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Outcome of antiemetic prophylaxis among pediatric cancer patients receiving moderate to highly emetogenic chemotherapy at pediatric hemato-oncology ward of Tikur Anbessa specialized hospital: A prospective, observational, longitudinal study

By: Hawaryaw Mathewos (B.Pharm)

A Thesis Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in Partial Fulfillment for the Requirements of Master of Science Degree in Pharmacy Practice.

June, 2023
Addis Ababa, Ethiopia

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June, 2023
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This is to certify that the thesis prepared by Hawaryaw Mathewos, entitled: ***"Outcome of antiemetic prophylaxis among pediatric cancer patients receiving moderate to highly emetogenic chemotherapy at pediatric hemato-oncology ward of Tikur Anbessa specialized hospital: A prospective, observational, longitudinal study"*** and submitted in partial fulfillment of the requirements for the Degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the University and meets the accepted standards concerning originality and quality.

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Abstract

Outcome of antiemetic prophylaxis among pediatric cancer patients receiving moderate to highly emetogenic chemotherapy at pediatric hemato-oncology ward of Tikur Anbessa specialized hospital: A prospective, observational, longitudinal study

Hawaryaw Mathewos

Addis Ababa University, 2023

Background: Chemotherapy induced nausea and vomiting (CINV) remains to be an important concern in pediatric patients receiving chemotherapy. However, outcomes of antiemetic prophylaxis in pediatric cancer patients are not well studied, especially in developing countries like Ethiopia.

Objective: The study objective is to determine the outcome of antiemetic prophylaxis among pediatric cancer patients admitted at Tikur Anbessa specialized hospital Addis Ababa Ethiopia.

Methods: A longitudinal prospective observational study design was carried out. Patients were prospectively observed for up to 120 hours post chemotherapy. The proportion of patients who had a complete response (no vomiting, no retching, and/or no need for rescue therapy) in the acute, delayed and overall phases was evaluated using descriptive statistics. Binary logistic regression was used to identify risk variables associated with the outcome of antiemetic prophylaxis with a p-value of 0.05 and 95 % confidence interval (CI). The Kaplan–Meier method was used to assess the time to first emesis event. Cox regression was used to analyze factors associated with the first emesis event using hazard ratio.

Results: A total of 201 pediatric cancer patients were studied. The majority of patients 75.1% in the acute and 63.7% in the delayed phase received combination prophylactic antiemetics regimen. In the acute, delayed, and overall phases, the complete response rates were 71.1%, 68.2%, and 51.2%, respectively. A daily range of 0-8 episodes of emesis per single patient was observed in acute phase and 0-18 episodes in delayed phase. Emesis peaked on day one of treatment, occurring among 28.4% of patients and, decreased steadily throughout follow-up. Multivariable analysis revealed that emesis during the acute phase was associated with a history of motion sickness ([OR] odds ratio, 4.31, 95% CI [1.93, 9.64]), platinum-based chemotherapy (OR 5.42, 95% CI [1.97, 14.98]) and with a history of prior CIV (OR 5.02, 95% CI [2.24, 11.23]). Emesis during the delayed phase was associated with a multiple-day chemotherapy (OR 6.44, 95 % CI [1.9, 21.98], a history of prior CIV (OR 6.27, 95% CI [1.81, 21.7]), a receipt of rescue antiemetics at the acute phase (OR 3.85, 95% CI [1.18, 12.6]), and a history of motion sickness (OR 3.2, 95% CI [1.34, 7.61]). However, the likelihood of CIV was found to be reduced when steroids were present in the

chemotherapy regimen, (OR 0.16, 95 % CI [0.04, 0.73]). The time to first emesis event was markedly late in patients who took moderate emetogenic chemotherapy compared to high emetogenic chemotherapy (log rank test, P=0.025). In the overall observation period, a faster rate of first emesis event was associated with a receipt of concomitant intrathecal chemotherapy (hazard ratio [HR] 6.11, 95% CI= [1.51, 24.8]), a history of prior CIV (HR 2.0 95% CI= [1.01, 3.94]), platinum-based chemotherapy (HR 2.22 95% CI= [1.22, 4.02]), and a history of motion sickness (HR 2.1 95% CI= [1.36, 3.12]).

Conclusion: A considerable number of participants could not achieve complete response. The platinum-based regimen, a history of motion sickness, and a history of prior CIV were found to have the poorest emesis control during the acute and delayed phases. Better CIV control was observed with combination antiemetic prophylaxis regimens. A delayed onset of emesis was observed with moderate emetogenic chemotherapy compared to high emetogenic chemotherapy.

Key words: Chemotherapy-induced, Vomiting, Antiemetic, Pediatrics

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Abbreviations & Acronyms:

5-HT3 RA - 5-hydroxytryptamine 3 receptor antagonist

AAU- Addis Ababa University

AC- Anthracycline

AHR- Adjusted Hazard Ratio

ALL- Acute Myeloid Leukemia

AOR- Adjusted Odds Ratio

CHS- College of Health Sciences

CINV - Chemotherapy-Induced Nausea and Vomiting

CIV- Chemotherapy-Induced Vomiting

CIN- Chemotherapy-Induced Nausea

CNS- Central Nervous System

CR - Complete Response

CTX- Cyclophosphamide

DERC- Department Ethical Review Committee

ERC - Ethics and Research Committee

ESMO - European Society of Medical Oncologists

HEC - High Emetogenic Chemotherapy

HR- Hazard Ratio

IV - Intravenous

IT- Intrathecal

MASCC - Multinational Association of supportive Care in Cancer

MAM- Moderate Acute Malnutrition

MEC - Moderate Emetogenic Chemotherapy

MHA- Methotrexate–Hydrocortisone–Cytarabine

MTX- Methotrexate

NK1 RA - Neurokinin- 1 Receptor Antagonist

MSc. - Master of science

OR- Odds Ratio

PLT- Platinum

POGO - Pediatric Oncology Group of Ontario

RCT- Randomized Clinical Trial

RR- Relative Risk

SAM- Severe Acute Malnutrition

SoP- School of Pharmacy

SPSS - Statistical Package for Social Sciences

TASH- Tikur Anbessa Specialized Hospital

1. Introduction

1.1 Background

Chemotherapy-Induced Nausea and Vomiting (CINV) is considered to be one of the many terrible and worried about side effects of cancer therapy [1, 2]. It often has considerable detrimental effects on the quality of life of cancer patients and is quite difficult for patients and providers to manage in oncology [3]. These two most common and troublesome side effects, nausea and vomiting (CINV), may decrease compliance; patients in some cases postpone chemotherapy cycles and plan to refuse treatment in the future due to the worry about anticipatory CINV [4].

Despite the fact that vomiting and nausea are collectively categorized in CINV, and frequently present concurrently, they may also present separately [5]. A sense of soon-to-be vomiting characterizes nausea [6]. Usually nausea can occur before vomiting, however in the case of severe nausea it may occur despite the occurrence of vomiting [6]. Vomiting is defined as evacuation of the contents of the gut via the mouth and gagging or retching; it also involves a profuse discharge of saliva and shiver [7]. Based on the onset time there are five unique CINV groups of symptoms that may be used to categorize vomiting during chemotherapy [7].

Different treatment plans are needed for each of the CINV syndromes (anticipatory, acute, delayed, breakthrough, and refractory), that usually comprise corticosteroids, serotonin (5-HT3) receptor antagonists, and neurokinin (NK1) receptor antagonists [8]. CINV symptoms may occur at different phases of chemotherapy. Acute vomiting is regarded as a vomiting that occurs 24 hours following chemotherapy initiation and mostly mediated by serotonin [1, 9]. Although antiemetic prophylaxis is provided, almost 13% of patients encounter acute vomiting and 35% develop acute nausea [10, 11]. Central nervous system's NK1 receptors are the primary mediator of delayed CINV, which develops 25–120 hours (5 days) following treatment [1, 9]. After antiemetic prophylaxis, delayed nausea and vomiting is encountered by 20–50% of people [11, 12]. Anticipatory CINV can be described as nausea and vomiting that happen prior to chemotherapy treatment as a result of CINV occurring in earlier cycles [13]. According to the Pediatric Oncology Group of Ontario (POGO), 8 to 14% of children suffer anticipatory CINV and it becomes more likely with every consecutive treatment cycle [14]. Breakthrough CINV usually demands the administration of rescue antiemetic medication, and around 44% of patients, despite antiemetic prophylaxis, develop it within five days of chemotherapy [15]. Refractory CINV developed during subsequent chemotherapy cycles as a

result of prophylactic antiemetic medications failure on earlier chemotherapy cycles, and it is resistant to antiemetic treatment or prophylactic medication adjustment [8, 16]

In the pediatric population, the main recognized risk factor for CINV is emetogenicity [17]. Additionally, emetogenicity, or a medicine's ability to cause vomiting or retching, has a significant influence on antiemetic prophylaxis; in the case of combination chemotherapy, emetogenicity is assessed using the combination's most emetogenic agent [18-20]. Accordingly, clinical practice guidelines outline antiemetic prophylaxis recommendations depending on the child's chemotherapy: minimal, low, moderate, and high [20, 21]. The use of antiemetics in children is guided by a number of standardized international guidelines, all of which generally accept the aforementioned classification of emetogenicity. Two such guidelines are the POGO [20], and the multinational association of supportive care in cancer (MASCC/ESMO) [21].

The paradigm for the prophylaxis of CINV has developed to encompass many classes of antiemetic medicines that target distinct receptors involved in the CINV process. [9, 22]. Antiemetic medicines such as serotonin antagonists, corticosteroids, NK antagonists, dopamine antagonists and cannabis are now utilized to prevent and treat CINV. Based on the chemotherapy's risk of emetogenicity, these medications can be administered alone or in combination. For a prophylaxis and treatment of CINV, the majority of practical evidence-based guidelines, POGO [20], MASCC/ESMO [21] and NCCN [9], advise using three or four-drug antiemetic regimens according to the emetogenicity of the chemotherapy regimen. According to the aforementioned guidelines, 5-HT3 RA monotherapy is advised for low emetogenic chemotherapy (LEC), a combination of 5-HT3 RA and corticosteroids is advised for moderate emetogenic chemotherapy (MEC), and a triple combination of corticosteroids, 5-HT3 RA, and NK-1 RA is advised for high emetogenic chemotherapy (HEC) [9, 20, 21].

Without any sort of prophylaxis, patients taking MEC or HEC typically have a 30 to 90% or more likelihood of developing emesis [23]. A randomized trial that included cancer patients in 1979 revealed an overall 83% of chemotherapy induced vomiting (CIV) incidence [24]. An observational study conducted two decades afterwards utilizing recently developed antiemetics revealed that 13% and 35% of patients receiving HEC and MEC had acute vomiting and nausea, respectively [10]. Many needs remain unmet, including the management of delayed CINV, creating effective CINV management protocols for patients on a multi-day chemotherapy, and offering choices for patients that remain susceptible to CINV in spite of therapy [8]. More research is needed to improve CINV management [8].

1.2 Statement of the Problem

Even with the advancement of more potent antiemetics, CINV continues to be one of the key concerns for the majority of pediatric patients receiving chemotherapy [8, 25]. According to estimates, up to 70% of children receiving chemotherapy may develop CINV [21]. This estimate is comparable to prevalence rates reported in adult patients, where they range between 60% and 72% [26]. Additionally, the solutions offered to pediatric patients are relatively limited. Following chemotherapy treatment, the likelihood of developing nausea and vomiting is influenced by a number of variables. Age and sex are two of these determinants, with female patients [27-29] and younger patients [29] having higher risk levels. Furthermore, according to studies done on adults, some patient traits, such as having a history of CIV [30], and a history of motion sickness [29] seem to indicate a higher frequency of CINV. However, these traits have not been clearly identified in youngsters [25]. Many risk factors for CINV in adults seldom readily relate to the pediatric population, in addition the risk variables that are unique to pediatrics are still not thoroughly investigated [31].

In comparison to adults, research on the effectiveness of antiemetic drug regimens in pediatrics is scant [32]. Although the antiemetic medications in use are largely the same, there is a limited amount of information about their effectiveness in pediatrics, especially in regard to the new therapeutic classes [33]. Furthermore, there are pediatric-specific treatment factors that need to be addressed, including the fact that pediatric regimens are frequently given over extended periods of time and frequently use multiple medicines given over several days [34, 35].

In pediatric patients, uncontrolled CINV can lead to significant consequences [21]. These consequences, including low appetite, weight loss, dehydration, electrolyte imbalance, and renal insufficiency might have an impact on the patients' physical health [1]. A recent observational survey of pediatric cancer patients receiving a steroid (dexamethasone) plus a 5-HT3 RA as a prophylaxis protocol reported that only 23% had complete CIV control during acute phase, 57% had complete acute CIV control, and 70% had complete CIV control during the delayed phase [17]. This finding backs up another study's [36] claim that most children with cancer do not achieve complete CINV control. CIV control is regarded as, according to FDA and POGO, having no vomiting, no retching and no requirement of antiemetics other than those prescribed for CINV prophylaxis. [37, 38].

From prior studies done in other countries, the outcomes of antiemetic prophylaxis and incidence of CINV in children were not documented well [39]. Just as recently as ten years back, there were few guidelines regarding

prophylaxis of CINV and scant historical data on the CINV prevalence in pediatrics [20]. Studies are much more difficult to come by when it comes to developing nations, who also face the sad dilemma of having only limited access to those extremely potent antiemetics. There has been one study conducted among adult cancer patients in Ethiopia, which indicated that 64.1% of patients experienced CIV (37.3% acute, 50% delayed) [40]. To date, no published study has been undertaken in Ethiopia to assess the outcomes of antiemetic prophylaxis or the prevalence of CIV among the pediatric cancer population. Thus, this study was carried out to address this gap through determining the outcomes of antiemetic prophylaxis among pediatric cancer patients admitted to Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia.

1.3 Significance of the Study

This study evaluated the outcomes of antiemetic prophylaxis among pediatric cancer patients at TASH. The results of this investigation can be used as a baseline information to estimate the incidence and control level of CIV among pediatric cancer patients in the hospital setting following HEC and/or MEC. Additionally, the information will help TASH assess existing protocols for managing CINV in pediatric patients and optimize antiemetic prophylaxis for pediatric cancer patients. Furthermore, pinpointing the association between CINV occurrence and relevant predictive indicators can assist in concentrating upon the appropriate variables when managing this medical condition. The study will undoubtedly aid towards raising awareness on pediatric CINV management and aid pediatric cancer patients receive the necessary and proper treatment for CINV. Since there has not been any study on CINV among pediatric patients in Ethiopia, this work will serve as a reference point for any researchers or professionals working on similar studies.

2. Literature Review

A review of the literature, including PubMed, MEDLINE, and Google Scholar, was conducted to assess the impact of CINV on children cancer patients. Pediatric, children, adolescent, cancer, and chemotherapy-induced nausea and vomiting were amongst the search terms. The goal of this review is to comprehend the latest recommendations for preventing CINV, determine antiemetic prophylaxis outcomes in various studies, assess the occurrence of CINV and identify pediatric chemotherapy-induced vomiting evaluation methodologies used in pediatric oncology.

2.1 Incidences of Chemotherapy Induced vomiting

Clinicians could appropriately record the incidence of acute CINV, but frequently (in about 75% of instances) underreported delayed vomiting and nausea incidence following chemotherapy, according to the research by Grunberg et al [10]. This would imply that delayed CINV is poorly handled since effective therapy requires knowledge of the issue [41]. Antiemetic medication modifications depending on the patients' actual degree of CINV have not traditionally been included in trial procedures. As a result, nothing is actually known regarding the effectiveness of treating CINV while receiving chemotherapy. Particularly, almost nothing is understood with regard to the modifications which are implemented to the selection of antiemetics in routine clinical settings.

2.1.1 CIV Incidence within HEC

A prospective observational investigation that compared the safety, effectiveness as well as cost-benefit of triple antiemetic combination regimen of aprepitant plus dexamethasone plus palonosetron versus olanzapine amongst patients undergoing HEC reported a complete response (CR) of 86% in the acute phase, 86% in the delayed phase and 80% in the overall phase in the aprepitant-based triple regimen, while from the olanzapine group reported a CRs of 84%, 88, and 78% [42]. As a result, this study from India displayed that olanzapine is an acceptable substitute as a prophylaxis of CINV in patients receiving HEC. Furthermore, the utilization of triple therapy with a NK_1 RA in HEC backs the multinational association of supportive care in cancer guideline suggestions [21].

2.1.2 CIV Incidences within MEC

Regardless of the use of antiemetic prophylaxis, an observational and prospective investigation involving cancer patients undergoing treatment with MEC found that the overall phase (120 hours) incidence of CIV

was 42% and the incidence of Chemotherapy induced nausea (CIN) was 20.8% [11]. When looking at the antiemetic agents used in this study, we see that a combination of dexamethasone and 5HT3 RA was used by 94.9% of the patients, a combination of dexamethasone and metoclopramide was used by 4.7% of the patients during the acute phase, and there was one patient who did not receive any prophylaxis, and similarly in the delayed phase, 56.2% of patients did not receive any prophylaxis [11]. So, in this study [11], the CR was observed in 84.2% of the participants during the acute phase, in 77% of the participants during the delayed phase and in 68.9% of the participants during the overall phase. Another observational study reported better CR outcome in the delayed phase, which is claimed to be caused by aggressive dexamethasone use in the delayed phase; in this study, among 201 patients undergoing treatment with MEC where dexamethasone is used through day one to three while a 5HT3 RA is used on day one, a complete response (no emesis) was observed with 95.5% of the patients during the acute phase and 92% of the patients during the delayed phase [43].

2.1.3 Incidence of CIV within Studies involving HEC and MEC

The percentage of patients who experienced CIV CR in the acute, delayed, and (acute plus delayed) overall phase was 72.4%, 65.5%, and 58.6%, according to an RCT [44] that assessed pediatric patients in Japan who were treated with HEC or MEC and were between the ages of 28 days and 18 years. As stated by a Kenyan observational study [45], complete responses were 53.41% in the acute, 55.68% in the delayed, and 34.1% in the overall phases. In this Kenyan study, 5HT3 receptor antagonists with or without dexamethasone were utilized, and only 11.4% of the participants had delayed phase prophylaxis. Likewise, a retrospective study [46] discovered that in cycle-based analysis, CR was attained in each patient in 63% of the initial cisplatin-based cycles and in 43% (46 of 107) of the total cycles. Acute and delayed CIV had been both noted in the study, occurring in 39 (36%) and 51 (48%) cycles, respectively.

In a noninferiority trial [47], 67% complete CIV control rate were observed in a subcategory of 339 MEC patients receiving ondansetron during the acute phase. In the study an unknown number of children received dexamethasone but its dosage was non-standardized. Furthermore, in one prospective study, children taking MEC and a 5HT3-receptor antagonist palonosetron had attained an 84.1% complete acute CIV control rate [48]. In all the above studies the emetogenicity level was determined using the 2019 and 2013 POGO guideline [20, 34] recommendations.

2.2 Risk factors associated with CINV

The occurrence of CINV has been scientifically linked to a number of risk factors. Numerous patient-specific variables had been demonstrated to be correlated with the risk of developing CINV in studies, along with clinical or treatment-specific variables like chemotherapy medication's emetogenicity and dose [49, 50]. These patient-specific factors consist of age, sex, and a substantial anticipatory nausea.

A recently published follow-up study of a formerly conducted prospective, multicenter trial [51], found that acute CINV was correlated children undergoing treatment with HEC. Furthermore, the study [51] found that inadequately controlling acute CINV was associated with a high likelihood of developing CINV delayed as well as receipt of cisplatin, and malignancies other than CNS origin were also associated with delayed CINV. The risk variables associated with both phases were examined utilizing the generalized estimating equation technique in this study.

A retrospective cohort study [52] among pediatrics undergoing MEC or HEC where antiemetic therapy to the HEC was fosaprepitant, ondansetron ± dexamethasone and also antiemetic prophylaxis for the MEC was alizapride, ondansetron, with or without dexamethasone revealed that acute phase CINV was correlated with non-hematological tumors (bone and sarcomas) (AOR=10.0 95%CI, 1.1-88.9, P= 0.039). The study also showed that patents who do not achieve an acute phase complete response have increased risk for delayed CINV (AOR= 11.8, 95% CI, 1.1, 131, P=0.044). Similarly, in individuals who took fosaprepitant or aprepitant, absence of a CR during the acute phase was related with development of delayed chemotherapy induced vomiting ([RR], 1.2; 95% CI, 1.1, 1.34) [31]. Additionally, the aforementioned study by Dupuis et al. [31], it was revealed that in pediatric who were getting antiemetic prophylaxis for MEC or HEC, a less prolonged acute-phase, and receipt of neurokinin-1 antagonists-based combination antiemetic protocol were all linked with a CR. More research needs to be conducted in this area to assess the practicality of customizing antiemetic preventive therapy to include patient-specific risk variables in pediatric cancer patients.

2.2.1 Age and Sex

One of the risk variables for development of CINV has been identified to be younger ages in adults [50] and age was also cited as a risk factor in pediatric [31]. In a study [31] aimed at assessing factors associated with CIV control among pediatric patients reported that CR in the acute phase was more uncommon in older pediatric patients (RR, 0.97). It was also shown by Holdsworth et al. [53] that CR in age group of 0-2 years of children is higher (77%) than older age group children. Another study demonstrated that the patient's age

represents one of a significant critical clinical variables impacting the failure to attain CR in children with acute leukemia of myeloid origin [54]. Additionally, the risk of CIV has been associated with older age (age >5 years) in two studies [53, 55] and age >2 years in one retrospective study [46]. The one retrospective study [55] that was cited earlier constituted that age > 5 years as risk for CIV occurrence (OR; 2.5, P =0.008). According to the findings of these publications, the incidence of CINV after antiemetic prophylaxis in children varies across patient's age. Although the explanation for the cause of this age impact is yet unknown, endogenous cortisol production has been suggested as a potential factor [53].

The development of CINV in adult cancer patients has been linked to female sex as a predictive factor. [27]. Similar to this, a retrospective study [55] found that females constituted a greater risk for incidence of CIV in pediatric patients with newly diagnosed ALL (OR 2.5 95%CI 0.2-0.8, P = 0.007).

2.2.2 Emesis history and other factors

Anxiety, concomitant opiate usage, and consumption of alcohol have all been proven to be risk factors of CIN as well as a previous history of nausea from different causes such as motion sickness, (morning-sickness) gestation-related nausea, or prior CIN) has additionally been identified as a factor to consider [56].

2.2.3 Emetogenicity of chemotherapy

For inherent emetogenicity potential anticancer agents are classed based on their ability to cause nausea and vomiting, without considering the use of any antiemetic prophylaxis [57]. Children have also been found to have poor control of CINV with a HEC (cisplatin-based regimens) receiving an antiemetic regimen of 5HT3RA and dexamethasone [53]. Chemotherapeutic compounds have been widely grouped into four primary groups as shown in the table beneath (high, low, minimal and moderate emetogenic chemotherapy agents). Therefore, the patient's current regimen's potential for emetogenicity plays a major role in the antiemetic prophylaxis selection [22].

Table 1: Classification of Emetogenic Risk of Anticancer Medications According to the Most Recent POGO Guidelines [20]

High risk (> 90%)		Moderate risk (30-90%)	
Single-agent regimens	**Multiple-agent regimens**	**Single-agent regimens**	**Multiple-agent regimens**
IV Methotrexate ≥ 12 g/m2	Actinomycin D ≥ 1 mg/m2/dose + Cyclophosphamide ≥ 600 mg/m2/dose	IV Cytarabine 75 mg/m2	IV Methotrexate120 mg/m2 + Cytarabine 60 or 90 mg/m2 +
Actinomycin D IV ≥ 1.35 mg/m2	Ifosfamide IV ≥ 1.2 g/m2/dose + Etoposide IV ≥ 60 mg/m2/dose	Doxorubicin IV 25 mg/m2	Doxorubicin liposomal IV 20–50 mg/m2 + topotecan PO 0.6
Asparaginase IV ≥ 20 000 IU/m2	Actinomycin D 900 micro g/m2/dose IV + ifosfamide 3 g/m2/dose	Cyclophosphamide IV 1000 mg/m2	mg/m2/day
Busulfan IV ≥ 0.8 mg/kg	Doxorubicin IV ≥ 60 mg/m2/dose + Dacarbazine ≥ 250 mg/m2/dose IV	Actinomycin D IV 10 micro g/kg	Prednisolone + etoposide IV 100 mg/ + cytarabine IV 100 mg/m2/
Cyclophosphamide IV ≥ 1200 mg/m2	Doxorubicin ≥ 40 mg/m2/dose + Cyclophosphamide ≥ 400 mg/m2/dose	IT Methotrexate	dose + daunorubicin IV 45 mg/m2 + m2 + thioguanine PO
Carboplatin IV ≥ 175 mg/m2	IV Methotrexate ≥ 150 mg/m2/dose + Cytarabine ≥ 90 mg/m2/dose IV	IV Methotrexate IV 5 g/m2	80 mg/m2
Cytarabine IV ≥ 3 g/m2/day			
Cisplatin IV ≥ 12 mg/m2			
Doxorubicin IV ≥ 30 mg/m2			
Low risk (10-30%)		**Minimal risk (<10%)**	
Single-agent regimens	**Multiple-agent regimens:**	**Single-agent regimens**	**Multiple-agent regimens**
IV Methotrexate 38-83 mg/m2	IV Methotrexate 90 mg/m2 + Cytarabine IV 60 mg/m2	Doxorubicin IV 10 mg/m2	Methotrexate PO ≤ 0.1 mg/kg/
IV cyclophosphamide ≤500 mg/m2		Vincristine IV ≤ 1.5 mg/m2	day + mercaptopurine PO ≤ 2.5 mg/kg
Mercaptopurine PO ≤ 4.2 mg/kg		Mercaptopurine PO ≤ 4.2 mg/kg	Intra-arterial doxorubicin ≤ 30
Imatinib PO 260 mg/m2/day		Doxorubicin Liposomal IV ≤ 50 mg/m2	mg/m2/dose + intra-arterial cisplatin ≤ 60 mg/m2
Melphalan PO 0.2 mg/kg		L-asparaginase (*Escherichia coli*) Intramuscular ≤ 6000 IU/m2	
Procarbazine PO 50-100 mg/m2/d		PO/subcutaneous Methotrexate ≤ 10 mg/m2	
Erlotinib PO 35-150 mg/m2/d		PO Chlorambucil ≤ 0.2 mg/kg/d	
PO cyclophosphamide 2-3 mg/kg			

2.3 Antiemetic medication used in CINV

2.3.1 Serotonin receptor antagonists

In any CINV prophylaxis regimen, 5-HT_3 receptor antagonists play a crucial role and are the backbone of prophylactic protocols for HEC and MEC [20, 58]. They work on targets found in peripheral and CNS sites, including vagal afferents in the colon and the region postrema [20]. These 5-HT3 receptor antagonists are classified based on generation; From first-generation ondansetron, tropisetron, granisetron and from second-generation palonosetron are endorsed for usage in children [21]. According to a Cochrane review [59], granisetron was more efficient than ondansetron in children, whereas palonosetron with its 30-times increased ligand binding capacity and prolonged half-life, was also found to be more efficient than the earlier generations in controlling delayed CINV. This review assessed a variety of antiemetics in pediatrics reinforced the effectiveness of 5-HT3 RAs in chemotherapy undergoing patients. Furthermore, the review [59] found that ondansetron with dexamethasone was considerably more effective than either medicine alone. Therefore, whether used in conjunction with a corticosteroid, an NK1 receptor antagonist, or both, these medications are useful in treating and prevention of acute and delayed CINV [21].

2.3.2 Corticosteroids

Corticosteroids are utilized for prevention of CINV in acute and delayed phases since they are affordable and efficacious antiemetic medicines [21]. The most widely utilized of these drugs are the two synthetic corticosteroids dexamethasone and methylprednisolone [20]. While the effectiveness of various steroids is comparable, availability in a variety of formulations, guideline recommended dosage, and frequency made dexamethasone to be the preferable option[60]. Despite the fact that the precise mode of action for the antiemetic effect is undetermined, it is believed that these substances function as a prostaglandin antagonist, regulate endorphin release in central nervous system receptors, and also have effect in peripheral receptors [61]. For mild emetogenic chemotherapy, they are frequently used as monotherapy, and for moderate to severely emetogenic chemotherapy, they are taken with 5-HT_3 RAs plus or minus neurokinin-1 antagonists [62]. Thus, high dose dexamethasone administered orally or intravenously (6 mg/m^2 six hourly) represents a key component of the children's antiemetic prophylactic regimens for MEC and HEC [21].

2.3.3 Neurokinin-1 receptor antagonists

Neurokinin-1 antagonists, that prevent substance P's actions, represent the most recent category of antiemetic drugs to be accepted by both pediatric and adult CINV guidelines [20]. In 2003, the FDA granted the first authorization for aprepitant use in adults, which is a strong and specific oral NK-1 RA [20]. In addition, the use of aprepitant, fosaprepitant, rolapitant, and netupitant/palonosetron has been authorized [22]. However, in low-income nations like Ethiopia, these agents are not readily available for the management of CINV, hence they are not used in Tikur Anbessa Specialized Hospital. The FDA authorized the administration of aprepitant in pediatrics between the ages of 12 and 17 and those under the age of twelve who weighed more than 30 kg in 2015 [21]. In the exact same year, the FDA approved the administration of aprepitant solution for pediatrics greater than six months and up [21]. There exists substantial evidence that NK-1 RAs are efficient in controlling CINV, particularly delayed onset CINV [63]. Correspondingly, in managing acute and delayed CINV, triple drug regimens comprising a 5-HT3RA, dexamethasone, and NK1 RA were demonstrated to be superior than dual medication regimens containing 5-HT3RA and dexamethasone [64].

2.3.4 Dopamine-Serotonin Receptor Antagonists

Similar to the serotonin and dopamine antagonists, metoclopramide as antiemetic actions in both low and high dosages. Thus, for the prevention of CINV in children, metoclopramide has been utilized [65]. It is recommended to use metoclopramide for pediatrics patients who cannot get corticosteroids for prophylaxis of acute CINV as a result of moderately emetogenic chemotherapy [34]. However, there is a concern while using metoclopramide since the European Medicines regulatory Agency imposed use limits due to the possibility of tardive dyskinesia and extrapyramidal syndromes. Metoclopramide was advised not to be used in children under the age of one and to be avoided in those under the age of five in this regulatory agency's updated labeling. It was discovered that high dosages or prolonged therapy both increase the probability of side effects. In light of this, the evaluation advised keeping treatment duration brief (up to 5 days) and capping the adult dosage at 10 mg three times per day [66].

2.4 CINV prophylaxis according to current guidelines

2.4.1 CINV Control and guideline adherence

International antiemetic guidelines recommendations focus mostly on prevention. It is crucial to control emesis and nausea properly throughout the first chemotherapy cycle since CINV that occurs after the initial dose of emetogenic chemotherapy is linked to a higher incidence of CINV in following cycles [49, 67]. Prophylaxis strategies can successfully reduce emesis and, at a smaller degree, nausea in the majority of cancer patients when used according to guidelines [26]. On the other hand, poor CINV management results from disobeying antiemetic guidelines [68]. However, several studies in both Europe [68, 69] and the US [70] have found a low degree of patient compliance to guidelines among those receiving MEC and HEC. Adherence to clinical practice guidelines (CPGs) enhances total CINV management, according to several studies in adult oncology patients [34, 68]. There is no evidence that following CPGs in children leads to better outcomes, however a recent study found that better compliance with antiemetic recommendations in children improves nutritional status, nausea, and vomiting [71].

2.4.2 Guideline Recommendations

We made an effort to review two important clinical practice guidelines [21, 72] for the prophylaxis of CINV in pediatrics that had been newly published. Table 2 and 3 below provide an overview of the recommendations given by each of the above guidelines.

The emetogenic risk of a patient's chemotherapy treatment is taken into account when making recommendations. Although the strengths or levels of confidence in both guidelines' recommendations are largely comparable, there are some differences. This is probably due to the various methodological techniques adopted by each guideline panel when choosing articles and developing guideline recommendations. The POGO guideline's recommendations are based on randomized clinical trials, case reports as well as retrospective and prospective observational studies, as opposed to the MASCC/ESMO guideline's recommendations, which were based only on pediatric RCT data.

Table 2: MASCC/ESMO (2017) guideline recommendations for prophylaxis of CINV in pediatrics [21]

Level of Emetogenicity	Contraindications	Recommendation (Level of Confidence)
		1 month to <18 years
Minimal	No contraindications to antiemetics	no routine prophylaxis (Moderate)
LEC	No contraindications to antiemetics	5-HT3 RA(Moderate)
MEC	No contraindications to antiemetics	5-HT3 RA + dexamethasone (Moderate)
	Contraindication for dexamethasone	Aprepitant +5-HT3 RA (Moderate)
	Contraindication to aprepitant + Dexamethasone	no recommendation
HEC	No contraindications to antiemetics	5-HT3 RA + dexamethasone + aprepitant (High)
	Contraindication to aprepitant	Dexamethasone +5-HT3 RA + (Moderate)
	Contraindication for dexamethasone (acute lymphoblastic leukemia, brain tumor)	5-HT3 RA + aprepitant (Moderate)
	Contraindication to aprepitant + dexamethasone	No recommendation

Table 3: POGO (2019) guideline recommendations for prophylaxis of CINV in pediatrics [20]

Level of Emetogenicity	Contraindications	Recommendation (Level of Confidence)	
		1 - <6 months	**≥6 months**
Minimal	No contraindications to antiemetics	no routine prophylaxis (Strong)	
LEC	No contraindications to antiemetics	ondansetron or granisetron (Strong)	
	No contraindications to antiemetics	5-HT3 RA + dexamethasone (Strong)	
MEC	Contraindication to dexamethasone	palonosetron (Weak)	5-HT3 RA + aprepitant (Weak)
	Contraindication to aprepitant + dexamethasone	not applicable	palonosetron (Weak)
HEC	No contraindications to antiemetics	5-HT3 RA + dexamethasone (Strong)	5-HT3 RA + dexamethasone + aprepitant (Strong)
	Contraindication to aprepitant	not applicable	5 HT3 RA + dexamethasone (Strong)
	Contraindication to dexamethasone	palonosetron (Weak)	palonosetron + aprepitant (Strong)
	Contraindication to aprepitant + dexamethasone	not applicable	palonosetron (Weak)

Table 4: Antiemetics Dosing recommendations for CINV prophylaxis as per POGO [20]

Level of Emetogenicity	Antiemetic medication	Dosage
HEC	Aprepitant	In day one, 125 mg orally once; In day two and up 80 mg orally once daily
HEC and MEC	Ondansetron	0.15 mg/kg/dose or 5 mg/m^2/dose or intravenously/orally prechemotherapy, then every 8 hours
HEC	Dexamethasone	6 mg/m^2/dose intravenously/orally every 6 hours
MEC		BSA≤ 0.6m^2: 2mg/dose intravenously/orally every 12 hours BSA> 0.6m^2: 4mg/dose intravenously/orally every 12 hours
MEC	Metoclopramide	prechemotherapy 1 mg/kg/ dose IV then 0.0375 mg/kg/ dose orally every 6 hours

2.5 Antiemetic Prophylaxis Outcome Assessment Methods

The assessment of CINV can be done using a variety of methodologies, including structured questionnaires, which are the most typical, patient diaries, and the recording of clinical observations by clinicians. and in most studies, a combination of these data collection strategies can be utilized [73]. Proxy measurements of caregivers/guardians and/or clinicians to enhance the self-reported information have been utilized by a substantial proportion of studies [47, 53]. In order to assess anticipatory, acute, and delayed nausea, vomiting and retching caused by chemotherapy, the assessment of CINV should be done at several time periods. A patient's whole experience might not be captured by the intensity of their symptoms at one particular time point, therefore assessing recurrent CINV may call for special care. Additionally, it's crucial to remember that, as a subjective form of suffering, nausea can occur simultaneously alongside various comorbidities (apart from cancer), which includes, mucositis pain of surgery, diarrhea, and mucositis. Most, yet not all, studies examining the outcomes of various antiemetic drugs in children and adults employed CR as a main endpoint [26, 34]. Consequently, in this study we have employed the aforementioned methodology to evaluate antiemetic prophylaxis outcomes.

3. Objectives

3.1 General Objective

To determine the outcome of antiemetic prophylaxis and associated factors among pediatric cancer patients receiving moderate to highly emetogenic chemotherapy at pediatric hemato-oncology ward of Tikur Anbessa specialized hospital.

3.2 Specific Objectives: -

- To determine the outcome of antiemetic prophylaxis at acute, delayed, and overall phases among pediatric cancer patients at TASH.
- To determine the incidence of chemotherapy-induced vomiting among pediatric cancer patients at acute, delayed, and overall phases at TASH.
- To determine factors associated with the outcome of antiemetic prophylaxis among pediatric cancer patients at TASH.
- To evaluate the time to first emesis event among pediatric cancer patients at TASH
- To determine factors associated with time to first emesis event among pediatric cancer patients at TASH.

4. Methodology

4.1 Study setting

The study was carried out at TASH's pediatric Hemato-oncology ward, which is the oldest and most prominent specialized hospital in Ethiopia. The hospital was established in 1972 and is situated at Lideta Sub-City, Addis Ababa, Ethiopia. TASH offers comprehensive, interdisciplinary medical treatments, including cancer care. TASH's cancer treatment includes inpatient and outpatient care, as well as the country's sole radiation department. TASH's pediatric hematology/oncology unit provides both outpatient and inpatient care. On average, 400-600 pediatric cancer patients attend TASH each year (source: unprinted Health Management Information System data from TASH's pediatric hemato-oncology inpatient abstract registration book for 2018-2020). The healthcare providers in the unit consist of hemato-oncologists, hemato-pathologists, resident physicians, and nurses.

4.2 Study design

The study followed a hospital based prospective, longitudinal and observational study design

4.3 Population

4.3.1 Source Population

All pediatric cancer patients diagnosed and on treatment with moderate to highly emetogenic chemotherapy at the pediatric hemato-oncology ward of TASH during the study time frame (September 01, 2021 to February 28, 2022).

4.3.2 Study population

All pediatric cancer patients with cancer diagnosis and receiving moderate to highly emetogenic chemotherapy and who fulfilled the inclusion criteria at TASH

4.4 Eligibility Criteria

4.4.1 Inclusion criteria

- Pediatric patients who were admitted to the hemato-oncology ward
- Pediatric patients who underwent moderate to highly emetogenic chemotherapy regimen.

4.4.2 Exclusion criteria

- Pediatric patients who dropped out and were lost to follow-up.
- Pediatric patient for whom consent/ assent was not obtained.

4.5 Sample size

All patients who were admitted during the six months study period (01 September, 2021 to February 28, 2022) and who fulfill the inclusion criteria had been included in the study.

4.6 Sampling Procedure

Consecutive sampling was used within the months of data collection.

4.7 Study Variable

4.7.1 Dependent variables

- Antiemetic prophylaxis outcome (CR vs No CR)
    - During the acute phase.
    - During the delayed phase.
    - During the overall phase.
- Incidence of CIV
- Time to first emesis event

4.7.2 Independent variables

- Demographic variables (sex, age, residency...)
- Type of cancer
- Chemotherapy regimen
- Emetogenicity
- Chemotherapy frequency
- Concomitant Intrathecal chemotherapy use
- Antiemetic prophylaxis choice
- Antiemetic prophylaxis duration
- Presence of comorbid illness
- Rescue antiemetic use

4.8 Data Collection Method and Instrument

All children admitted for therapy in consecutive days were assessed for eligibility. The investigator sought patients who fulfilled the eligibility requirements and briefed them about the study's objectives. Before participating in the study, the primary caregiver/guardian and the participant both provided consent and assent. Patient medical chart abstraction, a structured questionnaire, and a CIV event registration structured Performa were employed to gather the data. The data collection instrument that has four parts, was designed from a review of literature to capture the demographic characteristics as well as clinical variables of patients in order to assess the outcome of antiemetic prophylaxis. (*See* Appendix IV: Data Collection Instrument)

The first part has questions that are used to capture socio-demographic characteristics of the patient.

The second part assesses the patient's clinical characteristics. This section of the instrument includes questions regarding the patient's prior medical history, prior and present treatments, as well as current symptoms. The question used to capture clinical characteristics such as history of CINV with prior chemotherapy, cancer diagnosis and stage, chemotherapy regimen, duration chemotherapy regimen, and other current medications etc.

The third part of the data collection instrument focused on capturing information about antiemetic prophylaxis regimen for CINV. The questions included were antiemetic medications prescribed, the dosage, the route and time of administration.

The fourth part of the data collection instrument is the CIV event registration Performa. This part is designed to capture the specific occurrence of CIV episodes, including date and time, the rescue treatments and medications taken— if any.

4.8.1 Data collection procedure

The data was collected with five well-trained data collectors (3 nurses with BSc. in general nursing and 2 nurses having M.Sc. in oncology nursing). Demographic and baseline clinical parameters were recorded using a structured questionnaire that was structured to capture the following information: patient socio-demographic characteristics, patient's CIV experience with prior emetogenic chemotherapy, and history of motion sickness. Using medical chart abstraction, type of cancer, weight, BSA, chemotherapy regimen, doses of current chemotherapy agents, prior chemotherapy agents, all antiemetics prophylaxis given, comorbidities at the time of chemotherapy initiation and type plus number of rescue medications up to 120 hours following

chemotherapy administration were recorded. The CIV event registration structured Performa was utilized to collect information on the child's CIV episodes by asking the child's primary caregiver/guardian. Patients were routinely checked by the data collectors two times per day at 8 am and 8 pm, and all occurrences of vomiting and retching were prospectively documented on the CIV event registration structured Performa by asking the child's primary caregiver/guardian to report all episodes of emesis. Outcome data were collected and recorded beginning on the first day of treatment and ending five days thereafter by the data collectors. The data collector documented the daily number of emesis events. In addition, the patient's primary caregiver/guardian was also questioned about whether the child had vomited in the hour before treatment. To avoid loss to follow-up, particularly for patients who were discharged before the five-day follow-up period, data on the occurrence of CIV was obtained twice per day through a cell phone call to the primary caregiver/guardian. Furthermore, with just the intention of administering rescue antiemetic medications, the investigator discussed with primary care doctors and nurses about patients who had a severe emesis episode, defined as more than 5 episodes of emesis.

The gathering of information from the primary caretakers/guardians was classified into two phases. The initial data collecting period (acute) occurred within 24 hours, and the second collection period (delayed) was between 24 and 120 hours following MEC or HEC administration.

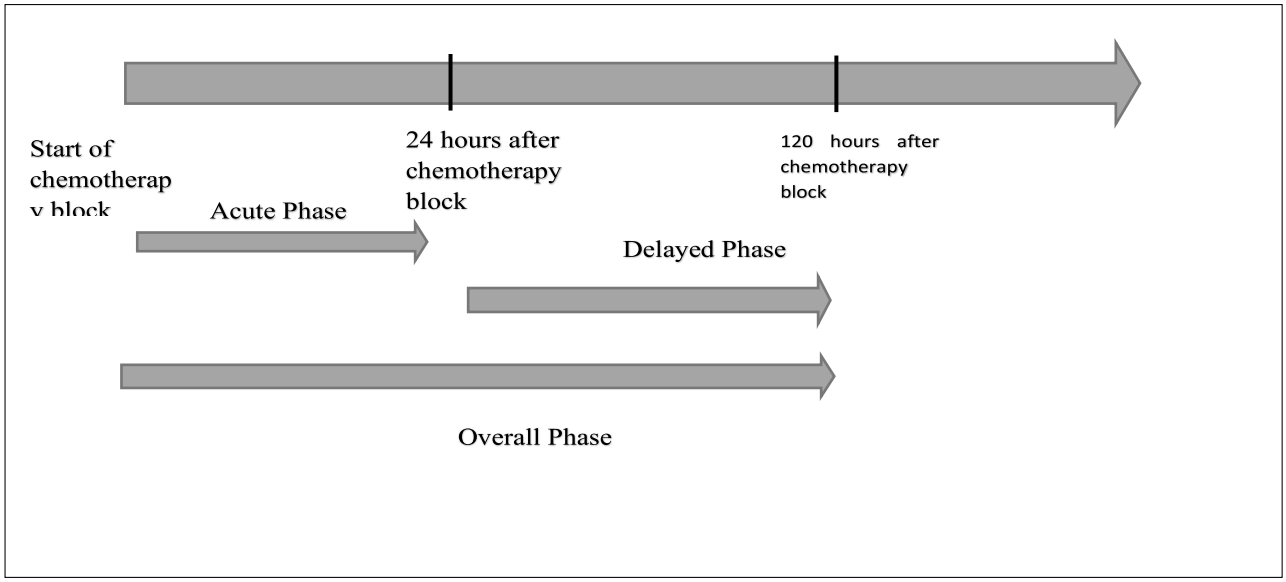

Figure 1: Timeline and procedure of data collection

4.9 Study outcome Variables

The evaluation of antiemetic prophylaxis outcome was based on the following parameter: Complete response (no emesis and no use of rescue); CR was evaluated in three phases: acute, delayed and overall. In the three

periods; the proportion of participants who experienced CR, defined as no vomiting, no retching, and no use of rescue medication after initiation of emetogenic chemotherapy. The POGO Guideline was utilized to define and classify the emetogenicity of a chemotherapy regimen [20].

4.10 Data Quality Assurance

Prior to the actual collection of data, a pretest was undertaken upon 10 patients that had not participated in the actual study at the hemato-oncology ward of TASH. Based on the outcomes of the pretest, changes were made to the data collection instrument. The modifications were mainly on the chemotherapy-induced vomiting assessment timing and documentation. The data collectors were given a six-hour training session prior to data collecting utilizing standardized procedures. Throughout the data collecting period, the principal investigator conducted ongoing follow-ups, and before entering the data, the correctness and completeness of the information was verified.

4.11 Data Analysis

Data was cleaned, and entered to Epi Data Version 3.6.1 and transported to the SPSS Version 25.0 statistical software for statistical analysis. Descriptive statistics such as frequency, and percentage were made to describe socio-demographic and clinical characteristics. The number of patients who attained a complete response during the acute/delay/overall phases had been described using frequency distribution table, and percentage. A multivariable logistic regression model was conducted to determine variables linked with the occurrence of CIV or ‘no complete response’ outcome during acute and delayed phases. Variables which had p-value less than 0.25 when performing the bivariate test were considered in the multivariable model and odds ratio was used to ascertain the strength of associations between the variables. A P value less than 0.05 was considered statistically significant; all tests were two-tailed. To evaluate viable trends in the connection among development of CIV and the number of predictive factors that were determined by the multivariable logistic regression model, the Cochran-Armitage trend test was carried out. Furthermore, the time to first emesis event curve was examined utilizing the Kaplan-Meier technique. We used the log-rank test to compare between-group comparisons in the Kaplan-Meier analysis, the group was divided by regimen emetogenicity and chemotherapy regimen composition category. Hazard ratios and 95% CI for the time to first emesis event was evaluated using Cox regression model to determine risk variables for the time-to-first emesis event.

4.12 Plan for dissemination of results

The study's findings will be communicated to pharmacy school staff and other interested parties. Photocopy of the research will be given to the AAU School of Pharmacy. The results of this study will be printed in the appropriate scholarly journals.

4.13 Ethical considerations

Ethics approval has been gained from the department ethical review committee (DERC) of pharmacy school with reference number *ERB/SOP/267/13/2021* and a data collection permit from the department of pediatrics and child health with reference number *ሕ/ህ/519/13*, college of health sciences (CHS), AAU. Informed consent has been acquired. from all primary caregiver/guardians, and, where appropriate, assent was obtained from participants, respectively, after thoroughly explaining objectives and benefits of the study. Data confidentiality was maintained by omitting the name and address of the patients. Data collected for this study was not to be used for other studies without approval of each participant. Detailed emphasis was given to explain that there was not any special benefit for the participants who volunteered to take part in the study.

4.14 Operational definition

Acute CIV – is defined as an emesis that happens within 24 hours after receiving chemotherapy [20].

Antiemetic prophylaxis outcome: is defined by the presence of emesis event and is categorized as “Complete response” or “No complete response” to antiemetic prophylaxis.

Breakthrough CIV – is defined as an emesis that happens within five days following chemotherapy, regardless the administration of the recommended antiemetic prophylaxis [21].

Complete response – Regarded as no emetic episodes and/or no rescue antiemetic use within the specified observation period [21].

Comorbid illness - Chronic or acute illnesses and/or conditions that existed or may co-occur within one person throughout the clinical journey of a participant who has the type of illness under study.

Delayed CIV - is defined as an emesis that happens after 24 hours post chemotherapy administration [20].

Moderate risk emetogenicity - Chemotherapy medications which induce 30 to 90% vomiting assuming preventative antiemetic medication is not administered [21].

High risk emetogenicity - Chemotherapy medications which induce more than 90% vomiting assuming preventative antiemetic medication is not administered [21].

Mild vomiting - Occurrence of 1 - 2 emesis episodes within the specified observation period.

Moderate vomiting - Occurrence of 3 -5 emesis episodes within the specified observation period.

Multiple day chemotherapy - Chemotherapy regimen that is administered for greater than one day in successive days.

No complete response- Defined as occurrence of any number of episodes of emesis and/or rescue antiemetic medication use within the specified observation period.

Prophylaxis - Refers to antiemetic preventive medication that is administered according to guidelines to avoid CINV.

Time to-first-emesis event- defined as the time to first emesis episode over the follow-up period.

Partial Response - Defined as 1 or 2 emetic episodes within the specified observation period.

Rescue therapy- Antiemetic medication that is used when CINV fails to respond effectively to standard preventative antiemetic medication administered according to guidelines.

Retching - A failed movement or effort of the esophagus or stomach to vomit.

Severe vomiting - occurrence of ≥ 5 vomiting episodes within the specified observation period.

Uncontrolled Response: Defined as ≥3 emetic episodes within the specified observation period.

Vomiting - Forcible expulsion of stomach contents via mouth.

5. Results

5.1 Study Participant Recruitment

Between September 2021 and February 2022, a total of 204 consecutive children with a confirmed cancer diagnosis receiving HEC or MEC in an inpatient setting, were approached and provided informed consent/assent. Of these, 3 (1.5 %) were subsequently removed from the analysis due to withdrawal to consent (n = 1), death of the participant (n = 1), and not finishing the dataset (n = 1). Thus, complete data were available for 201 patients.

5.2 Demographic Characteristics of the Study Participants

The study comprised participants with a median age of 5.0 years (range from 2 months to 15 years). The study included (60.7%) males and (39.3%) females. About half (54.3%) of the participants were below the age of 5 years. The mean values of weight, height, and BMI of the children in this study were 17.7 kg (SD=6.8), 107.1 cm (SD=22.5), and 14.8 (SD=2.32), respectively. According to the residence of the children 59.4 % were from urban areas and the majority (39.8 %) were from Oromia region followed by 18.9 % from Amhara, 17.9% from SNNPR and 16.7 % from Addis Ababa *(Table 5).*

Table 5: Demographic characteristics (N=201)

Characteristics	N (total)	Percentage (%)
Age (years)		
≤ 5	109	54.3
5-10	66	32.8
10-15	26	12.9
Sex		
Male	122	60.7
Female	79	39.3
BSA category		
≤ 0.6 m2	73	36.3
> 0.6 m2	128	63.7
BMI (age percentile)		
Underweight (< 5th PCTL)	76	37.8
Healthy Weight (5th PCTL to < 85th PCTL)	119	59.2
Overweight (85th PCTL to < 95th PCTL)	3	1.5
Obesity (≥ 95th PCTL)	3	1.5
Residence		
Urban	120	59.7
Rural	81	40.3
Region/country		
Amhara	38	18.9
Oromia	80	39.8
SNNPR	36	17.9
Addis Ababa	33	16.4
Somali	7	3.5
Others*	7	3.5

Abbreviation: SNNPR- South nations nationalities people region, PCRL- Percentile
Note: * Sidama=1, Benishangul =1, Dire Dawa=1, Eritrea (abroad)=4

5.2.1 Characteristics of the Caregiver/Guardian

Majority of the patient's caregivers (52.2 %) were mothers, followed by fathers (46.3%), sisters or brothers (1%) and other relatives (0.5%).

5.3 Clinical Characteristics of the Patients

5.3.1 Cancer Type

Patients in the study had diverse cancer diagnoses. Out of 201 pediatric hematology/oncology patients 44.2% had hematologic malignancies. Acute lymphoblastic leukemia (ALL) was the most prevalent malignancy, involving 27.9% of patients, subsequently accompanied by retinoblastoma 13.4% and rhabdomyosarcoma (RMS) 12.4 %. The median time since cancer diagnosis was three months.

At the time of chemotherapy treatment, the majority 59.7% did not have any comorbid conditions. The most prevalent illnesses among those who did so were infections 31.3%, malnutrition, that consists of both moderate (MAM) as well as severe (SAM) acute malnutrition 14%, and hypertension 5.5%. Fourteen (22.2 %) of the infections were categorized as being acquired in a hospital.

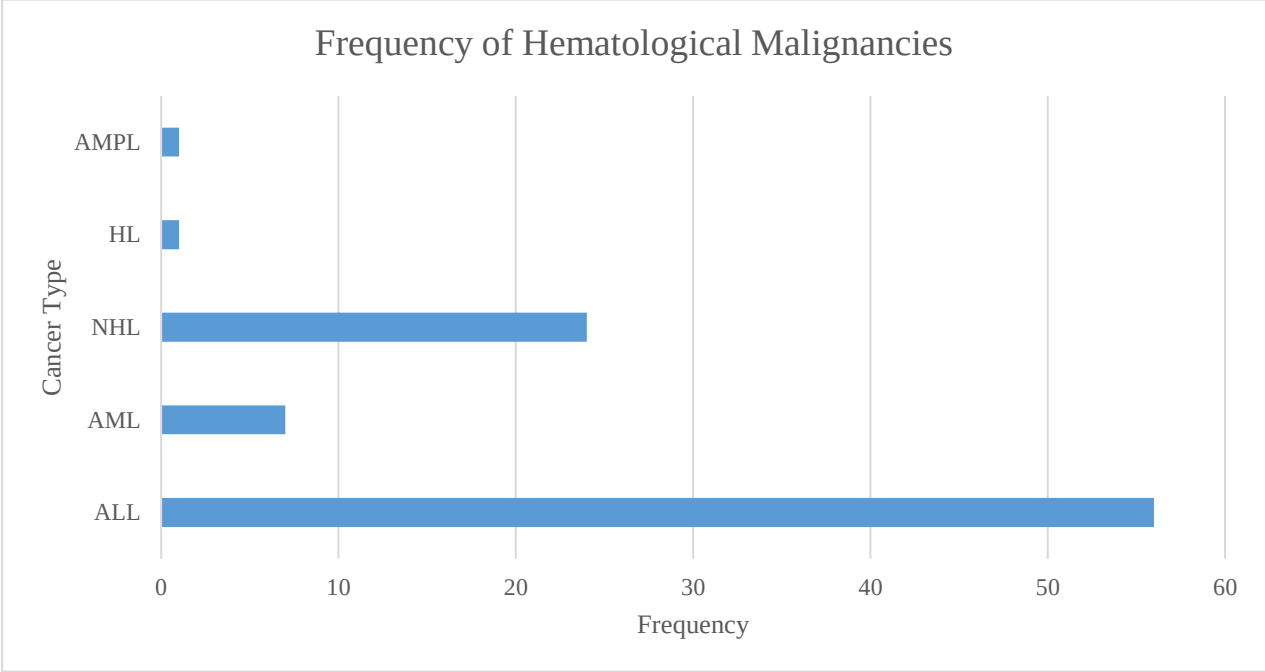

Figure 2: Hematological Malignancies frequency

Abbreviations: ***AMPL****: Acute promyelocytic leukemia,* ***HL****: Hodgkin lymphoma,* ***NHL****: Non-Hodgkin lymphoma, AML: Acute myeloid leukemia,* ***ALL****: Acute lymphoblastic leukemia*

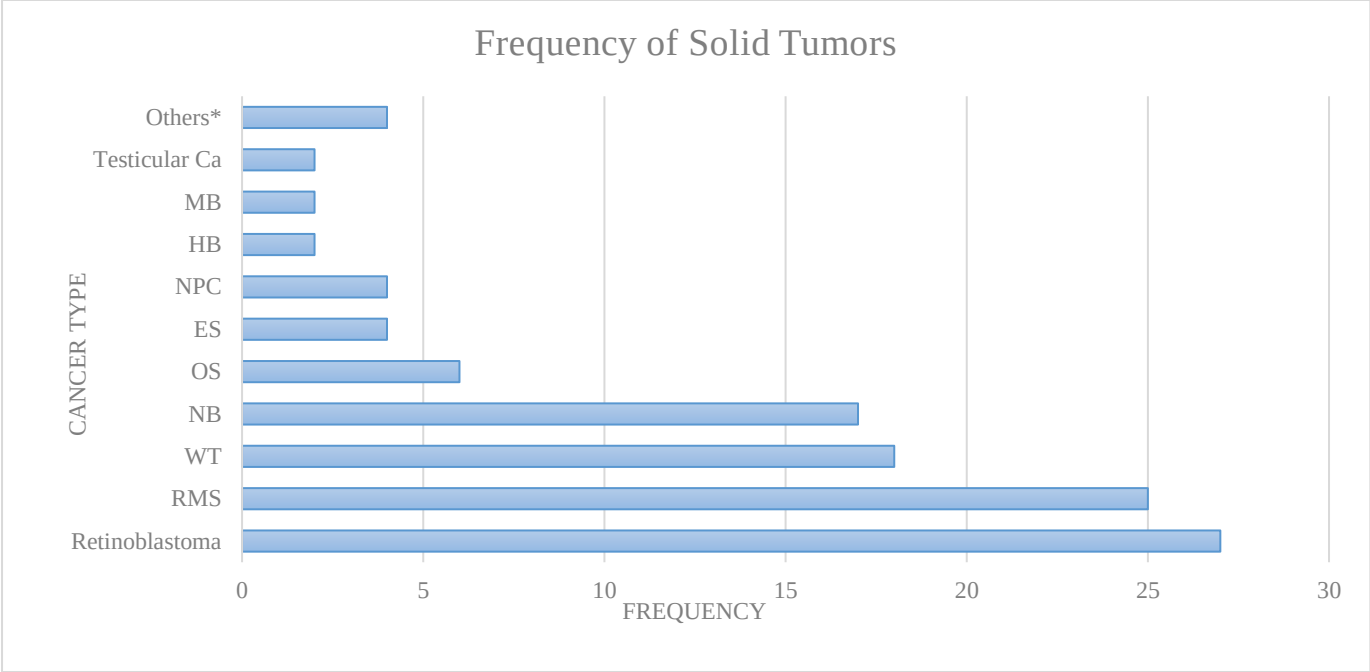

Figure 3: Solid Tumors frequency

Note: Others***;** *Pineal gland germinoma, Sacrococceygeal teratoma, Thymom*a
***Abbreviations: MB**: Medulloblastoma, **HB**: Hepatoblastoma, **NPC**: Nasopharyngeal carcinoma, **ES**: Ewing Sarcoma, **OS**; Osteosarcoma, **NB**: Neuroblastoma, **WT**; Wilms tumor, **RMS**: Rhabdomyosarcoma*

5.3.2 Emesis History

Furthermore, when patients were enrolled, patient characteristics that are known to affect the likelihood of vomiting were documented. From the study participants who had prior chemotherapy exposure, 70.6% had reported a prior chemotherapy induced emesis history. A history of motion sickness and history of admission to a medical facility due to severe CIV were reported by 33.3% and 2.5 % of the participants, respectively *(Table 6).*

Table 6: Emesis history of the participants

Characteristics	N	Percentage (%)
History of emesis with prior chemotherapy ***(N=109)***		
Yes	77	70.6%
No	32	29.4%
History of admission/went to a health facility due to sever CIV	5	2.5%
History of motion sickness		
Yes	67	33.3
No	134	66.7

5.3.3 Chemotherapy Regimen Administered

Most patients (54.2 %) were undergoing treatment and had had a previous exposure to or received chemotherapy earlier to enrollment to the study. All the patients included in the study were scheduled to receive chemotherapy with highly and moderately emetogenic potential. According to the regimen that the patients are on, 53.7% patients were administered HEC and 46.3% with MEC *(Table 7*). Highly emetogenic regimens were chiefly platinum-based 45/108 (41.7%). Of all the administered chemotherapy protocols, the most frequently prescribed chemotherapy medications were vincristine (143 prescriptions), cyclophosphamide (88 prescriptions), etoposide (69 prescriptions), doxorubicin and LASP (54 prescriptions), carboplatin (38 prescriptions) and cisplatin (31 prescriptions).

Most of the regimens—159 in total—were administered as multi day treatments. Additionally, the presence of intrathecal chemotherapy was evaluated. Of the participants, 28.1% have received concomitant intrathecal methotrexate, while 3.5% have gotten a triple intrathecal therapy, which combines methotrexate, cytarabine, and hydrocortisone.

Table 7: Chemotherapy regimens administered to study participants

Characteristics	Category	N (total)	Percentage (%)
Prior chemotherapy exposure	chemotherapy naïve	92	45.8
	Have exposure	109	54.2
Level of Emetogenicity	HEC	108	53.7
	MEC	93	46.3
Duration of chemotherapy block (chemotherapy Schedule)	Single day	42	20.9
	Multiday	159	79.1
Treatment Modality	Recipient of single agent	14	7
	Combination	187	93
Concomitant IT chemotherapy	IT-MTX	58	28.9
	IT-MHA	7	3.5
	No-IT	136	67.7
Presence of steroid	Steroid containing regimen	68	33.8
	Non-steroid containing regimen	133	66.2

Abbreviations: MTX, methotrexate; IT-MHA, intrathecal methotrexate-hydrocortisone-cytarabine; IT, intrathecal

Furthermore, chemotherapy protocols were divided into six categories, including cyclophosphamide-based, platinum-based, anthracycline-based, and cyclophosphamide L-asparaginase (LASP)-based ALL induction, and platinum-based combination regimens *(Figure 4*). Chemotherapy protocols which did not fit into one of those categories were categorized as "others" Cyclophosphamide-based regimens made up the majority of the combination, accounting for 32.4 %, followed by platinum-based regimens (22.4%).

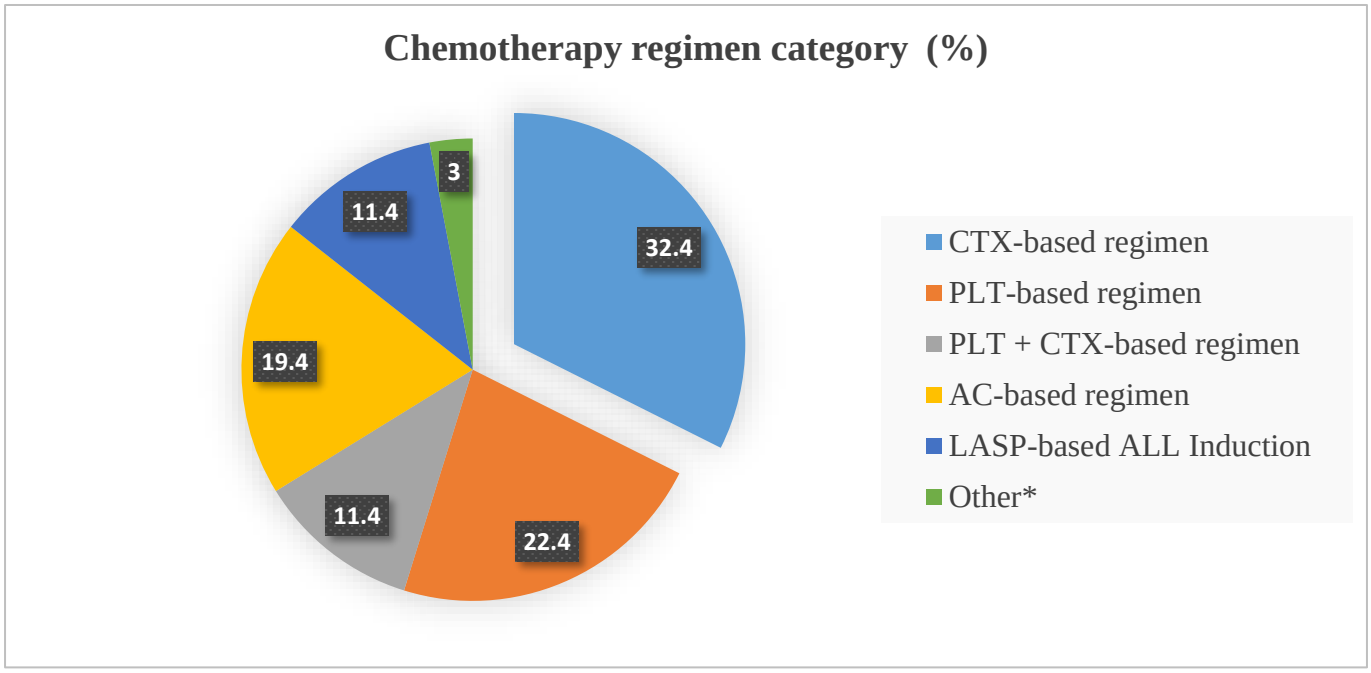

Figure 4: Categorical classification of chemotherapy Regimens (N=201)

Abbreviation: AC- Anthracycline, CTX- cyclophosphamide, PLT- platinum

Note: others*, AML-Consolidation (cytarabine)=2 protocols, Vincristine/Actinomycin-D= 4 protocols

Table 8: Chemotherapy regimen distribution by emetogenicity

Level of Emetogenicity	Chemotherapy protocols Category					
	CTX-based	**PLT-based**	**PLT + CTX-based**	**AC-based**	**LASP-Based Induction**	**Other**
HEC	31 (28.7%)	45 (41.7%)	23 (21.3%)	7 (6.5%)	-	2 (1.9%)
MEC	34 (36.6%)	-	-	32 (34.4%)	23 (11.4%)	4 (2.0%)

Table 9: Chemotherapy regimen distribution by cancer type

Cancer Diagnosis Category	Cancer Type	CTX-based	PLT-based	PLT + CTX based	AC-based	LASP-based	Others
Leukemias	ALL	7 (3.5%)			26 (12.9%)	23 (11.4%)	
	AML				5 (2.5%)		2(1%)
	APML				1 (1.6%)		
Lymphomas	HL			1 (0.5%)			
	NHL	19 (9.5%)	1 (0.5%)		4 (2%)		
Solid Tumors	Retinoblastoma		26(12.9%)		1 (0.9%)		
	RMS	25 (12.4%)					
	WT	5 (2.5%)	3 (2.7%)	4 (2%)	2 (1%)		4 (2%)
	Germ cell tumor		1 (0.9%)				
	Neuroblastoma	1 (0.5%)	1 (0.9%)	15 (7.5%)			
	OS	4 (2%)	2 (1%)				
	ES	4 (2%)					
	NPC		4 (2%)				
	Others*		7 (3.5%)	3 (1.5%)			

Note: Others*: *Hepatoblastoma, Medulloblastoma, Pineal gland germinoma, Sacrococceygeal teratoma, Testicular Cancer, Thymom*a

5.4 Antiemetics Prophylaxis Administered and Incidence of Overall, Acute, Delayed, Emesis

5.4.1 Overall Incidence of Chemotherapy-Induced Emesis

Despite the administration of preventive antiemetics, 98 patients (48.8%) reported vomiting at certain time throughout the 120 hours period after chemotherapy treatment. The mean documented time to the first incident of vomiting was 24.5 hours.

Based on emetogenicity, 67.6 % (73/108) of the patients undergoing chemotherapy with HEC have got two-antiemetic combination (ondansetron/metoclopramide), while 24.1% (26/108) of the patients received a triple-antiemetic combination (ondansetron/metoclopramide/dexamethasone) (*Table 10*). Among patients receiving MEC, 47.3 % (44/93) received single antiemetic and 40.9 (38/93) received dual antiemetics. The most often utilized prophylactic antiemetic for MEC was a single agent ondansetron 41.9% (39/ 93). Based on the severity of emetogenicity, the number of antiemetic medications used increased. In each course, a median (mean) of antiemetics used was 1 (1.4) ***(****Table 10).*

Table 10: Antiemetic prophylaxis regimen distribution by Level of Emetogenicity (N=201)

	Level of Emetogenicity	
Antiemetic prophylaxis	**HEC [a] N, (%)**	**MEC [b] N, (%)**
Ondansetron Alone	3, (2.8%)	39, (41.9%)
Ondansetron + Metoclopramide + Dexamethasone	26, (24.1%)	10 (10.8%)
Ondansetron + Metoclopramide	73, (67.6%)	25, (26.9%)
Ondansetron + Dexamethasone	2, (1.9%)	4, (4.3%)
Metoclopramide + Dexamethasone	1, (0.9%)	10, (10.8%)
Metoclopramide Alone	3, (2.8%)	5, (5.4%)

Note: a, the total numbers of patients taking HEC are 108, **b,** total number of patients taking MEC are 93.

5.4.1.1 Acute Emesis

The incidence of vomiting was 28.9% during the acute phase. In the acute phase all patients had received prophylactic antiemetics and the most frequent single agent antiemetic prophylaxis in 20.9 % of the patients was ondansetron, followed by metoclopramide 4%. From the combination regimen the most commonly utilized were the combination of metoclopramide and ondansetron in 98 (48.8%) of the participants, followed by a triple combination of metoclopramide, ondansetron and dexamethasone in 36 (17.9 %) of the participants. Every patient that got 5-HT 3 RA before chemotherapy, as per the hospital's protocol, received ondansetron in the acute phase 15–30 minutes before chemotherapy started.

5.4.1.2 Delayed Emesis

Prophylaxis was given less frequent during the delayed phase, 70.6 % (142/201) of patients had antiemetic prophylaxis during the delayed phase, while all participants took during the acute phase (100%). Delayed emesis was documented in 31.8% of the study participants, and of them 73.4% have received prophylaxis The majority of those who got antiemetics during the delayed phase—90.1%—had a combination antiemetic regimen. Similar to the acute phase, ondansetron was the most frequent single-agent antiemetic used in the delayed phase among 11/142 participants. From the combination regimens, a combination of metoclopramide + ondansetron + dexamethasone was used in 36/142 of the participants. Furthermore, 25.9% of patients received a dexamethasone-containing prophylaxis regimen during the delayed phase *(Table 11).*

Table 11: Delayed emesis and antiemetic prophylaxis during the delayed phase (N=201)

Characteristics	Category	N	(%)
Antiemetic prophylaxis	Ondansetron Alone	11	5.5%
	Metoclopramide Alone	3	1.5%
	Ondansetron + Metoclopramide	76	37.8%
	Dexamethasone + Ondansetron + Metoclopramide	36	17.9%
	Dexamethasone + Metoclopramide	11	5.5%
	Dexamethasone + Ondansetron	5	2.5%
	No antiemetics	59	29.4%

5.4.2 Rescue Antiemetic Medications

Rescue antiemetic medication had been needed by 31 (15.4%) of the participants in the acute phase and by 4 (2%) of the participants in the delayed phase. Participants used a range of rescue antiemetics, although 5HT3 antagonists (ondansetron) and dopamine antagonists (metoclopramide) were the two medications that were prescribed frequently. The overall rescue antiemetic prescription contains 66.7% 5HT3-antagonists alone, 9.5% a 5HT3-antagonist mixed with anti-dopaminergic agent, and 19 % anti-dopaminergic agent alone. Only 0.5% of the total rescue prescription was a steroid.

5.5 Antiemetic Prophylaxis Outcome (Response Rate)

Complete response (no vomiting and/or no rescue antiemetic use post-chemotherapy) was attained by 51.2 % of all evaluable participants over the entire observation period (0-120 hr.). During the acute phase, 71.1 % experienced a CR and during the delayed phase, 68.2 % of patients achieved complete response (*Table 12*).

Table 12: Antiemetic prophylaxis outcome distribution by phase

		Phases		
Outcome		**Acute N (%)**	**Delayed N (%)**	**Overall N (%)**
CR	**Complete response**	143 (71.1%)	137 (68.2%)	103 (51.2%)
No CR	**Partial response**	36 (17.9%)	44 (21.9%)	57 (28.4%)
	Uncontrolled	22 (10.9%)	20 (10%)	41 (20.4%)

Note: complete response= no vomiting and/or no rescue medication, Partial response= 1-2 vomiting episodes/phase, Uncontrolled= ≥3 vomiting episodes/phase,

Patients in the study encountered an average of 2.3 (±1.4) episodes of vomiting during the acute phase and 3.1 episodes (±3.1) throughout the delayed phase and a median of 2 vomiting events throughout all phases, during the times wherein emesis happened. Emesis peaked on the first day of treatment 57 (28.4%), decreased steadily throughout the course of the follow-up period, and peaked the least on the fifth day after chemotherapy 12 (6%) *(Figure 5)*. A maximum of 8 episodes of vomiting per single patient was recorded throughout the acute phase and as 18 episodes of vomiting during the delayed phase, with a daily range of 0-8 episodes throughout the acute phase and 0-18 episodes throughout the delayed phase. The maximum vomiting episode score recorded per single patient in acute, delayed and overall phases were 8, 18, 22 episodes of vomiting.

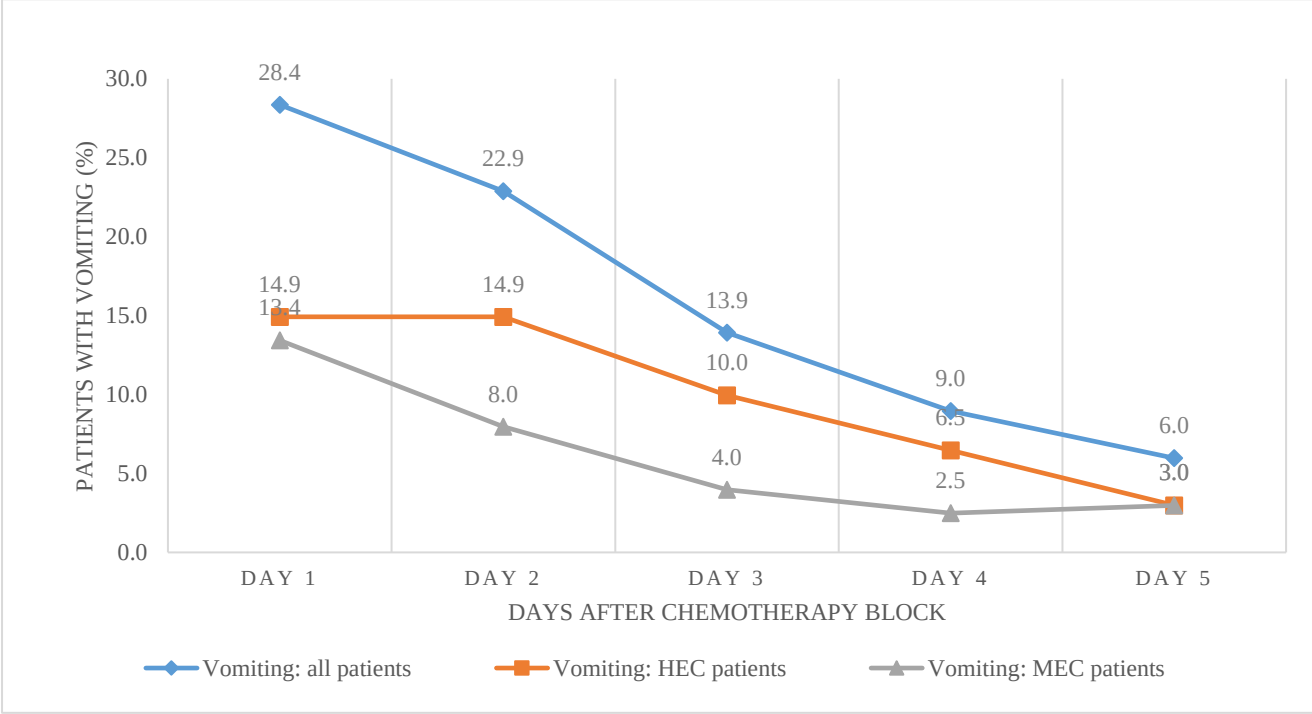

Figure 5: Number of patients with CIV day 1-day 5 following chemotherapy administration

The severity of vomiting was divided into three categories according to the number of episodes per each phase: severe, which is regarded as > 5 emesis episodes/phase, moderate, which is regarded as 3 to 5 emesis episodes/phase and mild, which is regarded as, 1 to 2 emesis episodes/phase. Over the whole 120-hour observation period, there had been 14 (7%) occurrences of severe vomiting, 27 (13.4%) occurrences of moderate vomiting, and 57 (28.4%) occurrences of mild vomiting *(Table 13)*.

Table 13: CIV severity distribution by phase

	Phase		
Severity of vomiting	**Acute**	**Delayed**	**Overall**
No vomiting	143 (71.1%)	137 (68.2%)	103 (51.2%)
Mild 1-2 episodes	36 (17.9%)	44 (21.9%)	57 (28.4%)
Moderate 3-5 episodes	20 (10%)	12 (6%)	27 (13.4%)
Severe >5 episodes	2 (1%)	8 (4%)	14 (7%)

5.5.1 Sociodemographic factors and antiemetic prophylaxis outcome

Male patients had shown a higher complete response than females in all phases. According to *Table 14* below, in the overall phase younger age group patients (<5 years) have the highest incidence of CIV and patients aged 5 to 10 years had the highest incidence of CR (24.9%), which is the highest compared to other age categories.

Table 14: Distribution of antiemetic prophylaxis outcome by sociodemographic factors

Phase	**Variable**	**Category**	**Emesis (no CR)**	**No emesis (CR)**
Acute	Gender	Male	90 (44.8%)	32 (15.9)
		Female	53 (26.4%)	26 (12.9)
	Age (years)	<5	36 (17.9%)	73 (36.3%)
		5-10	12 (6.0%)	54 (26.9%)
		10-15	10 (5.0%)	16 (8.0%)
	Residency	Rural	21 (10.4%)	60 (29.9%)
		Urban	37 (18.4%)	83 (41.3%)
Delayed	Gender	Male	35 (17.4%)	87 (43.3%)
		Female	29 (14.4%)	50 (24.9%)
	Age (years)	<5	42 (20.9%)	67 (33.3%)
		5-10	10 (5%)	56 (27.9%)
		10-15	12 (6%)	14 (7%)
	Residency	Rural	23 (11.4%)	58 (28.9%)
		Urban	41 (20.4)	79 (39.3%)
Overall	Gender	Male	55 (27.4%)	67 (33.3%)
		Female	43 (21.4%)	36 (17.9%)
	Age (years)	<5	66 (32.8%)	43 (21.4%)
		5-10	16 (8%)	50 (24.9%)
		10-15	16 (8%)	10 (4.9%)
	Residency	Rural	34 (16.9%)	47 (23.4%)
		Urban	64 (31.8%)	56 (27.9%)

5.5.2 Clinical Factors and Antiemetic Prophylaxis Outcome

5.5.2.1 Regimen Level of Emetogenicity

Complete response outcomes of the two chemotherapy regimens, HEC and MEC, are illustrated on *Table 15*. During the overall phase, complete response was registered with 46/108 HEC patients and with 57/98 MEC patients.

Table 15: Distribution of antiemetic prophylaxis outcome by level of emetogenicity

		Level of Emetogenicity	
Phase	**Outcome**	**HEC, N (%)**	**MEC, N (%)**
Acute	CR	79 (39.3%)	64 (31.8%)
	No CR	29 (14.4%)	29 (14.4%)
Delayed	CR	59 (29.4%)	78 (38.8%)
	No CR	49 (24.4%)	15 (7.5%)
Overall	CR	46 (22.9%)	57 (28.4%)
	No CR	62 (30.8%)	36 (17.9%)

5.5.2.2 Chemotherapy Regimen Category

Chemotherapy regimen composition has an effect on the incidence of vomiting. Accordingly, in all phases the highest emesis count or a decreased CR was registered with patients on platinum-based regimen. In the acute phase 18 (9.0%), in the delayed phase 30 (14.9%) and in overall phase 38 (18.9%) of emesis count was from patients with platinum compound consisted regimens *(Table 16).*

Table 16: Proportions of patients with CIV episode by regimen category (N=201)

	Phase	**Acute**	**Delayed**	**Overall**
		No CR (%)	**No CR (%)**	**No CR (%)**
Regimen	CTX-based	16 (8.0%)	13 (6.5%)	22 (10.9%)
	PLT-based	18 (9.0%)	30 (14.9%)	38 (18.9%)
	PLT + CTX-based	3 (1.5%)	14 (7.0%)	15 (7.5%)
	AC-based	5 (2.5%)	2 (1.0%)	5 (2.5%)
	LASP-Based ALL induction	14 (7.0%)	4 (2.0%)	16 (8.0%)
	Others	2 (1.0%)	1 (0.5%)	2 (1.0%)
	Total	**58**	**64**	**98**

Because steroids are mostly incorporated in the management of leukaemia, chemotherapy regimens were further categorized into steroid containing and non-steroid containing regimens. In all the three phases steroid-containing chemotherapy regimens had registered lower frequency of severe vomiting (>5 emesis episodes/phase) when compared to non-steroid Containing regimens (*Table 17*). Furthermore, in the overall phase from the total of 41 uncontrolled (≥3 vomiting episodes) emesis responses, steroid containing regimen had the lowest (19.5%) and the rest (73.2%) was accounted for non-steroid containing regimen (*Table 17*).

Table 17: CIV severity distribution by presence of steroid in the regimen

		Vomiting Severity		
Phase	**Chemo-Regimen**	**Mild**	**Moderate**	**Severe**
Acute	Non-steroid Containing	19	14	2
	Steroid containing	17	6	0
Delayed	Non-steroid Containing	36	10	6
	Steroid containing	9	2	2
Overall	Non-steroid Containing	41	19	12
	Steroid containing	16	8	2

Note: Severe: >5 emesis events/phase, Moderate: 3 to 5 emesis events/phase, Mild: 1 to 2 emesis events/phase

5.5.2.3 Chemotherapy Exposure and Emesis History

In all phases patients with a prior chemotherapy exposure registered the highest no CR outcome than patients who were chemotherapy naïve. Patients with history of motion sickness had a higher registration of CIV (52/98, or 53.1%) overall in this study (*Table 18)*.

Table 18: Distribution of antiemetic prophylaxis outcome by chemotherapy exposure and history of emesis (N=201)

		Phase					
		Acute		Delayed		Overall	
		CR (%)	No CR (%)	CR (%)	No CR (%)	CR (%)	No CR (%)
Prior chemotherapy exposure	Chemo-naïve	68 (33.8)	24 (11.9)	77 (38.3)	15 (7.5)	56 (27.9)	36 (17.9)
	Have-exposure	75 (37.3)	34 (16.9)	60 (29.9)	49 (24.4)	47 (23.4)	62 (30.8)
History CIV with Prior chemotherapy	Yes	49 (24.4)	28 (13.9)	35 (17.4)	42 (20.9)	26 (12.9)	51 (25.4)
	No	94 (46.7)	30 (14.9)	102 (50.7)	22 (11)	77 (38.3)	47 (23.4)
History of Motion Sickness	Yes	40 (19.9)	27 (13.4)	34 (16.9)	33 (16.4)	21 (10.4)	46 (22.9)
	No	103 (51.2)	31 (15.4)	103 (51.2)	31 (15.4)	82 (40.8)	52 (25.9)

5.5.2.4 Duration of Chemotherapy Block and CIV

We exhibited the impact of chemotherapy block duration on incidence of CIV since longer-term exposure to chemotherapeutic agents results in larger cumulative dosages. Participants receiving multi day chemotherapy (chemotherapy protocols given on two or more consecutive days) experienced more vomiting episodes than those receiving single day of chemotherapy.

Table 19: Proportion of patients with CIV episode by duration of chemotherapy block

	Phase		
	Acute	Delayed	Overall
Duration of chemotherapy block	No CR (%)	No CR (%)	No CR (%)
Single day	14 (7%)	6 (3%)	15 (7.5%)
Multiple day	44 (21.9%)	58 (28.9%)	83 (41.3%)

5.5.3 Antiemetics Prophylaxis and Its Outcome

5.5.3.1 Acute phase antiemetics

Despite the usage of antiemetics, 58 (28.9%) of patients don't achieve complete response. Participants who received combination antiemetic regimen have experienced higher acute phase complete response; of these, the highest CR frequency was registered by patients who got combinations of ondansetron + metoclopramide

73 (36.3%), followed by triple agent combination of ondansetron + metoclopramide + dexamethasone 25 (12.9%) (Figure 6). As well, acute phase CR was observed by 26 (12.9%) of patients who had received single agent ondansetron *(Table 20)*.

Table 20: Distribution of acute phase antiemetic prophylaxis outcome by prophylaxis modality

Prophylaxis Modality	CR (%)	No CR (%)
Single agent	32 (15.9%)	18 (9%)
combination agent	111 (54.7%)	40 (19.9%)

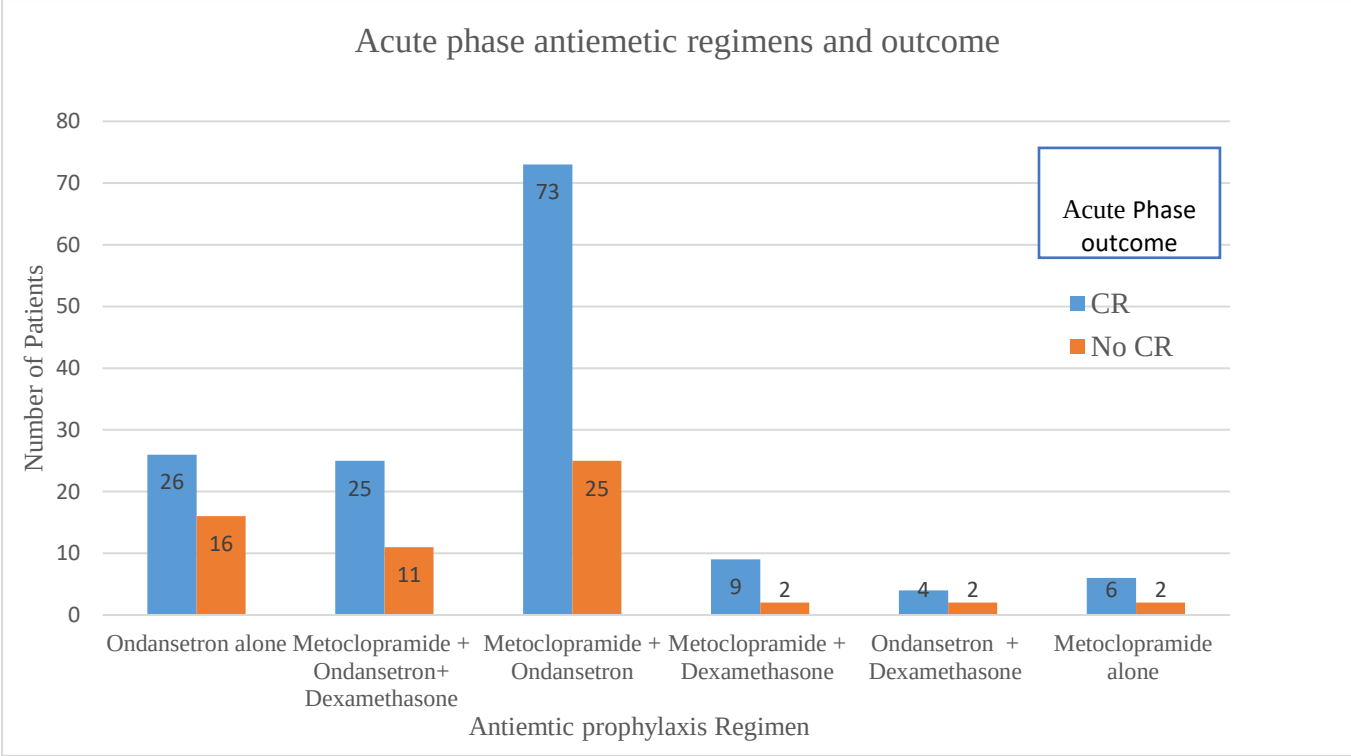

Figure 6: Distribution of antiemetic prophylaxis outcome by acute phase antiemetic regimens

5.5.3.2 Delayed Phase Antiemetics

Among patient who had got prophylaxis during the delayed phase, the highest CR (19.4%) frequency was observed by patients who received an ondansetron-containing dual antiemetics (ondansetron + metoclopramide) compared with patients treated with other triple or single antiemetic regimens (*Table 21*).

Table 21: Distribution of antiemetic prophylaxis outcome by delayed phase antiemetic prophylaxis (N=201)

Antiemetic prophylaxis	No CR (%)	CR (%)
Dexamethasone/Ondansetron/Metoclopramide	9 (4.5%)	27 (13.4%)
Ondansetron/Metoclopramide	37 (18.4%)	39 (19.4%)
Dexamethasone/Metoclopramide	3 (1.5%)	8 (4%)
Dexamethasone /Ondansetron	1 (0.5%)	4 (2%)
Metoclopramide Only	1 (0.5%)	2 (1%)
Ondansetron Only	1 (0.5%)	10 (5.0%)

We also looked at how the presence of dexamethasone in the delayed phase antiemetic prophylaxis regimen affected the antiemetic prophylaxis outcome with respect to chemotherapy regimen emetogenicity. As described in *Table 22*; from a total of 108 patients treated with HEC, patients who did not got dexamethasone during the delayed phase experienced more emetic episodes compared to those who had got dexamethasone (39.8% Vs 5.6%).

Table 22: Presence of dexamethasone in delayed phase and prophylaxis outcome with respect to regimen emetogenicity

HEC Regimen Delayed Phase outcome (N=108)		
Delayed Phase antiemetic	**CR (%)**	**No CR (%)**
With Dexamethasone	23 (21.3%)	6 (5.6%)
No Dexamethasone	36 (33.3%)	43 (39.8%)
MEC Regimen Delayed Phase outcome (N=93)		
Delayed Phase antiemetic	**CR (%)**	**No CR (%)**
With Dexamethasone	16 (17.2%)	7 (7.5%)
No Dexamethasone	62 (66.6%)	8 (8.6%)

5.6 Predictors of CIV/No Complete Response (Logistic regression)

5.6.1 Factors Associated for Developing CIV/No Complete Response within the Acute Phase

To evaluate the independent determinants of CIV occurrence during the acute phase, multivariable logistic regression analysis involving multiple baseline factors were carried out. For the regression analysis purpose chemotherapy regimen category was recategorized into two categories in addition prior CIV history was also recategorized into two categories. The multivariable model for logistic regression proved to be significant with $p < 0.000$, Chi-square (X^2) = 79.197 (N = 201). The model described 45.6% (Nagelkerke R2) of the variation in CIV and properly categorized 83.6% of cases, with independent variables added. Thus, having a history of motion sickness was related with a 4.31-times increased likelihood of CIV occurrence during the acute phase (P < 0.000; 95% CI= [1.93, 9.64]) and a history of CIV with prior chemotherapy was also associated with increased risk of CIV occurrence by 5 odds (P = 0.000; 95% CI= [1.03, 4.65]). Furthermore, receipt of platinum-based chemotherapy regimen has been identified for being a predictor of a higher likelihood of acute CIV (AOR= 5.42 ,95% CI= [1.97, 14.98]) (*Table 23)*.

Table 23: Multiple logistic regression for chemotherapy induced vomiting in acute phase.

Variables	**Category**	**CIV**		**Univariate analysis**		**Multivariable analysis**	
		N	**Y**	**COR (95%CI)**	***P***	**AOR (95%CI)**	***P***
Age (years)	< 5	73	36	1		1	
	5-10	54	12	0.45 (0.22, 0.95)	0.035	0.56 (0.21, 1.47)	0.240
	≥10	16	10	1.27 (0.52, 3.07)	0.60	1.77 (0.59, 5.35)	0.310
Sex	Male	90	32	1		1	
	Female	53	26	1.38 (0.74, 2.56)	0.30	1.65 (0.74, 3.64)	0.219
History of CIV in	No	94	30			1	
Prior chemotherapy	Yes	49	28	1.79 (0.96, 3.31)	0.066	5.02 (2.24, 11.23)	**0.000***
History of Motion	No	103	31	1		1	
sickness	Yes	40	27	2.24 (1.19, 4.22)	0.012	4.31 (1.93, 9.64)	**0.000**
Malignancy type	Leukemia	45	19	1		1	
	Lymphoma	21	4	0.45 (0.17, 1.5)	0.192	3.22 (0.7, 14.74)	0.132
	Solid Tumor	77	35	1.08 (0.55, 2.1)	0.829	3.21 (0.94, 10.97)	0.062
Comorbid illness	Absent	89	31	1		1	
	Present	54	27	1.44 (0.78, 2.66)	0.250	0.48 (0.19, 1.19)	0.112
Chemotherapy	Non-PLT based	96	37	1		1	
regimen	PLT-based	47	21	1.93 (0.96, 3.88)	0.064	5.42 (1.97, 14.98)	**0.001***
Acute phase	Single Agent	32	18	1		1	
Antiemetic prophylaxis	Combination	111	40	1.95 (0.79, 3.09)	0.200	0.35 (0.1, 1.23)	0.100

*****Significant at P< 0.005

5.6.2 Factors Associated for Developing CIV/No Complete Response within the Delayed Phase

The multivariable model for the logistic regression proved to be significant with p = 0.000, Chi-square (X^2) = 99.413 (N = 201. The model described 54.7% (Nagelkerke R^2) of the variation in CIV and properly categorized 84.1% of cases, with independent variables added.

During the delayed phase, multivariable analysis found the variables enumerated below to be related with increased likelihood of CIV: having a history of CIV with prior chemotherapy (AOR 6.27, 95% CI [1.81, 21.7]), receiving a multiple day chemotherapy (AOR 6.44, 95 % CI [1.9, 21.98] and having a history of motion sickness (AOR 3.2, 95% CI [1.34, 7.61]). Furthermore, patients who received rescue antiemetics in the acute phase were 3.85-times more likely to develop CIV as opposed to patients who do not receive rescue antiemetics. On the contrary, receipt of a steroid contained chemotherapy regimen has been associated with reduced likelihood of CIV, (AOR 0.16, 95% CI [0.04, 0.73]) (*Table 24*).

Table 24: Multiple logistic regression for chemotherapy induced vomiting in delayed phase.

Variables	Category	CIV		Univariate analysis		Multivariable analysis	
		N	Y	COR (95% CI)	*P*	AOR (95%CI)	*P*
Age (years)	< 5	67	42	1		1	
	5-10	56	10	0.29 (0.12-0.62)	0.002	1.19 (0.35, 4.07)	0.784
	≥10	14	12	1.37 (0.58-3.24)	0.477	2.18 (0.53, 9.02)	0.284
Sex	Male	87	35	1		1	
	Female	50	29	1.44 (0.79-2.63)	0.234	1.28 (0.54, 3.01)	0.571
BSA	≤ 0.6 m^2	40	33	1		1	
	> 0.6 m^2	97	31	0.39 (0.21, 0.72)	0.002	0.51 (0.16, 1.69)	0.271
Chemotherapy	Chemo-naïve	77	15	1		1	
exposure	Yes	60	49	4.19 (2.15, 8.19)	0.000	1.16 (0.33, 4.06)	0.817
History of CIV in	No	102	22	1		1	
Prior chemotherapy	Yes	35	42	5.56 (2.93, 10.6)	0.000	6.27 (1.81, 21.7)	**0.004***
History of Motion	No	103	31	1		1	
sickness	Yes	34	33	3.23 (1.73-6.02)	0.000	3.2 (1.34, 7.61)	**0.009***
Duration of	Single day	36	6	1		1	
chemotherapy	Multiple day	101	58	3.45 (1.37-8.67)	0.009	6.44 (1.9, 21.98)	**0.003***
Steroid in the	Non-steroid	77	56	1		1	
regimen	steroid containing	60	8	0.18 (0.08-0.41)	0.000	0.16 (0.04, 0.73)	**0.018***
IT chemotherapy	No	83	53	1		1	
	Yes	54	11	3.14 (1.5, 6.53)	0.002	2.1 (0.46, 9.55)	0.338
Chemotherapy	Non-PLT based	113	20	1		1	
regimen	PLT-based	24	44	7.18 (3.47, 14.84)	0.000	2.7 (0.86, 8.24)	0.090
Rescue Antiemetic	No	126	44	1		1	
use in Acute phase	Yes	11	20	5.2 (2.31-11.73)	0.000	3.85 (1.18, 12.6)	**0.025***
Was Antiemetic	No	99	50	1		1	
dexamethasone given	Yes	38	14	0.64 (0.31, 1.31)	0.221	0.34 (0.11, 1.01)	0.051

*****Significant at P< 0.005

5.6 First Emesis Event

The Kaplan–Meier method was performed to estimate the time to first emesis event among patients who received MEC compared to HEC.

Figure 7, illustrates the Kaplan-Meier plots for the time to first emesis event in relation to the level of emetogenicity. The time-to-first emesis event was delayed in patients who received MEC compared to HEC. The log rank test indicated that there was a statistically significant difference between the two emesis-event onsets (P=0.025). Patients who received MEC exhibited an extended period of protection from the first emesis episode: the Kaplan-Meier plots for time to first emesis began to display a visible divergence at approximately 40 hr. In patients who received HEC the median time to first emesis event had been 55 hours (95% CI [14.27, 95.73]), whereas more than 50% of patients who received MEC do not experienced an emesis event from the time of inclusion to end of the observation period. Furthermore, the mean time-to-first emesis event for the patients who received HEC was 67.32 hours (95% CI [58.12, 76.52]) and for patients who received MEC was 80.62 hours (95% CI [70.20, 91.04]).

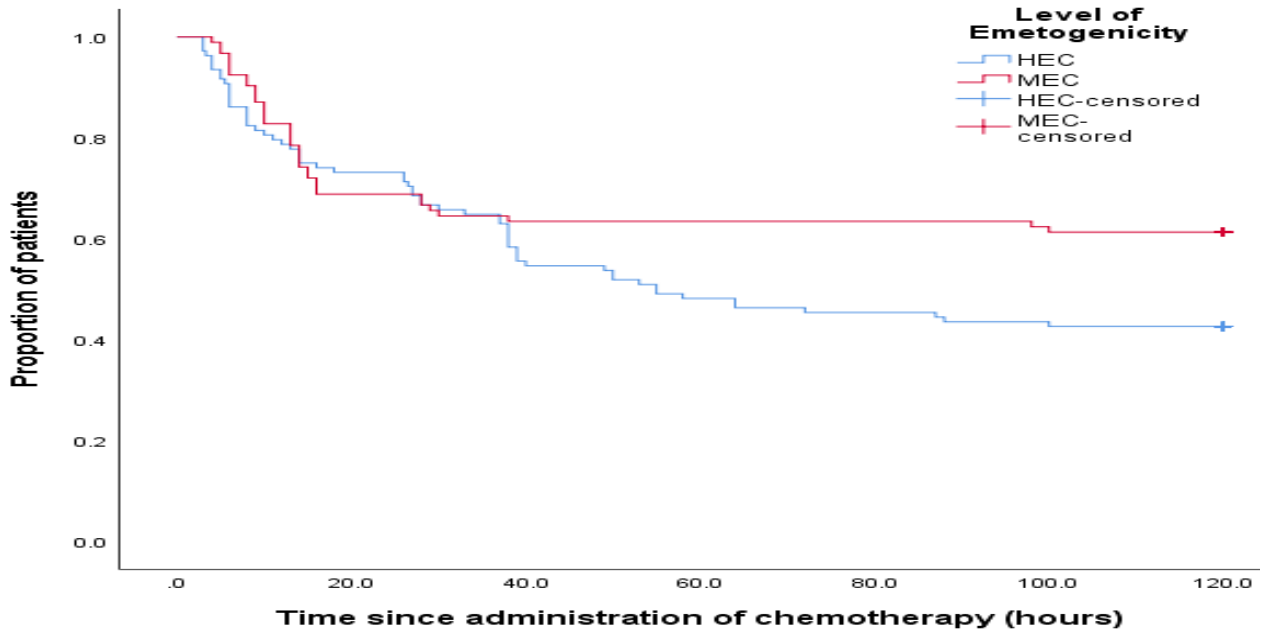

Figure 7: Time to first emesis event curve stratified by level of emetogenicity

Furthermore, when stratified by chemotherapy regimen categories, the time to first emesis event found to be significantly quicker among patients taking chemotherapy containing platinum compound (p= 0.000, through log-rank test; *Table 25* and Figure 8.

Table 25: Means and medians for first emesis event stratified by chemotherapy regimen category

Chemotherapy Regimen Category	Number of cases	Number of events	Number censored	Mean time-to-first emesis event in hrs. (95% CI)	Median time-to-first emesis event in hrs. (95% CI)
CTX + PLT-based	23	15	8	65.52 (48.3, 82.74)	53.0 (27.96, 78.04)
CTX-based	65	22	43	86.59 (74.64, 98.6)	NR
PLT-based	45	38	7	43.37 (31.52, 55.2)	28.0 (13.54, 42.46)
LASP, or Others or AC-based	68	23	45	83.54 (71.4, 95.7)	NR

Abbreviation: NR, Not reached

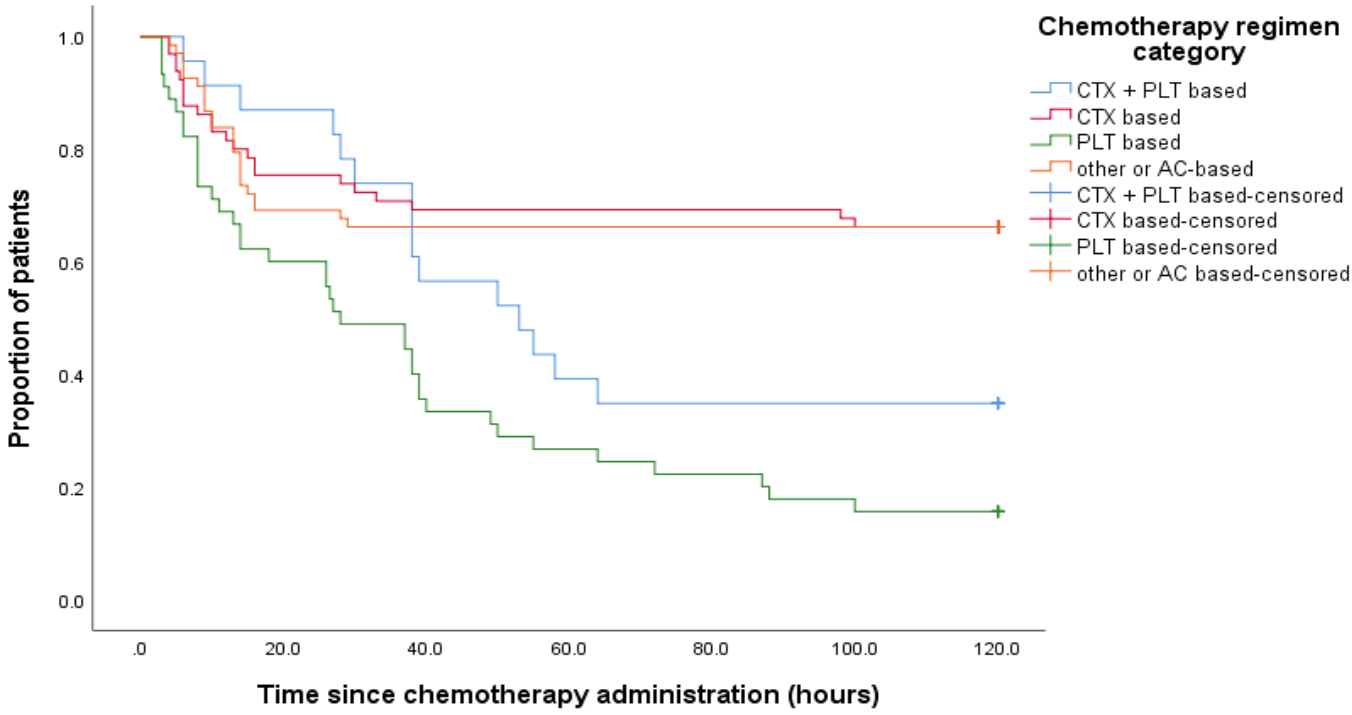

Figure 8: Time to first emesis event curve stratified by chemotherapy regimen category

5.7 Risk Factors for with First Emesis Event within 120 hours post Chemotherapy Initiating

Effects for different variables were evaluated employing Cox regression model. Each variable that could be associated with the likelihood of the first emesis event after starting chemotherapy was determined. The time to first emesis event is typically measured from the start of chemotherapy to the onset of vomiting.

The hazard of developing the first emesis event within 120 hours post chemotherapy did not significantly differ between sex categories despite controlling for covariates (AHR, 1.19 (p= 0.466; 95% CI= [0.76, 1.84]). Similarly, body surface area category, steroid-containing chemotherapy regimen as well as duration of chemotherapy block weren't significantly related to the hazard of developing emesis event. However, a receipt of concomitant intrathecal chemotherapy was associated with a significantly faster rate of first emesis event (AHR, 6.11, 95% CI= [1.51, 24.8]). Also receipt of a platinum-based chemotherapy regimen was associated with 2.22-times faster rate of first emesis event (95% CI= [1.22, 4.02]). Additionally. a history of CIV with prior chemotherapy (AHR, 2.0, 95% CI= [1.01, 3.94]) and a history of motion sickness (AHR, 2.0, 95% CI= [1.36, 3.12]) were also linked with an increased rate of developing first emesis event. In contrast, the age group 5-10 years was associated with delayed hazard of developing the first emesis event as compared to the younger age group < 5 years (AHR, 0.49, 95% CI= [0.27, 0.94]). This analysis's specifics are presented in *Table 26.*

Table 26: Hazard ratio of factors for first emesis event in overall phase

Variables	Category	Crude Hazard ratio (95%CI)	*P*	Adjusted Hazard ratio (95%CI)	*P*
Age (years)	< 5	1		1	
	5-10	0.32 (0.2, 0.56)	0.000	0.49 (0.27, 0.94)	**0.031***
	≥10	0.96 (0.56, 1.66)	0.882	0.86 (0.44, 1.7)	0.673
Sex	Male	1		1	
	Female	1.34 (0.9, 2.0)	0.148	1.19 (0.76, 1.85)	0.446
BSA	≤ 0.6 m^2	1		1	
	> 0.6 m^2	0.56 (0.37, 0.83)	0.004	1.14 (0.65, 2.03)	0.645
Malignancy type	Leukemia	1		1	
	Lymphoma	0.87 (0.39, 1.95)	0.730	0.58 (0.23, 1.52)	0.269
	Solid Tumor	2.04 (1.26, 3.3)	0.004	3.15 (0.9, 11.43)	0.082
History of CIV with	No	1		1	
Prior chemo	Yes	2.14 (1.44, 3.19)	0.000	2.0 (1.01, 3.94)	**0.047***
History of Motion	No	1		1	
sickness	Yes	2.25 (1.51, 3.35)	0.000	2.1 (1.36, 3.12)	**0.001***
Duration of	Single day	1		1	
chemotherapy	Multiple day	1.43 (0.82, 2.48)	0.202	1.11 (0.56, 2.22)	0.763
Chemotherapy	Chemo-naïve	1		1	
exposure	Yes	1.61 (1.1, 2.42)	0.024	0.85 (0.4, 1.78)	0.663
Steroid in the	Non-steroid	1		1	
regimen	Containing				
	Steroid-Containing	0.57 (0.36, 0.91)	0.018	0.65 (0.21, 2.06)	0.466
Chemotherapy	Non-PLT based	1		1	
regimen					
	PLT-based	3.02 (2.0, 4.55)	0.000	2.22 (1.22, 4.02)	**0.009***
IT chemotherapy	No	1		1	
	Yes	0.77 (0.49, 1.2)	0.249	6.11 (1.51, 24.8)	**0.011***

***Significant at P< 0.005

5.8 Relationship between CIV Development (No CR outcome) and the Number of Identified Factors

To see whether holding increased or decreased risk factors had a linear trend with development of CIV Cochran-Armitage test for trend was conducted. According to the multivariable analysis outcomes, one patient- specific variable (having a history of motion sickness) and three treatment-related factors (multiple day chemotherapy, rescue antiemetic use during acute phase and a history of CIV from prior chemotherapy) were established to be significant independent predictive factors for development of CIV during the delayed phase. In the acute phase having a history of motion sickness, prior CIV history and Platinum-based chemotherapy regimen were found to be significant independent predictive variables for the CIV development or no CR outcome.

Having an increased amount risk factors was associated to the number of no CR outcome during delayed phases ($P < 0.000$).'No complete response' outcome to antiemetic prophylaxis or development of CIV was observed in none of patients who had no risk factors, 15.9% of those who had one risk factor, 33.8% of those who had two risk factors, 73.9% of those who had three risk factors, and 100% of those who had four risk factors (Table 27). During the acute phase, having an increased count of identified risk variables was also significantly correlated with the development of CIV (no CR outcome), following similar trend as in the delayed phase ($P < 0.001$).

Table 27: Relationship between CIV development or 'no CR outcome' and number of risk factors

Number of identified risk factors	**Acute Phase**		**Delayed Phase**	
	N	**no CR (%)**	**N**	**no CR (%)**
0	75	13 (17.3%)	15	0 (0.0%)
1	78	24 (30.8%)	82	13 (15.9%)
2	37	15 (40.5%)	71	24 (33.8%)
3	11	6 (54.5%)	23	17 (73.9%)
4	-	-	10	10 (100%)
Cochran-Armitage test for trend		***P* < 0.001**		***P* < 0.000**

N= number of patients

6. Discussion

In this single-center, prospective, observational study, we evaluated the outcome of antiemetic prophylaxis and the incidence of chemotherapy induced vomiting among 201 patients who received moderately to highly emetogenic chemotherapy. Different methods are used to evaluate CINV and antiemetic prophylaxis outcomes in children [73]. By measuring the number of vomiting episodes, emesis can indeed be readily evaluated. Correspondingly in this study, we used the emesis episode counting approach, which has been mentioned elsewhere in different studies [53, 74], to record CIV incidents by asking a proxy. As far as we know, there have been no previous investigations on pediatric populations CIV in Ethiopia, and the fact that this is a longitudinal, prospective study is a bright spot in this study.

Acute lymphoblastic leukemia was the malignancy with the highest frequency, followed by retinoblastoma and rhabdomyosarcoma, in the sample, which was primarily made up of male pediatric patients. Due to the fact that this study included more male than female cancer patients, the patient sample reflected the trend documented in literature. Dorak et al [75] also noted that boys continue to typically have an increased chance of developing cancer compared to girls. ALL being the majority cancer diagnosis within the current study was also in accordance with another study assessing CIV from Kenya [45] as well as with more recent statistics from South Africa [76] that reported leukemia to be the most frequently diagnosed malignancy in children. Likewise, Mark Holdsworth et al. [53] reported comparable results in their research of pediatric patients.

For both moderate and high emetogenic chemotherapies, the incidence of CIV during the acute phase (28.9%) was lesser in the delayed period (31.8%), with a peak on the first day following chemotherapy administration. A higher percentage of HEC regimen patients than MEC regimen patients have experienced CIV (24.4 Vs 7.5) in the delayed phase when emetogenicity is taken into account.

The percentages of CRs obtained during the acute, delayed, and overall phases were 71.1 %, 68.2%, and 51.2%, respectively. This outcome exceeded the CR reported by a study done in Kenya [45], where the CR was reported as 53.41% during the acute, 55.68% during the delayed, and 34.1% during the overall phases. The Kenyan study solely used 5-HT antagonists (ondansetron or granisetron) with or without dexamethasone as an antiemetic regimen, which could be the cause. However, our results for complete response during the overall phase were lower that of a study [17] done in Canada, which indicated a CR of 67%.

Patients who have had chemotherapy may suffer CINV, depending on a variety of factors. The main contributing factors for CINV are regarded to be the doses given and the emetogenicity of the anti-cancer

medications employed in the patient's treatment regimen [77]. Participants on MEC experienced CR rates of 31.8% and 38.8% in the acute and delayed periods, respectively. The CR rate among patients undergoing HEC was 39.3% during the acute and 29.4% during the delayed phase and a higher frequency of complete response for vomiting have been seen in a prior study by Holdsworth et al. [53], with a CR of 73.1% during the acute and 61.3% during the delayed phase. A study done in Kenya [45] likewise revealed that after receiving HEC, the CR rate was 43.48% in the acute phase and 43.48% in the delayed phase. In contrast to the present study and the study carried out in Kenya, where ondansetron 0.15mg/kg prophylaxis was used, the patients (0-11 years) in the study by Holdsworth et al. [53] were administered with higher dose of ondansetron prophylaxis (0.3mg/kg). Furthermore, in a recent observational study [17] done in Canada among children aged 4-18 years, an antiemetic regimen of 5-HT antagonists (granisetron or palonosetron or ondansetron) either alongside or in without dexamethasone resulted in CRs of 57% and 70% during the acute and the delayed phase, correspondingly. This finding also ranked higher than the present study, which can be attributed to the use of newer 5-HT antagonists that were not used in our investigation.

Different combination methods are obviously necessary so as to enhance CINV control in children on a cancer chemotherapy protocol [17]. Current pediatric practice guidelines [20, 62, 78] recommend tripled combinations of antiemetic prevention regimen with a 5-HT3 RA, aprepitant, and dexamethasone in patients receiving HEC. However, because aprepitant was not available in the country, it was not administered to the participants in this study. Moreover, participants took antiemetic prophylaxis with a combination of ondansetron and metoclopramide for about 67.6% of the HEC regimen in the present study. It is unknown why dexamethasone was not provided to some HEC regimen patients, although there was allegedly an occasional dexamethasone stockout at the hospital.

Gender, age, malignancy type, the regimen level of emetogenicity, and choice of prophylactic medicines have all been demonstrated in studies [21, 58, 79] to influence the rate of CR. sex, age, regimen of treatment, and usage of rescue drugs were all investigated as potential risk variables that could alter the outcome during the acute and delayed phases of the study. These variables show differences depending on the phase (delayed or acute phase), these variables differ. The presence of steroids in chemotherapy regimen during the delayed phase, a history of motion sickness and a history of prior CIV in both the acute and delayed phases, duration of chemotherapy block during the delayed phase, receipt of platinum-based chemotherapy in acute phase were discovered to be statistically significant CIV predictor factors in the present study. Other variables, including sex, age, as well as type of cancer, did not appear to be statistically significant predictors of CIV.

The risk of CIV in the acute phase was increased when the chemotherapy regimen consisted of platinum compound. The risk of emesis is higher by 5.42 odds compared to other regimens that do not contain a platinum compound. This mirrors with the findings that showed an increased risk of chemotherapy induced nausea during the acute phase among pediatrics receiving a platinum compound cisplatin ≥ 50 mg/m^2/dose, (AOR, 3.7, 95% CI= [2.1, 6.0]) [51]. Likewise, findings from another study [45] showed patients taking platinum-based protocols became almost 5-times more prone to develop CIV in the delayed phase (AOR , 4.76, P <0.017).

The incidence of delayed CIV increases by six to seven odds with multiple-day chemotherapy in the current study; comparable results have been reported in other studies. Consistent with our finding, one study [45] revealed a nearly 5-times (AOR, 4.91, P<0.004) increased risk of suffering from CIV among individuals receiving a multiple day chemotherapy during the delayed phase than those receiving single day chemotherapy. As described by Dupuis et al. [31], the increased risk of CIV among patients undergoing multiday chemotherapy is supported by the pathophysiology of CIV. In the following and successive days of a multiple day cancer treatment course, for instance, a patient can have an acute CIV, anticipatory CIV due to anticancer agent that will be administered the next day, and delayed CIV as a result of the chemotherapy previously administered [31].

A history of vomiting or nausea owing to factors such as prior emetogenic chemotherapy, motion sickness and surgery has furthermore been recognized to be risk variables for developing CINV among adults [56]. Hence, we also identified that the odds of developing both acute and delayed CIV was greater among patients who had suffered CIV with prior chemotherapy. This is one of the clear clinical messages that was provided by our data. Patients who had CIV in a previous chemotherapy cycle were shown to be 5-6.27 times prone to experience complete response in successive cycles. Previous studies on the incidence of CIV during prior and successive chemotherapy rounds discovered that individuals who had emesis in their previous treatment were substantially more likely to develop vomiting in the following cycle [80, 81]. A prospective, non-interventional multinational study on patients undergoing moderate to highly emetogenic chemotherapy in six Asia Pacific countries revealed that odds of emesis was 12.7-times (95 % CI, 8.47–18.9) higher for patients with prior CIV compared to individuals without a history of prior CIV [80]. Similarly, Molassiotis et al. [49] discovered in a study employing an identical prospective research methodology that having a history of CIV (no complete response) in the previous chemotherapy round appeared to have a 6.6-7.9 times increased odds to experience no complete response in the current cycle. As a result, managing CINV successfully in the previous cycle is a

key method to greatly improve antiemetic prophylaxis outcomes in following cycles. This is as well the advice of MASCC in terms of anticipatory CINV symptoms [60].

In the current study, having a history of motion sickness has been correlated with higher odds of developing CIV (no complete response) during both the acute and delayed phases. This finding is corroborated by prior research that has found that there is an increased risk of CIV in pediatric patients who have a history of motion sickness. In this observational study, [82] which included 101 children receiving HEC or MEC, vulnerability to motion sickness was linked to acute chemotherapy induced nausea (AOR] 5.73, CI [36–33.7]). Furthermore, in the current study having a history of motion sickness was one of the predictive variables found to be significantly correlated with increased risk of experiencing CIV in both acute phase and delayed phase in addition to prior CIV history. This finding offered evidence that pediatric patients having a history of motion sickness had better be regularly monitored for CIV and that healthcare professionals take into account the higher risk of CIV when developing treatment protocols for pediatric patients that have motion sickness history.

Receipt of a combination antiemetic regimen scored the uppermost CR rate during the acute phase. Prophylaxis using ondansetron plus metoclopramide resulted in an acute phase CR among 36.3 % of the study subjects. Likewise, in the delayed phase the highest CR is observed among patients who received ondansetron plus metoclopramide antiemetic prophylaxis (19.4%) followed by triple antiemetic of dexamethasone plus ondansetron plus metoclopramide (13.4%). Moreover, the administration of dexamethasone in patients undergoing treatment with HEC accompanied with fewer emetic episodes than those who had not got dexamethasone (5.9% vs 39.8%). This optimal response was seen when compared to the antiemetic prophylaxis without dexamethasone in the delayed phase. A meta-analysis [59] supports the usefulness of dexamethasone for completely controlling CIV in children, which found considerably higher responses when dexamethasone and 5-HT3 RA were combine as opposed to when dexamethasone was used alone (Relative Risk=2.0, 95%CI =1.35-3.0). In fact, in the current investigation, certain patients receiving HEC who should have gotten dexamethasone in the delayed phase of their antiemetic prophylaxis regimen according to evidence-based guidelines like POGO were not given dexamethasone. There was also a study [83] that reported dexamethasone removal from regimen due to concerns about increased susceptibility to fungal and bacterial infections especially in ALL patients. Then again, the inclusion of steroids in the course of the chemotherapeutic protocol was the only predictor associated with a decreased odds of experiencing CIV in the delayed phase in the current study. In line with our findings, prior research found that patients on steroid-

comprising protocols were far less probable to develop vomiting than those on non-steroid regimens (AOR 0.15; 95% CI, [0.04, 0.61]).

Acute CIV control was previously acknowledged to be the factor related with CIV control in the delayed phase among adult cancer patients [84]. In the current study we have found that receiving rescue antiemetic during the acute phase that means failure to have CR was associated with three to four times increased likelihood of experiencing no complete response in the delayed phase. Consistent to this finding one study [31] described that complete control of CIV in the acute phase was related with a complete control of CIV in the delayed phase among pediatric cancer patients on a multivariable analysis (Relative risk, 2.05; 95% CI, [1.58, 2.66]). Further to that, in pediatric patients, Holdsworth et al. [53] discovered that complete control of CIV during the acute phase is indeed an important predictor of complete control of CIV during the delayed phase. According to Holdsworth et al, among the chemotherapy regimens with CR in the acute phase (835 regimens), CR became most common during the delayed phase (637 regimens; 76.3%), and there was also a considerably decreased CR ($P<0.001$) during the delayed period (155 regimen; 36.8%) among the courses that did not have CR in the acute period (421 regimens).

In the current study the time for development of the first emesis event was also found to be 6.11-times faster in patients receiving concomitant intrathecal chemotherapy compared to patients that do not receive intrathecal chemotherapy in the overall phase. Correspondingly, one study [85] reported that concomitantly receiving intrathecal chemotherapy was significantly linked to quicker hazard of experiencing emesis event in the acute phase among pediatric patients. In this study concomitant administration of IT methotrexate-hydrocortisone-cytarabine was discovered to be linked to roughly 4-times faster hazard of experiencing emesis in the acute phase (adjusted HR= 4.26, 95% CI= [1.65-11.03]). Also in the present study, receipt of platinum compound containing chemotherapy regimen was associated with two times faster risk of developing emesis event in overall phase compared to those patients who had not received platinum compound consisted chemotherapy regimen.

7. Strength and Limitation of the Study

7.1 Strength

Our study's prospective methodology for gathering both objective and subjective data about the CIV experience is one of its key strengths. This design allows the collection of data in the context of actual setting, which increases the external validity of the results. By monitoring patients across a period time frame, the study was able to capture the longitudinal course of chemotherapy-induced vomiting, which will provide valuable insights into the natural history of this condition. The other strength is the study population of pediatrics patients receiving chemotherapy, which allows for the analysis of a specific population that is often under-represented in research. The other strong aspect of this study was being a foundation to carry out further studies on this topic.

7.2 Limitation

As a limitation we mainly relied on the patient’s caregiver/guardian report to measure the incidence of chemotherapy induced vomiting. This approach may have introduced under-reporting or over-reporting of the incidence. Though, this was reduced by cross-checking vomiting events reported by the parents or guardians with the nursing follow-up record and by communicating the parents to prompt them to carefully monitor and document vomiting occurrences. The study was solely focused on chemotherapy induced vomiting and other symptoms such as nausea were not captured.

8. Conclusion and Recommendation

8.1 Conclusion

Finally, this study provides important insights into the prevention of CIV among pediatric cancer patients. A considerable number of participants in this prospective observational study could not achieve complete response. Furthermore, the result of this study provided clues that the rate of acute and delayed emesis control was poorest with platinum-based regimen. Better CIV control was observed with combination antiemetic regimens. The study also identified several factors associated with a higher risk of CIV, including a motion sickness history, receipt of platinum-based chemotherapy, receiving rescue antiemetics at the acute phase and history of prior CIV. Also, an adequate acute emesis control is essential for preventing delayed CIV. Furthermore, this information can assist clinicians in identifying patients who may require more aggressive antiemetic management.

8.2 Recommendations

So based on our observation in general the findings observed in our study ought to be taken into account while planning the antiemetic protocols and some of the recommendations are:

- To tailor the antiemetic prophylaxis regimen to the specific chemotherapy regimen, as well as to the patient’s CINV history and other factors that may affect the risk of emesis.
- To consider complete response as a primary endpoint and to provide patients and their families with education and resources to manage symptoms of chemotherapy-induced emesis. This includes providing them with information on how to communicate with their health care providers.
- A complete strategy for antiemetic prophylaxis selection based on emetogenicity degree and other risk variables needs to be included in the hospital's antiemetic prophylaxis protocol guideline.
- Patients concomitantly receiving intrathecal administered chemotherapy require special consideration and need to be thoroughly monitored for chemotherapy-induced vomiting, since it was found to fasten the time to first emesis event. Similar attention should also be considered among patients with prior CIV, history of motion sickness and receiving platinum-based regimen as it also fastens the time first emesis
- Furthermore, another research that can assess pediatric chemotherapy-induced nausea using a validated nausea assessment is necessary to capture this common side effect of chemotherapy.

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Appendix

Appendix I: Information Sheet

Title of study: Outcome of antiemetic prophylaxis among pediatric cancer patients receiving moderate to highly emetogenic chemotherapy at pediatric hemato-oncology ward of Tikur Anbessa specialized hospital: A Prospective observational study

Hello! I am _____ a member of the research team of the department of clinical pharmacy and pharmacology, AAU, CHS, Sop. I am going to carry out a study on; Outcome of antiemetic prophylaxis among cancer patients undergoing moderate to highly emetogenic chemotherapy. Medicines are not always safe, chemotherapy medications can cause nausea and vomiting as a side effect. Another type of medication is administered in order to stop the vomiting. Thus, we want to know if the vomiting can be stopped by this medication. This will assist clinicians in avoiding vomiting in children who take chemotherapy medications like you.

Therefore, I am requesting you to consent to your child taking part in this research. This study has 5 days of flow up. Your participation in this study is entirely voluntary so you had the choice to decline, decline to participate, or discontinue the interview at any point. During the follow-up days, researchers will be asking both you and your child certain inquiries concerning the occurrences of vomiting. It won't require more than ten minutes per day if you choose to participate.

Appendix II: consent Form

AAU, CHS, School of pharmacy, department of clinical pharmacy and pharmacology, consent form for "Outcome of Antiemetic Prophylaxis among Pediatric Cancer Patients Receiving Moderate to Highly Emetogenic Chemotherapy at Pediatric Hemato-oncology Ward of Hospital."

You have already received an in-depth description of the research and are aware of its purpose. SO, would you kindly let me know if you consent to take part in the study??

1. **Agreed, Proceed the interview**

2. **Not-agreed, Go to the subsequent Subject**

I was informed regarding the study, and I was able to comprehend its objectives as well as advantages. I was aware that no data about my child, including his name and any responses I provided, might be shared with someone else. I have become aware that I have the choice to participate in the research or not, as well as to drop out at any moment.

You have consented to take part in the research by signing here.

Sign of the Participant _____

Name of the interviewer: _____ Sign_____

Name of the Supervisor: _____**Sign_____**

Principal investigator- Hawaryaw Mathewos Hadero

Address- Addis Ababa

Mobile: 0937735217 **Email**: hawaryaw12@gmail.com

Appendix III: Assent Form

AAU, CHS. SoP, department of clinical pharmacy and pharmacology, individual consent form for "Outcome of Antiemetic Prophylaxis among Pediatric Cancer Patients Receiving Moderate to Highly Emetogenic Chemotherapy at Pediatric Hemato-Oncology Ward of Hospital: A Prospective Observational Study"

Purpose of the Study: The objective of this study is to assess the outcome of antiemetic prophylaxis in preventing nausea and vomiting in pediatric patients receiving moderate to highly emetogenic chemotherapy at the pediatric hemato-oncology ward of the hospital. The study will be conducted as a prospective observational study.

What You Will Do in the Study: If you accept to be in this study, you will be required to:

- Allow the study team to observe and record your symptoms during chemotherapy treatment.
- Allow the study team to review your medical records to collect information about your treatment and any other relevant medical information.

Duration of Participation: Your participation in this study will last for 5 days during your chemotherapy treatment.

Possible Risks and Discomforts: There are no known risks associated with this study. However, as a part of the study, you may experience some mild discomfort during the observation of your symptoms.

Possible Benefits: The findings of this study can help improve the care of pediatric cancer patients by identifying effective antiemetic prophylaxis for moderate to highly emetogenic chemotherapy. If you do not want to be in this study, you can still receive standard care for your cancer treatment.

Confidentiality: The information you provide will be kept private. The study team will not share your information with anyone outside of the study team without your permission.

Voluntary Participation: Your involvement in this research is entirely voluntary. You may opt not to take part or withdraw at any moment with no consequence.

By signing below, I indicate that I have read and understand this assent form and that I agree to participate in this study.

_____ _____/_____/_____
Name and Sign of Child/Minor Date

_____ _____/_____/_____
Sign of Parent Date

_____ _____/_____/_____
Name and Sign of Person Obtaining Assent Date

Appendix IV: Data Collection Instrument

Date …. /…../…. Patient Unique Identification Number _____

Data collectors name and sign _____

	Part I: Demographic Characteristics	
101	Age (years)	_____years
102	Sex	Female ☐ Male ☐
103	Wight	_____kg
104	Height	_____
105	BMI _(kg/m^2)	< 18 ☐ 18 – 25 ☐ 25 – 30 ☐ 31 – 35☐ Above 35 ☐
106	BSA	_____ m^2
107	Residence	Rural ☐ Urban☐
108	Region/country	Tigray☐ Amhara ☐ Oromia ☐ SNNPR ☐ Addis Ababa ☐ Others (specify) _____
109	Child's birth order	_____
	Regarding caregiver/Guardian	
110	Who is the primary Caregiver/Guardian	Mother ☐ Father ☐ Sister/brother ☐ Other relatives ☐

	Part-II Clinical characteristics of the patient	
201	Previous uncontrolled CINV History	Admission for uncontrolled CINV ☐ Hospitalization for uncontrolled CINV ☐
202	Does your child have History of motion sickness?	Yes☐ No☐
203	Cancer Diagnosis	Current Stage
204	Date since first Diagnosis (in days)	
205	Cancer chemotherapy regimen **[_____]** ***(write specific Protocol name)***	
	Chemotherapy Regimen (Mediations)	Dosing, route, Administration time

206	Was a corticosteroid given as a part of chemotherapy?	Yes ☐ No ☐
207	Chemotherapy Cycle	specify_____
208	Emetogenicity Level	High ☐ Moderate ☐
209	Concurrent illnesses	Present ☐ Absent ☐ (If present specify) _____ _____ _____
210	What other medication the patient is taking for the Concurrent illnesses?	Specify_____ _____ _____

211	**Other medications**	**Yes, (medications name)**	**No**
	Antivirals	☐	☐
	Antifungal	☐	☐
	Antibiotic	☐	☐
	Narcotics	☐	☐
	Others		

212	Recorded other chemotherapy-induced side effects	Mucositis ☐ Tumor lysis syndrome ☐ Febrile neutropenia ☐ Thrombocytopenia ☐ Typhlitis ☐ Leukopenia ☐ Thrombophlebitis ☐

	Part-III Antiemetic Prophylaxis			
301	Antiemetic prophylaxis protocol			
	Date	**Antiemetic medication, Route**	**Dose, Frequency, Duration**	**Administration Time**

	Part IV: Chemotherapy-induced vomiting event registration Performa			
401	Was the child vomited one hour before chemotherapy administration?		Yes ☐ NO ☐	
402	If the answer for Q #401 is YES Specify the emesis episodes?		_____	
403	Acute phase emesis episodes measuring Performa within 24 hours following chemotherapy ***(Day 1 of chemotherapy)***			
	Day 1 of chemotherapy	0 - 12 hours post chemotherapy	0 - 12 hours post chemotherapy	Day 1 Total vomiting episodes
	Does your child vomit? Yes ☐ No☐ If yes, specify the number of vomiting episodes?			

404	Delayed phase emesis episodes measuring Performa from day two through day five following chemotherapy each morning and evening			
		Specify the daily number of vomiting episodes (below)		
	Days	**Morning measurement**	**Evening measurement**	**Total vomiting episodes**
	Day two			
	Day three			
	Day four			
	Day five			
405	Time of the first episode of the emesis event. ***(Please write the time in front of the day where the first emesis event occurred.)***			
		Time in (hours)		
	Day one			

	Day two	
	Day three	
	Day four	
	Day five	

406	Were rescue antiemetic medications administered?	Given ☐ Not given ☐ List below if given.

	Date	**Rescue antiemetic medications**	**Dose, Frequency, Duration**	**Administration Time**

Appendix V: Amharic Version Information Sheet
የአማርኛ ትርጉም የተሳታፊ መረጃ ቅጽ

አዲስ አባባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ የፋረማሲ ትምህርት ቤት

መግለጫ

የጥናቱ ርዕስ፡ በጥቁር አንብሳ ሰፔሻላይዝድ ሆስፒታል በሕፃናት ካንሰር ህክምና ክፍል በሕፃናት የካንሰር ሕመምተኞች ለይ ከመካከለኛ እስከ ከፍተኛ የማስታወክ ደረጃ ባላቸው የካንሰር ህክምና መድሃኒቶች ምክንያት የሚፈጠርን ማቅለሽለሽ እና ማስታወክ መከላከያ ህክምና ውጤት ምልከታ፡፡

ሰላም! እኔ_____በኤአዩ ፣ በጤና ሳይንስ ኮሌጅ፤ በፋርማሲ ትምህርት ቤት፤ በክሊኒካል ፋርማሲ እና ፋርማኮሎጂ የት/ት ክፍል የጥናት ምርምር ቡድን ውስጥ እየሰራሁ ነው በሕፃናት የካንሰር ሕመምተኞች ለይ ከመካከለኛ እስከ ከፍተኛ የማስታወክ ደረጃ ባላቸው የካንሰር ህክምና መድሃኒቶች ምክንያት የሚፈጠርን ማቅለሽለሽ እና ማስታወክ መከላከያ ህክምና ውጤት ላይ ጥናት ላካሂድ ነው፡፡ መድኃኒቶች ከሚሰጡት በተለየ መልኩ የጎንዮሽ ጉዳት ያስከትሉ፡፡ የካንሰር (የኬሞቴራፒ) መድኃኒቶችም እንደዚሁ ማቅለሽለሽ እና ማስታወክን እንደ የጎንዮሽ ጉዳት ሊያስከትሉ ይችላሉ ፡፡ እነዚህን የጎንዮሽ ጉዳቶችን ለመከላከል እና ለማስቆም ሌሎች መድሃኒቶች ይሰጣሉ፡፡ በዚህ ጥናት ላይ እነዚህ ለመከላከያ የሚወጡ መድሃኒቶች የማቅለሽለሽ እና ማስታወክን ማቆም መቻላቸውን ለማወቅ እንፈልጋለን ፡፡ ይህ እርስዎ ከሚወስዷቸው መድኃኒቶች ጋር የሚመሳሰሉ መድኃኒቶችን የሚወስዱ ሌሎች ሕፃናት የጎንዮሽ ጉዳቶች እንዳይከሰቱ ይረዳናል ፡፡

ከጥናቱ ተሳታፉ ምን ይጠበቃል

ይህ ጥናት የ 5 ቀናት ክትትል አለው ፡፡ በእነዚህ ቀናት እርስዎን ስለልጅዎ የማስታወክ ክስተቶች አንዳንድ ጥያቄዎችን እንጠይቃለን፡፡

የጥናቱ ጠቀሜታ

ከጥናቱ በቀጥታ የሚያገኙት ጥቅም የለም ፡፡ ነገር ግን የጥናቱ ዉጤት የእርስዎ ልጅ ከሚወስዷቸው መድኃኒቶች ጋር የሚመሳሰሉ መድኃኒቶችን የሚወስዱ ሌሎች በሆስፒታሉ የሚገኙ ሕፃናት የካንሰር ህሙማን ላይ የጎንዮሽ ጉዳቶች እንዳይከሰቱ ለማድረግ ይረዳናል፡፡

ሚስጥራዊነት

የተሰበሰቡ ማናቸዉም ግላዊ መረጃዎች ሚስጥራዊነታቸዉ የተጠበቀ ይሆናል፡፡ ከልጆ ማንነት ጋር በቀጥታ ተያያዥነት ያላቸዉ መረጃዎች በሙሉ በዋናዉ ተመራማሪ ሚስጥራዊ በሆነ የመረጃ ጥንቅር ዘዴ ከተቀየሩ በኋላ ብቻ በምርምር ሂደቱ የሚዉል ይሆናለ፡፡ዋናዉ ተመራማሪ ብቻ የዕርሶን የመረጃ ጥንቅር ዘዴ ይጠቀማል፡፡

የመሳተፍ እና ያለመሳተፍ መብት

በዚህ ጥናት ላይ መሳተፍ በሙለ ፈቃደኝነት ላይ የተመሰረተ ነዉ ስለሆነም በጥናቱ እንዲሳተፉ ፍቃደኝነትዎን እንጠይቃለን፡፡ ይህ ጥናት በፈቃደኝነት ላይ የተመሰረተ እንደመሆኑ መጠን በማንኛዉም ወቅት በፍቃድዎ ከጥናቱ መዉጣት ይችላል፡፡ ከጥናቱ እራሶን ቢያገሉም ልጆ ከሆስፒታሉ ማግኘት ያለበትን እርዳታ ወይም ጥቅም አይቀርበትም፡፡ እባክዎ ይህን ጥናት በተመለከተ ወይም ከዚህ ጋር በተዛመደ መልኩ ስለ ሚያጋጥሙ ችግር ወይም ጥያቄ ካሎዎት በሚከተለዉ አድራሻ መግለጥ ይችላሉ፡፡

የዋና ተመራማሪው ስም - ሐዋርያው ማቲዎስ ሀደሮ **አድራሻ - አዲስ አበባ ፣ ኢትዮጵያ**

የሞባይክ ስልክ: - 0937735217 **የኢሜል አድራሻ**: hawaryaw12@gmail.com

Appendix VI: Amharic Version Consent Form

አዲስ አባባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ የፋረማሲ ትምህርት ቤት

የስምምነት ቅጽ

የጥናቱ ርዕስ፡ በጥቁር አንብሳ ስፔሻላይዝድ ሆስፒታል በሕፃናት ካንሰር ህክምና ክፍል በሕፃናት የካንሰር ሕመምተኞች ለይ ከመካከለኛ እስከ ከፍተኛ የማስታወክ ደረጃ ባላቸው የካንሰር ህክምና መድሃኒቶች ምክንያት የሚፈጠርን ማቅለሽለሽ እና ማስታወክ መከላከያ ህክምና ውጤት ምልከታ::

የጽሑፍ ስምምነት ቅጽ

ቀደም ሲል ስለ ጥናቱ በአጭሩ እንዲያውቁ ተደርጓል እና ዓላማውን በግልጽ ተረድተዋል :: አሁን በጥናቱ ለመሳተፍ ከተስማሙ እባክዎን ንገሩኝ?

1. ተስማማ ፣ አመሰግናለሁ! ቃለመጠይቁን ያካሂዱ
2. አልተስማማም ፣ አመሰግናለሁ! ወደ ቀጣዩ ብቁ ተሳታፊ ይቀጥሉ

በጥናቱ መግለጫ ገጽ ውስጥ ያለውን መረጃ ሰምቻለሁ እና የጥናቱን ዓላማ እና ፋይዳ ተረድቻለሁ :: ልጄን የሚመለከቱ መረጃዎች ሁሉ እንደ ስም እና የምሠጣቸዉ መልሶች ሁሉ ወደ ሶስተኛ ወገን እንደማይተላለፉ ተረድቻለሁ :: በተጨማሪም በጥናቱ ላይ ለመሳተፍ ወይም ላለመሳተፍ ወይም በማንኛውም ጊዜ ከጥናቱ ለመላቀቅ መወሰን እንደምችል ተረድቻለሁ ::

ከዚህ በታች ያለው ፊርማዎ በዚህ ጥናት ውስጥ ለመሳተፍ መስማማትዎን ያሳያል ::

የተሳታፊ ፊርማ ፡ _____

የቃለ-መጠይቅ ጠያቂው ስም: _____ **ፊርማ** _____

ተቆጣጣሪ ስም: _____**ፊርማ** _____

የዋና ተመራማሪው ስም - ሐዋርያው ማቲዎስ ሀደሮ

አድራሻ - አዲስ አበባ ፣ ኢትዮጵያ

የሞባይል ስልክ: - 0937735217 **የኢሜል አድራሻ**: hawaryaw12@gmail.com

Appendix VII: Amharic Version Assent Form

አዲስ አባባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ የፋረማሲ ትምህርት ቤት

የጥናቱ ተሳታፍ የስምምነት ቅጽ

የጥናቱ ርዕስ፡ በጥቁር አንብሳ ሰፔሻላይዝድ ሆስፒታል በሕፃናት ካንሰር ህክምና ክፍል በሕፃናት የካንሰር ሕመምተኞች ለይ ከመካከለኛ እስከ ከፍተኛ የማስታወክ እና ማቅለሽለሽ ደረጃ ባላቸው የካንሰር ህክምና መድሃኒቶች ምክንያት የሚፈጠርን ማቅለሽለሽ እና ማስታወክ መከላከያ ህክምና ውጤት ምልከታ::

የጥናቱ ጠቀሜታ

የዚህ ጥናት ዓላማ በሆስፒታሉ የሕፃናት ሄማቶ-አንኮሎጂ ክፍል ከመካከለኛ እስከ ከፍተኛ የማስታወክ እና ማቅለሽለሽ ደረጃ ባላቸው የካንሰር ህክምና መድሃኒቶች በሚወስዱ የሕፃናት ታካሚዎች ላይ ማቅለሽለሽ እና ማስታወክን ለመከላከል የሚሰጠዉን መከላከያ ህክምና ውጤትን ለመገምገም ነው::

በዚህ ጥናት ውስጥ ለመሳተፍ ከተስማማህ የሚከተሉትን እንድታደርግ ይጠየቃል።

- የጥናት ቡድኑ በኬሞቴራፒ ሕክምና ወቅት ምልክቶችዎን እንዲመለከት እና እንዲመዘግብ ይፍቀዱለት።
- የጥናት ቡድኑ ስለ ህክምናዎ እና ስለማንኛውም ተዛማጅ የህክምና መረጃ ለመሰብሰብ የእርስዎን የህክምና መዝገቦች እንዲገመግም ይፍቀዱለት።

የተሳትፎ ጊዜ፡ በዚህ ጥናት ውስጥ ያለዎት ተሳትፎ ለ 5 ቀናት የኬሞቴራፒ ሕክምና ጊዜ ይቆያል።
በጥናቱ ተሳትፎ ሊሆኑ የሚችሉ አደጋዎች እና ምቾት ማጣቶች፡ ከዚህ ጥናት ጋር የተያያዙ ምንም የሚታወቁ አደጋዎች የሉም። ነገር ግን፣ እንደ የጥናቱ አካል፣ ምልክቶችዎን በሚታዩበት ጊዜ መጠነኛ የሆነ የምቾት መጓደል ሊሰማዎት ይችላል።

በጥናቱ ተሳትፎ ሊገኙ የሚችሉ ጥቅማ ጥቅሞች፡ የዚህ ጥናት ውጤት ከመካከለኛ እስከ ከፍተኛ የማስታወክ እና ማቅለሽለሽ ደረጃ ባላቸው የካንሰር ህክምና መድሃኒቶች በሚወስዱ የሕፃናት ካንሰር ታካሚዎች እንክብካቤ ለማሻሻል ይረዳል። በዚህ ጥናት ውስጥ መሳተፍ ባይልፈለጉ እንኳን፣ ለካንሰር ህክምናዎ መደበኛ እንክብካቤ አሁንም ማግኘት ይችላሉ።

ምስጢራዊነት፡ ከእርስዎ የሚሰበሰበው መረጃ በሚስጥር ይጠበቃል። የጥናት ቡድኑ ያለእርስዎ ፍቃድ መረጃዎን ከአጥኚ ቡድኑ ውጭ ለማንም አያጋራም።

በፈቃደኝነት ተሳትፎ፡ በዚህ ጥናት ውስጥ ያለዎት ተሳትፎ በፈቃደኝነት ነው። ላለመሳተፍ መምረጥ ወይም በማንኛውም ጊዜ ያለ ምንም ቅጣት መሳተፍ ማቆም ይችላሉ።

ከላይ የተዘረዘሩትን መረጃዎች በመረዳት በዚህ ጥናት ለመሳተፍ እንደተስማማሁ አመልክቻለሁ።

_____ _____/_____/_____

የልጁ ስም ፊርማ እና ቀን

_____ _____/_____/_____

የወላጅ/አሳዳጊ ስም ፊርማ እና ቀን

_____ _____/_____/_____

የመረጃ ሰብሳቢ ስም ፊርማ እና ቀን

የዋና ተመራማሪው ስም - ሐዋርያው ማቲዎስ ሀደሮ አድራሻ - አዲስ አበባ ፣ ኢትዮጵያ

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