting are reported more frequently in females than in males, and more frequently in adolescents than in younger children (9-11). In our study, no statistically significant difference in sex distribution was found between patients with acute and delayed vomiting. When stratified by age group, the highest rate of acute vomiting was observed in patients older than 15 years.

Vomiting is more frequently observed in patients with tumors that exert pressure on the gastrointestinal organs or increase intracranial pressure (10). In our cohort, acute vomiting was most frequently observed in patients with malignant bone tumors, whereas delayed vomiting was most common in patients with Wilms tumor. In contrast, no acute vomiting episodes were observed among patients with neuroblastoma. In our clinic, treatments for Wilms tumor are administered in the outpatient chemotherapy unit, which consists of 10 beds. Therefore, we consider that the shared treatment environment may have contributed to acute vomiting. In this unit, chemotherapy is administered following granisetron infusion. Granisetron should ideally be administered half an hour before chemotherapy; however, this timing may not always be followed due to patient volume. In malignant bone tumors, the increased frequency of vomiting may be attributed to the high emetogenicity of the administered agents.

Refractory vomiting is more frequently observed in patients who do not receive adequate antiemetic prophylaxis during

their initial chemotherapy cycles (11). In our study, refractory vomiting was more commonly observed in older patients and in those with germ cell tumors. This may be related to the administration of platinum-based chemotherapy in germ cell tumors. Furthermore, anticipatory vomiting was observed in 17.9% of the cycles. These were patients in whom nausea and vomiting had not been adequately controlled during previous chemotherapy cycles. This suggests that stricter antiemetic management is necessary from the very first cycle.

The incidence of radiation-induced nausea and vomiting ranges from 40% to 80% (12). It is associated with either direct irradiation of tissues during radiotherapy or the release of emetogenic substances from the irradiated regions (7). In our cohort, radiotherapy was not administered concurrently with chemotherapy. Among patients who received radiotherapy, additional granisetron was most frequently required in those with a history of abdominal irradiation (50%). However, no statistically significant difference was found with respect to the irradiation site (p=0.827).

Surgical intervention is a fundamental component of oncology treatment. Nausea and vomiting of varying severity may occur following surgery (13). Surgeries lasting longer than 30 minutes, patients older than 3 years, and a family history of postoperative nausea and vomiting are among the factors that increase the risk of postoperative vomiting (14). At our center, chemotherapy cycles were administered at least six weeks after craniotomy, and between one and six weeks after other surgical interventions. No association was observed between surgical treatment and nausea or vomiting. Intrathecal therapy may cause nausea and vomiting. However, because sedatives and intravenous chemotherapeutic agents are often co-administered, it is difficult to determine which agent is responsible for the reaction. In patients with leukemia, excellent antiemetic responses have been achieved with prophylaxis among those receiving intrathecal methotrexate and intravenous vincristine (15). In our study, intrathecal therapy was administered to patients diagnosed with non-Hodgkin lymphoma according to standard chemotherapy protocols. Midazolam was used for sedation. No routine antiemetic prophylaxis was administered before the procedure, and 66.6% of these patients required granisetron afterward.

International pediatric oncology groups, such as the Children's Oncology Group, define the treatment of chemotherapy-induced nausea and vomiting as a cornerstone of supportive care in pediatric patients with cancer (16). Due to its minimal side effects and lower interindividual metabolic variability, granisetron is often preferred in clinical practice. In our study, granisetron was the most commonly used antiemetic. In Türkiye, relatively low use of aprepitant is attributed to reimbursement restrictions. The study highlighted the need to increase training in the effective use of antiemetic guidelines.

In addition to pharmacological measures, complementary approaches that promote patient comfort are recommended for the prevention of chemotherapy-induced nausea and vomiting. Non-pharmacological strategies such as mindfulness, distraction, and relaxation techniques may be employed (17). However, evidence supporting the efficacy of non-pharmacological methods remains limited, and they are therefore not included in most standard guidelines (18). The Pediatric Oncology Group of Ontario guidelines include these measures only as weak recommendations (19,20). In our study, lower frequencies of acute vomiting were observed among patients who engaged in play activities or watched TV or videos during chemotherapy. However, no association was observed between these activities and delayed vomiting.

Parents' education level may lead to improved monitoring of children with chronic illnesses. However, we found no studies investigating the relationship between chemotherapy-induced nausea and vomiting and parental education level. While we believe that parents with higher education levels may report nausea to healthcare personnel more promptly, no statistically significant association was found in our study.

Among adults receiving chemotherapy, those who smoke experience nausea and vomiting more frequently than non-smokers (21). In our study, there was no statistically significant difference in the incidence of vomiting between patients with smoking caregivers and patients with non-smoking caregivers. Nevertheless, we believe that unpleasant odors from caregivers who smoke may trigger nausea and vomiting in children.

Study Limitations

The study may have included a limited number of patients and was conducted at a single center, which may limit the generalizability of the findings. Differences in age, type of cancer, chemotherapy protocols, and supportive care regimens may have introduced variability that influenced the results.

CONSLUSION

Chemotherapy-induced nausea and vomiting are common adverse effects. Further studies may be needed to reduce these side effects in pediatric cancer cases. Administering

effective antiemetic treatment during therapy enhances both treatment success and patient adherence. Further research into alternative treatments may improve adherence among pediatric patients. In addition to clinical factors, our study uniquely evaluated the potential associations of parental smoking, patients' activities during chemotherapy, and parental education level with chemotherapy-induced nausea and vomiting in a pediatric population.

Beyond pharmacological antiemetic strategies, clinicians should emphasize supportive care interventions in the management of chemotherapy-induced nausea and vomiting. Developing standardized institutional chemotherapy-induced nausea and vomiting protocols and regularly monitoring their implementation and feasibility in clinical practice may improve symptom control in pediatric patients.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Bursa Uludağ University Faculty of Medicine, Clinical Research Ethics Committee (approval no: 2021-13/7, date: 22.09.2021).

Informed Consent: Retrospective study.

FOOTNOTES

Derived from Gunel Abdulaliyeva's thesis.

Authorship Contributions

Concept: A.T., Design: A.T., Data Collection or Processing: G.A., G.R.A., Analysis or Interpretation: G.A., Literature Search: G.A., Writing: G.A., A.T., B.B.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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