Addis Ababa University

College of Health Sciences

School of Pharmacy

Department of Pharmacology and Clinical Pharmacy

Identification and Resolution of Drug Related Problems in Pediatric Hematology/Oncology Ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

By: Malede Berihun

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A Thesis Submitted to 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

Addis Ababa University

School of Graduate Studies

This is to certify that the thesis prepared by Malede Berihun entitled "Identification and Resolution of Drug Related Problems in Pediatric Hematology/Oncology Ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia" and submitted in partial fulfilment for the requirements of Master of Science Degree in Pharmacy Practice complies with the regulations of the university and meets the accepted standards with respect to originality and quality.

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Abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AML	Acute Myeloid Leukemia
AOR	Adjusted Odds Ratio
ATC group	Anatomical Therapeutic Chemical group
BSA	Body Surface Area
COR	Crude Odds Ratio
DRP	Drug Related Problem
HL	Hodgkin's Lymphoma
IT MTX	Intrathecal Methotrexate
IQR	Interquartile Range
LMIC	Low and Middle-Income Countries
NF	Neutropenic Fever
NHL	Non-Hodgkin Lymphoma
PCNE	Pharmaceutical Care Network in Europe
SR-ALL	Standard Risk- Acute Lymphoblastic Leukemia
TASH	Tikur Anbessa Specialized Hospital
TMP/SMX	Trimethoprim– Sulfamethoxazole
WHO	World Health Organization
ZMRH	Zewditu Memorial Referral Hospital

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Abstract

Identification and Resolution of Drug Related Problems in Pediatric Hematology/Oncology Ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Malede Berihun
Addis Ababa University, 2019

Even though, medications play a major role in the cure, palliation and inhibition of disease, they also expose patients to drug related problems. Drug related problems are frequent and may result in reduced quality of life, and even morbidity and mortality. Many studies have shown that clinical pharmacists can effectively identify and resolve clinically significant drug related problems. There is no data regarding drug related problems in pediatric cancer patients in Ethiopia. This study was aimed to identify and resolve drug related problems in Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. A prospective interventional study was used to assess drug related problems on patients admitted at the Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital between 25 June to 25 October, 2018. Data were obtained from the patients' medical chart, physician, patient/care giver, pharmacists and nurses. All the collected data were entered and analyzed using the Statistical Package for the Social Sciences version 25 software. Among the total 156 participants, Drug related problems were identified in 68.6% of the study subjects. Dosing problems which includes dosage too low and high were the top ranking (39.3%) of all drug related problems followed by needs additional therapy (27.2 %) and non-adherence (14.0%). Anti-infectives for systemic use were the most common drug classes involved in drug related problems followed by antineoplastic and immunomodulating agents. Trimethoprim-sulfamethoxazole, methotrexate, vincristine, ondansetron and metoclopramide were the top ranking drugs involved in drug related problems. Addition of drug and change in drug dose were the two most proposed intervention types. Among the proposed interventions, 223 (92.15%) were fully accepted, 9 (3.72%) partially accepted and 10 (4.13%)not accepted. Length of hospital stay (AOR = 30.63, 95%; CI: 6.72, 139.63; P=0.000) was found to be a risk factor for occurrence of drug related problems. Drug related problems are common among Pediatric Hematology/Oncology ward patients. The study also demonstrated that clinical pharmacists can effectively identify and resolve clinically significant dug related problems. Length of hospital stay is an important risk factor for DRPs, but there is no significant

association between occurrence of DRP and sex, age, presence of neutropenic fever in the study subjects.

Key words: Drug related problems, Pediatric Hematology/Oncology ward, Tikur Anbessa Specialized Hospital

1. Introduction

1.1. Background

According to an international study conducted by Steliarova-Foucher *et al* (1), childhood cancer was 13% more common than in the 1980s, reaching an annual incidence rate of 140 per million children (age 0–14 years) worldwide based on the records of about 300,000 cancer cases. The annual incidence rate in adolescents (age 15–19 years) was 185 per million, based on records of about 100,000 cancer cases.

In the United States, there are approximately 14,500 new cases of cancer diagnosed each year in children from birth up to 19 years. Approximately 1800 to 1900 of these patients will die from the disease. Despite the progress that has been made in the treatment of these patients, death from cancer remains the leading cause of death from disease in children (2).

Globally, the number of new cancer cases in all age groups will increase from 12.7 million in 2008 to 22.2 million by 2030 (3). An increasing proportion of this cancer burden falls on low and middle-income countries (LMICs) (4). Demographic change, prevalence of infectious diseases and a transition in risk factors resulting from globalization of economies and behaviors contributed for the high burden of cancer in LMICs (5, 6).

In Ethiopia, national data on prevalence and incidence of cancer are lacking. However, extrapolation from clinical records of the Tikur Anbessa Specialized Hospital (TASH) Radiotherapy Centre estimates that there are 120,500 new cancer cases and approximately 6000 new cases of pediatric cancer each year. Most of the pediatric cancer patients present with advanced disease and there is a high rate of abandonment of treatment which leads to high mortality rates (7).

There are many types of cancer treatment modalities, which include surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy, stem cell transplant and precision medicine. Selection depends on the type and staging of the cancer diagnosis (8). Even though, medications play a major role in the treatment of disease, they also expose patients to drug

related problems (DRPs). Therefore, the concept of DRPs is essential for pharmaceutical care, and the care process (9). Children are particularly susceptible to DRPs as they vary in weight, body surface area (BSA) and organ maturity which can affect their ability to metabolize and excrete medications effectively (10).

In systemic cancer therapy, drug regimens are administered following established protocols which have been carefully evaluated in clinical trials. The more complex drug therapy is the higher the risk of experiencing DRPs such as adverse effects, interactions, medication errors, and non-adherence (11). Nausea and vomiting, infections, neutropenia, fever and/or chills, and anemia are common during treatment with cytotoxic medications which ultimately leads to a higher incidence of DRPs as compared to other medications (12).

Outcome of children with cancer in LMICs is highly affected by DRPs such as non-adherence to the prescribed medications, suboptimal supportive and palliative care, and limited access to curative therapies (13). In addition, 2/3rd of childhood cancer survivors will experience severe long-term sequelae of their treatment (14, 15).

There are a variety of definitions and classifications of DRPs. According to the Pharmaceutical care network in Europe (PCNE), DRPs have been defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" (16). A potential problem is not manifestation, but if left unresolved, it may lead to drug related harm to the patient. However, an actual problem has resulted in clinical manifestations like adverse drug reaction (ADR) or therapy failure due to incorrect dosage (17).

According to Cipolle *et al* (18) classification system all patient problems involving medications can be categorized into one of the seven types of DRPs. These include unnecessary drug therapy, need for additional drug therapy, ineffective drug, dosage too low, adverse drug reaction, dosage too high and non-adherence.

DRPs may occur at any stage of the medication prescribing, dispensing, administration and use process. Unless appropriately identified and managed at its occurrence stage, DRPs will negatively affect patients' treatment outcome as shown in Figure 1.

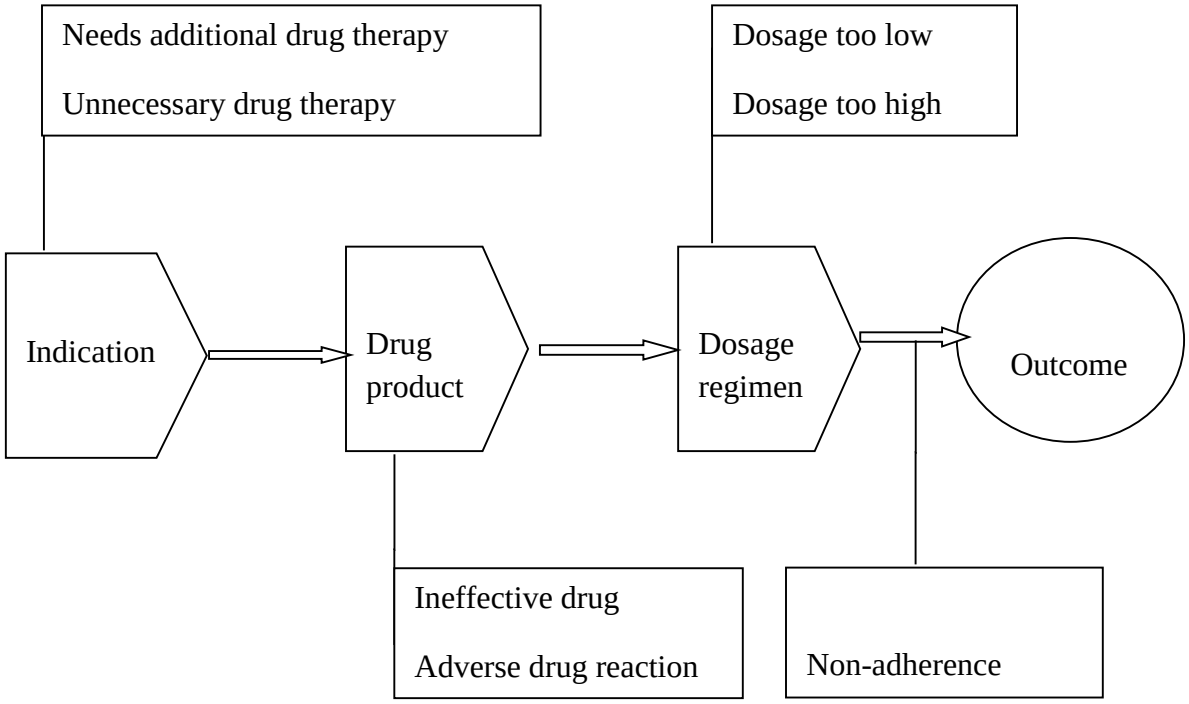

Figure 1: Drug Related Problems stages of occurrence.

Clinical pharmacists' intervention may help to avoid DRPs and improve patients' therapeutic outcome and quality of care (10, 19-22).

1.2. Statement of the problem

DRPs are a major issue in pharmacotherapy. The prevalence of DRPs varies depending on the setting, country, type of medications used and disease conditions. Cancer pharmacotherapy is more complex that requires the use of many drugs, which ultimately increases the occurrence of DRPs (11).

Pediatric patients with cancer had more frequent DRPs than those without cancer. While most DRPs in cancer patients were caused by antitumor agents, other medications could also cause the greatest proportion of fatal or life-threatening DRPs (23).

It would be much better to prevent DRPs than to correct them, but this is not always possible because of the complexity of pharmacotherapy, lack of training and knowledge of health care providers and behavior of the medicine users. Some pharmacotherapy problems are also the result

of an unexpected reaction of the individual, like allergies, and cannot always be predicted. Therefore, even if one could analyze the medication and patient related factors during a medication review before a medicine is handed over to the patient, evaluation of the pharmacotherapy after it has been initiated still remains important to detect DRPs and optimize treatment outcomes (9).

Approximately, 80% of children undergoing treatment for high-risk cancer experience severe, life-threatening or fatal side effects at some point during their treatment. The side effects are diverse and dependent upon a number of factors, including therapeutic modalities used, types of drugs and doses of drugs administered, and age of the child undergoing treatment. Pediatric patients are most susceptible to DRPs due to the immature physiological functions (2). Even among pediatric patients, it was found that pediatrics aged ≤1 year were more prone to DRPs (10).

There are a number of consequences associated with DRPs, which include hospitalizations, long-term care admissions, emergency department visits, additional physician office visits, and additional prescriptions. In addition to these, substantial costs are also associated with DRPs. For example, the economic burden arising from drug related morbidity and mortality in USA was $177.4 billion annually (24). DRP induced pediatric hospital admission is also a major public health issue. For example, studies from Australia reported that 4.3% of pediatric admissions were related to DRPs. Direct costs associated with DRPs has been reported to be £100,707 (20).

Though there were different studies done focused on DRPs in different settings, there is no study on DRPs in Pediatric Hematology/Oncology ward of TASH, Addis Ababa, Ethiopia. Therefore, the objective of this study was to identify clinically significant DRPs and make appropriate intervention in Pediatric Hematology/Oncology ward of TASH, Addis Ababa, Ethiopia.

This study would add information regarding DRPs and might be useful to other researchers as a reference material while conducting further studies on related topics. Identification and intervention on actual and potential DRPs, along with awareness of drugs carrying a high risk for DRPs, are important elements of pharmacotherapy and may contribute to improve drug related morbidity and mortality. In addition, identification of predictors for the occurrence of DRPs may be helpful in finding patients at risk.

The findings of this study might also help in influencing the development of appropriate policies, plans and intervention programs for the prevention and management of DRPs. This in turn, might improve the quality of care for patients admitted in hospitals.

1.3. Literature review

Often the most cost-effective pharmacotherapy focuses on the prevention of illness. The same preventive focus is relevant when dealing with DRPs, as their occurrence is associated with negative health outcomes. Hence, the main objective should be to prevent drug related morbidity and mortality (17). Procedures for identification and intervention on clinically significant DRPs are an important elements of pharmacotherapy and may contribute to optimize treatment outcomes (25).

Clinical pharmacists play a vital role in a multidisciplinary health care team through early identification, prompt intervention and further prevention of DRPs, which will help to optimize patient drug therapy. The identification of DRPs and their prevention through pharmacist interventions in pediatrics drug therapy may help to avoid the unwanted harmful effects of drugs that will help in improving therapeutic outcome and quality of care (10).

In a retrospective study done in pediatric ward of Zewditu Memorial Referral Hospital (ZMRH), Addis Ababa, Ethiopia, the overall rate of DRPs was found to be 32%. The most frequently identified DRPs were dosing problems, with dose too low being 35% and dose too high being 7.5%. This was followed by drug–drug interactions (39%) and ADRs (8.5%) (26).

A multicenter prospective observational study in four pediatric centers done by Prot-Labarthe *et al* (27) identified 996 DRPs in 270 patients with an average of 3.7 DRPs per patient. The main DRPs were inappropriate administration technique (29 %), untreated indication (25 %) and supra-therapeutic dose (11 %). In a cross-sectional study conducted at TASH, Addis Ababa, Ethiopia, the prevalence of DRPs in adult cancer patients was found to be 75%. In this study, the most prevalent DRP was ADR (45.5%) followed by dosing problems (37.9%) (28).

In a prospective interventional study carried out in pediatric wards of a tertiary care teaching hospital of India, a total of 46 DRPs were identified from 39 patient case records. The number of DRPs was predominant in males than females. DRPs were commonly seen in patient's $\leq$ 1 years

of age. In this study, the most common DRPs were found to be drug- drug selection (71 %) followed by ADR (8.1%) (10).

A cohort study enrolling pediatric in-patients with and without cancer at two tertiary care teaching hospitals in Japan showed that adverse drug events (ADEs) occurred 28 times more frequently in pediatric patients with cancer than without cancer. The study identified in 20% of study subjects. The ADEs distribution was 7.1 and 0.25 per patient among cancer and non-cancer patients, respectively. The most common medications associated with ADEs in cancer patients were antitumor agents. However, sedatives (25%) and blood products (25%) were the most often medications associated with fatal or life-threatening ADEs in cancer patients (23).

In a study conducted in Norway, the majority of hospitalized patients had DRPs. Among the participants, 81% of them had DRPs and an average of 2.1 clinically relevant DRPs was recorded per patient. The DRPs most frequently recorded were dose related problems (35.1% of the patients) followed by need for laboratory tests (21.6%), non-optimal drugs (21.4%), need for additional drugs (19.7%), unnecessary drugs (16.7%) and medical chart errors (16.3%) (25).

In a prospective, descriptive, observational study carried out in France, the pharmacists identified 552 DRPs (12.6% of the prescriptions) primarily related to anti-infective agents (59.5%). Medication problems included inappropriate medications (20.6%), untreated indications (14.8%), inappropriate administrations (14.1%), under-dosing (11.7%), drug-drug interactions (14.3%), lack of monitoring (9.6%), overdosing (8.9%), administration omissions (3.5%) and side-effects (2.5%) (29).

In another prospective, descriptive, observational study done by Bulsink *et al* (30) in the Netherland, among 546 patients with cancer, 952 potential DRPs were identified with an average of 1.74 DRPs per patient. Of 952 DRPs, 474 were oncology-related. The DRPs were mainly drug interactions (246 drug interactions in 157 patients) and potential contraindications (201 potential contraindications in 143 patients).

In a study conducted in oncology ward of Norway by Cehajic*et al* (31), the clinical pharmacists identified 100 DRPs among 35 (73%) of the included patients, giving an overall frequency of 2.1

DRPs per patient. In this population of hospitalized cancer patients, the most frequent DRPs were related to the selection of drugs and drug dosage.

A prospective, observational study also identified 416 DRPs among 189 study subjects which was on average 2.2 DRPs per patient. Among different causes of DRPs that were identified during the study, the problems caused due to inappropriate drug selection were found to be the highest (22.17%), which was followed by inappropriate drug combination (16.39%) (32).

Non-adherence to the prescribed medications is also common in pediatric patients. A study conducted in Egypt children's cancer hospital showed that 68% of the participants were not adherent to their treatment. The main reasons for non-adherence were child resistance and inadequate information (33).

Clinical pharmacists' intervention can decrease the prevalence of DRPs and improve patients' treatment outcome. A prospective observational and interventional study carried out in pediatric inpatient department of a tertiary care hospital showed a gradual decrease in DRPs from 70% to 17.5% after incorporation of clinical pharmacists in wards which showed greater acceptance of clinical pharmacists' intervention (34). A study in Oslo University Hospital also showed a change in drug treatment as a result of interventions suggested by the clinical pharmacist in 75% of cases. Interventions suggesting different treatment options were implemented quite often (18 of 21 interventions), while the oncologists more often rejected interventions suggesting different dosages (10 of 19 interventions) (31).

In another study conducted to assess DRPs and clinical pharmacists' Interventions, the acceptance rate of clinical pharmacists' interventions was found to be 90% (22). A study in France also showed a high acceptance and implementation of clinical pharmacists' interventions (29). In this study interventions including treatment discontinuations (26.2%), drug dosing adjustments (21.5%), drug additions (16.9%), alternate routes of administration (11.7%), replacement of a drug by another one (10.7%), therapeutic drug monitoring (10.3%) and optimizing administration (2.6%) were made.

Though clinical pharmacists' interventions acceptance rate was high (75-96%) in many studies (22, 29, 31), a lower acceptance was also reported in a prospective, observational study conducted

in India (10). Among the total DRPs identified in this study, 125 (30.04%) interventions were accepted, 7 (1.68%) interventions were not accepted, while remaining (68.26%) accepted but no action was taken.

Identification of predictors for the occurrence of DRPs helps to prevent the occurrence of DRPs. A study conducted in the pediatric ward of ZMRH, Addis Ababa, Ethiopia showed that number of disease condition and number of drugs taken had significant association with DRPs. Based on this, patients who had 3 diseases condition were about 5 times more likely to have DRPs compared to those patients who had one disease condition. On the other hand, Patients who took 5 or more drugs were about 2 times more likely to have DRPs compared to those patients who took less than 5 drugs (26).

Number of prescribed medications also showed significant association with DRPs occurrence in a prospective cohort study conducted in seven Hong Kong hospitals. The result showed that a patient was more likely to experience a DRP if the average number of prescribed drugs per patient was ≥ 5 and/or the patient was diagnosed with infectious diseases (35). A study conducted in adult cancer patients also demonstrated that the number of medications, comorbidities and length of hospital stay have a significant effect on the occurrence of DRPs (28).

2. Objectives

2.1. General objective

To identify and resolve drug related problems in patients admitted to the Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

2.2. Specific objectives

- ✓ To determine the incidence of DRPs
- ✓ To identify the most common drugs and drug classes involved in DRPs
- ✓ To resolve the identified DRPs
- ✓ To determine acceptance rate of interventions
- ✓ To identify predictors for the occurrence of DRPs

3. Methods

3.1. Study setting

The study was conducted at Pediatric Hematology/Oncology ward of TASH, Addis Ababa, Ethiopia. TASH is the only highest level referral center for critical and complicated health problems of the country. It gives services to high number of patients. It offers comprehensive health care service for around half a million patients per year through specialty clinics and inpatient service departments. It has over 700 beds, and about 1700 professional and support staffs in inpatient, outpatient and emergency units.

Among the main inpatient service departments; Pediatric Hematology/Oncology ward is the one which provides comprehensive specialized services to pediatric cancer patients. In this ward there are 26 beds with a total of 2 oncologists, 6 residents and 9 nurses. On average, it gives services for around 260 patients per year.

3.2. Study design and period

A prospective interventional study design was used to asses DRPs in Pediatric Hematology/Oncology ward of TASH. The study was conducted for four months' period from 25 June to 25 October, 2018.

3.3. Source and study population

All patients admitted to Pediatric Hematology/Oncology ward of TASH formed the source population for this study. Whereas, all patients admitted to Pediatric Hematology/Oncology ward of TASH from 25 June to 25 October, 2018 and fulfilling the inclusion criteria constituted the study population

3.4. Sampling and sample size determination

Because of the low number of annual estimated patients admitted to Pediatric Hematology/Oncology ward of TASH, the study included all patients admitted to this ward and fulfilling the inclusion criteria during the study period.

3.5. Inclusion and exclusion criteria

Inclusion criteria:

- ✓ Admission to Pediatric Hematology/Oncology ward

Exclusion criteria:

- ✓ Refusal to participate
- ✓ Patients whose working diagnosis was not confirmed
- ✓ Repeatedly admitted patients
- ✓ Patients who were waiting only for surgical management

3.6. Study variables

Dependent variable:

- ✓ Drug related problem

Independent variables:

- ✓ Sex
- ✓ Age
- ✓ Resident
- ✓ Presence of comorbidity
- ✓ Neutropenic fever
- ✓ Length of hospital stay
- ✓ Number of drug prescriptions

3.7. Data collection and management

3.7.1. Data collection tool and procedure

Data was collected using pre-tested data abstraction format which can answer all the research questions. The data abstraction format includes relevant information about each patient like patient characteristics, physical examination, laboratory results, type of disease conditions, current

medications, co-morbidities, length of hospitalization, and relevant previous medical and medication histories. Supplementary information and clarifications on some patient's medical information was obtained through discussion with the care giver and the physician. Adherence and administration related problems were assessed through observation and discussion with physicians, patients/care givers and nurses. In addition, the availability, strength, dosage form selection and counselling issues of drugs were discussed with pharmacists. The patients were followed up on daily basis.

Once the data was collected, the principal investigator evaluated appropriateness of medical therapy using various references like Medscape, Up-to-date 21.6 version, Micromedex, standard and updated text books, and specific guidelines from National Comprehensive Cancer Network (NCCN) and American Academy of Pediatrics (AAP) based on the updated daily patient and clinical characteristics. Equations like modified Schwartz equation for creatinine clearance calculation, Du Bois method for BSA calculation, Calvert formula for carboplatin dose calculation were used. The doses of cytotoxic medications were evaluated based on the Hematology/Oncology Pharmacy Association (HOPA) guideline. A dose rounding within 10% of the prescribed dose was recommended for traditional cytotoxic agents according to the HOPA guideline, which was reviewed and endorsed by NCCN (36). Accordingly, dosing errors more than 10% was considered as DRP in this study

Possible intervention measures were then proposed and communicated to either the oncologists/hematologists/residents/nurses/pharmacists or the patients/care givers in order to resolve or prevent DRPs as soon as possible. The identified DRPs were recorded and classified using DRP registration format of Cipolle *et al* (18) and the status of interventions was documented. In addition, drugs associated with DRPs were classified using the Anatomical Therapeutic Chemical (ATC) classification system (37).

3.7.2. Data quality assurance

Data was collected by the principal investigator and trained data collectors (Two pharmacists and one nurse). In order to assure data quality, training was given for the data collectors about the aim of the study and content of the data abstraction format. Suitability of the data abstraction format was assessed through in depth discussion with experienced oncologists and research advisors.

Pretest was also done on 10 patients who were admitted to Pediatric Hematology/Oncology ward of TASH before data collection to ensure consistency of data collection format and appropriate modifications were made accordingly. The principal investigator together with the trained data collectors was responsible to review and update all patient data needed for the identification of DRPs on a daily basis. The principal investigator was also responsible for on spot supervision of the work of the data collectors.

3.7.3. Data entry, clean up and analysis

The collected data were categorized, coded, entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version25 software. Descriptive statistics such as mean, median, interquartile range (IQR), cross tabulation and frequencies were used to present the data. In addition, logistic regression was done for independent variables affecting the occurrence of DRPs. Univariate analysis was done to avoid confounders. Variables having p-value less than 0.25 with the outcome (DRP occurrence) in univariate analysis were considered for further analysis. Independent predictors were then identified by a multivariate logistic-regression analysis. All statistical tests were 2-tailed; a p value ≤ 0.05 was considered statistically significant.

3.8. Ethical considerations

Ethical approval was obtained from the School of Pharmacy, College of Health Sciences, Addis Ababa University Ethics Review Board and permission letter was also obtained from the pediatric department. Informed consent from a care giver and assent from participants aged 12 years and above was also obtained. Confidentiality of the information of study participants was ensured by omitting the patients name and using code number.

3.9. Operational definitions

Pediatric- patients with age less than or equal to 15 years.

Drug related problem - an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes and requires professional judgment to resolve.

Hospital stay - the time gap spent by the patient in the hospital from follow up start date till the follow up end date.

Fully accepted- the recommended intervention is accepted and implemented

Partially accepted-the recommended intervention is accepted and implemented with modification or not implemented at all

Not accepted-the recommended intervention is rejected

4. Results

4.1. Sociodemographic and clinical data

There were a total of 176 patients admitted during the study period. However, data for 20 patients were not included in the final analysis because of a variety of reasons (Figure 2). The sociodemographic and clinical characteristics of the study population are described in Table 1. Among the total of 156 patients followed and included in the final analysis, majority (62.8%) of them were males, most of them (87.2%) were children from 1 to 10 years and comorbid medical conditions were present in 16.0% of the study participants. The most common comorbid condition diagnosed was hypertension.

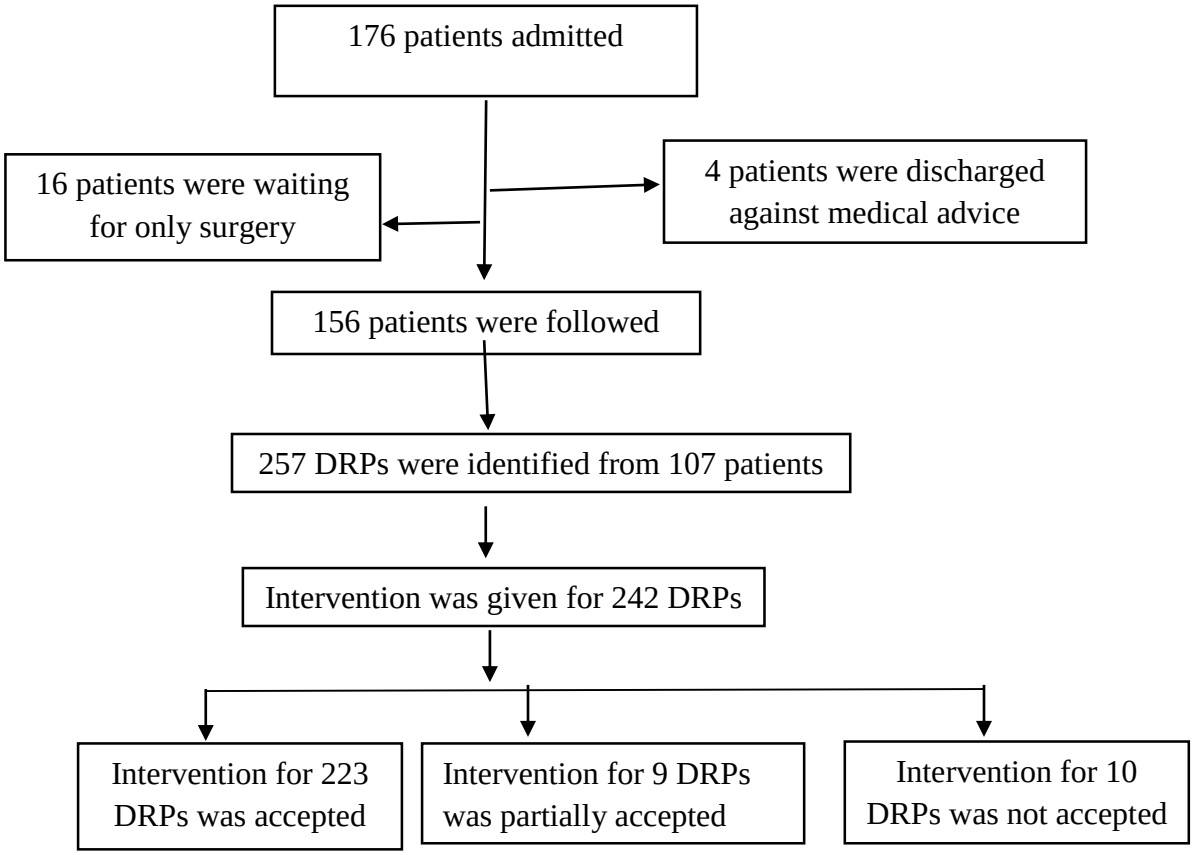

Figure 2: Flow chart showing included patients and intervention outcome for the identified drug related problems.

The median hospital stay of the participants was 9 (IQR= 6-19) days and the total number of patient days was 2203.A total of 1887 drug prescriptions were prescribed for 156 patients and the median number of drugs prescribed in the study population was 11 (IQR= 8-15).

Table 1: Sociodemographic and clinical characteristics of patients at Pediatric Hematology/ Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 25 June- 25 October, 2018.

Variable	Category	Number (%)
Age	≤ 1 year	10(6.4)
	>1 year to ≤ 5years	71 (45.5)
	>5 years to ≤ 10 years	65(41.7)
	>10 years to ≤ 15 years	10(6.4)
Sex	Male	98 (62.8)
	Female	58 (37.2)
Residence	Urban	86 (55.1)
	Rural	70 (44.9)
Family history of cancer	Yes	6 (3.8)
	Not known	150 (96.2)
Caregiver education	No formal education	21 (13.5)
	Grade 1-8	55 (35.2)
	Grade 9-12	42 (26.9)
	College and above	38 (24.4)
Hospital stay	≤10 days*	91 (58.3)
	>10days	65 (41.7)
Comorbid conditions	Yes	25 (16%)
	Hypertension	20 (12.8)
	Retroviral infection	4 (2.6)
	congestive heart failure	1 (0.6)
	No	131 (84.0)
Neutropenic fever presence	Yes	49 (31.4)
	No	107 (68.6)

Total number of prescriptions per patient	≤10 drug prescriptions	58 (37.2)
	>10 to ≤ 20 drug prescriptions	84 (53.8)
	> 20 drug prescriptions	14 (9.0)

***Short hospital stay is defined as hospital stay of less than or equal to 10 days in our ward.

Type of cancer

In the present study, hematologic malignancies were the most common types of cancer diagnosed in 106 (68%) of the patients (Figure 3). Renal tumor (10.9%) was the second most and carcinoma (0.6%) was the least commonly diagnosed cancer.

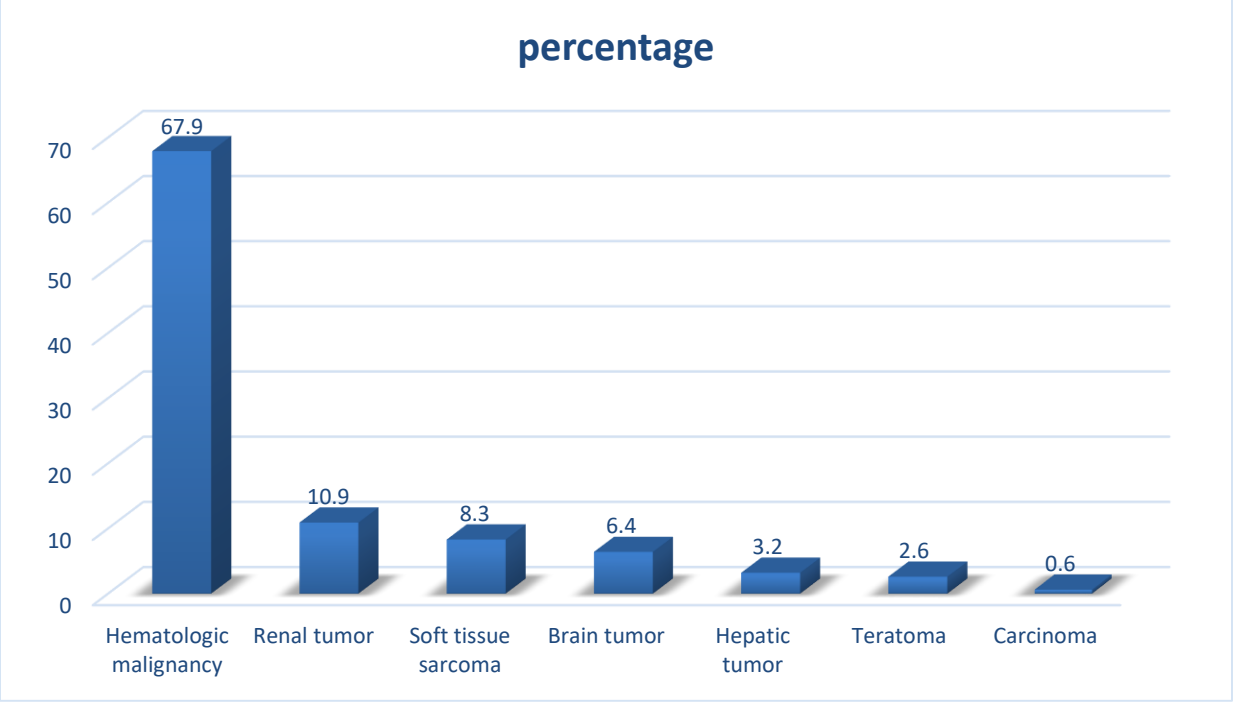

Figure 3: Types of cancer diagnosed at Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 25 June- 25 October, 2018.

4.2. Prevalence and types of drug related problems

A total of 257 DRPs were identified from 107(68.6%) of the study participants, out of which 1 DRP was found in 40 (25.6%), 2 DRPs in 31 (19.9%) and 3 or more DRPs in 36 (23.1%) of patients (Figure 4).

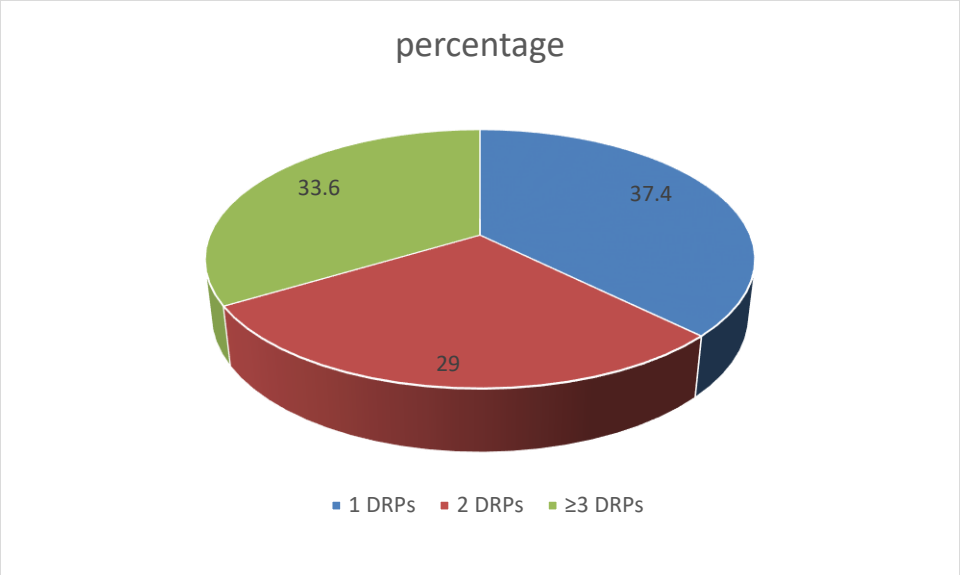

Figure 4: Number of drug related problems per patient at Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 25 June- 25 October, 2018.

Dosing problems which included dosage too low and high were the top ranking (39.3%) types of DRPs identified in the study subjects followed by need for additional drug therapy. Prescribing ineffective doses of drugs were the most common cause of dosing problem, whereas need for prophylaxis therapy to reduce the risk of developing new disease conditions were the common causes of need for additional therapy. However, DRPs related to ADR and ineffective drug accounted for less than 10%. The type and number of DRPs identified were depicted in Table 2.

Table 2: Types of drug related problems identified at Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 25 June- 25 October, 2018.

DRPs		**No. of DRPs**	**Total**	**(%)**
Unnecessary drug therapy	Duplicate therapy	12	25	9.7
	No medical indication at this time	13		
Needs additional therapy	Preventive therapy	49	70	27.2
	Untreated condition	20		
	Synergistic therapy	1		
Ineffective drug	More effective drug available	6	11	4.3
	Dosage form inappropriate	5		
Dosage too low	Ineffective dose	48	60	23.3
	Frequency inappropriate	10		
	Duration inappropriate	2		
Adverse drug reaction	Undesirable effect	6	14	5.5
	Drug interaction	1		
	Incorrect administration	1		
	Dosage increase/decrease too fast	6		
Dosage too high	Dose too high	28	41	16.0
	Needs additional monitoring	3		
	Frequency too short	7		
	Duration too long	3		
Non-adherence	Does not understand instructions	6	36	14.0
	Cannot afford drug product	1		
	Patient prefers not to take	5		
	Patient forgets to take	1		
	Drug product not available	22		
	Cannot swallow/administer drug	1		

4.3. Drugs and drug classes involved in drug related problems

Anti-infectives for systemic use (ATC group J) was the most common (30.7%) drug class involved in DRPs followed by antineoplastic and immunomodulating agents (ATC group L, 26.5%) and drugs acting on alimentary tract and metabolism (ATC group A, 23.0%) (Figure 5).

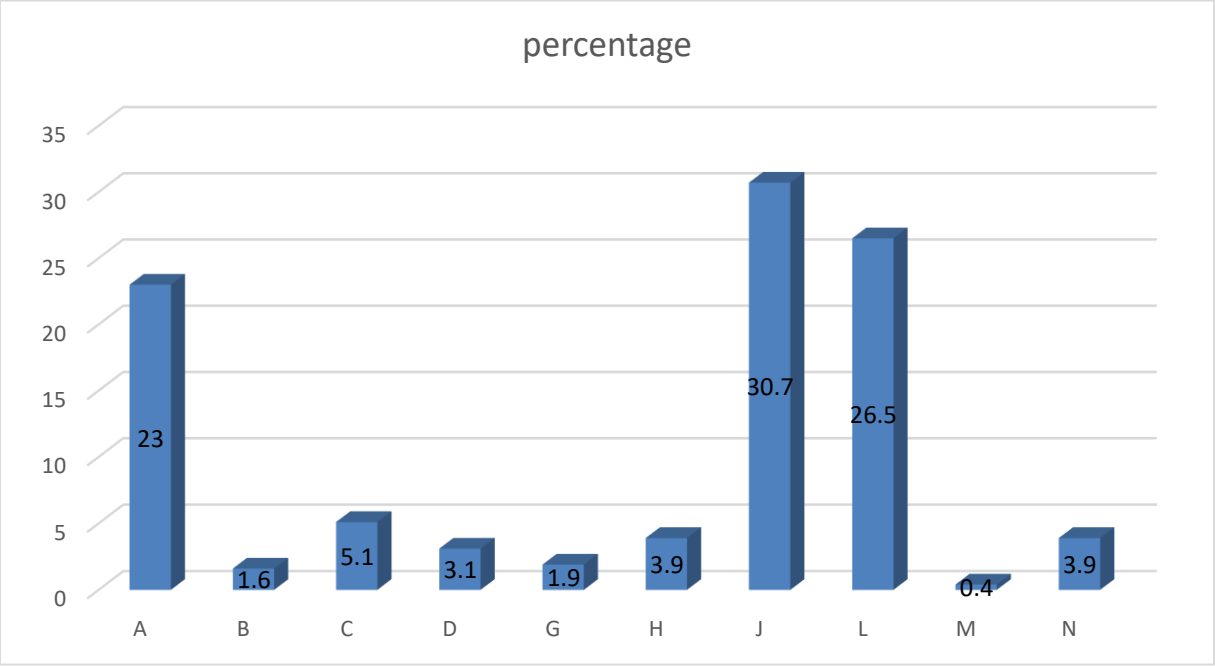

Figure 5: Percentage of drug related problems according to the Anatomical Therapeutic Chemical classification of the drug.

A-Drugs acting on alimentary tract and metabolism, B-Drugs acting on blood and blood forming organs, C-Drugs acting on cardiovascular system, D-Dermatologic drugs, G-Drugs acting on genitourinary system and sex hormones, H-Systemic hormonal preparations, excluding sex hormones and insulins, J-Anti-infectives for systemic use, L-Antineoplastic and immunomodulating agents, M-Drugs acting on musculoskeletal system, N-Drugs acting on nervous system.

A total of 57 drugs were involved in different types of DRPs. Among these the most frequently involved drugs were TMP/SMX (35), methotrexate (25), vincristine (12), ondansetron (12) and metoclopramide (11) (Table3).Needs additional drug therapy with TMP/SMX and non-adherence of methotrexate were the more frequent identified DRPs, which accounted for 16.3% of all DRPs.

Table 3: Top ten specific drugs associated with drug related problems at Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 25 June- 25 October, 2018.

Drug name	Drug related problem category							Total
	Unnece-ssary drug therapy	Needs additional therapy	Ineffective drug	Dosage too low	Adverse drug reaction	Dosage too high	Non adherence	
TMP/SMX	1	20	1	11	0	0	2	35
Methotrexate	0	2	0	0	0	1	22	25
Vincristine	3	1	0	6	0	2	0	12
Ondansetron	2	7	0	0	1	2	0	12
Metoclopramide	0	5	1	4	0	1	0	11
Doxorubicin	1	3	1	2	0	3	0	10
Cimetidine	1	0	2	4	0	2	0	9
Ceftriaxone	4	0	1	1	0	1	0	7
Diphenhydramine	1	2	0	2	0	2	0	7
KCl	0	4	0	0	0	1	1	6

KCl- Potassium chloride, TMP/SMX -Trimethoprim-sulfamethoxazole

4.4. Interventions for drug related problems

Appropriate interventions were made to correct the identified DRPs. Of the 257 DRPs, intervention was made for 242 (94.2%) of the identified DRPs. Addition of drug (76,31.4%) and change in drug dose (73, 30.2%) were the two most frequently provided intervention types as shown in Table 4. The rest of the interventions were cessation/discontinuation of drug, change in duration or frequency, substitution of drug, need for monitoring and change in dosage form. Among the provided interventions, 223 (92.15%) were fully accepted, while 9 (3.72%) partially accepted and 10 (4.13%) not accepted.

Table 4: Cross tabs showing the type of intervention given and its outcome at Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 25 June-25 October, 2018.

Type of intervention given	**Intervention outcome**			**Total**
	Fully accepted	Partially accepted	Not accepted	
Cessation/discontinuation of drug	25	2	3	30
Addition of drug	71	3	2	76
Change in drug dose	70	3	0	73
Change in duration or frequency	26	1	1	28
Substitution of drug	23	0	3	26
Need for monitoring	5	0	1	6
Change in dosage form	3	0	0	3
Total	223	9	10	242

4.5. Examples of drug related problems identified in the study subjects

Some examples of DRPs identified in the study subjects are described in Table 5.

Table 5: Examples of drug related problems identified in the study subjects at Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 25 June- 25 October, 2018

Sr. No.	**Description of the DRP**	**Intervention type**	**Intervention outcome**
1	Lyophilized-Amphotericin B (Brand name- Amphocare) was prescribed at a dose of 45mg IV daily for a 14kg patient for the management of radiographic documented aspergilloma.	Decrease the dose to 4.5mg/day since it is non-liposomal Amphotericin B formulation.	Accepted
2	A 2year and 1month female patient diagnosed with neuroblastoma and	Discontinue metronidazole or	Not accepted

	neutropenic fever (NF) of GI focus. Her weight was 10kg and she was taking meropenem 200mg iv TID, Ciprofloxacin 150mg iv BID and metronidazole 100mg iv TID for an indication of NF.	change to oral form if you suspect *C.difficile* infection.	
3	Hydroxyurea 500mg po TID was initiated for an indication of hyper leukocytosis (WBC count-$164*10^3$ cells/mm3) fora patient diagnosed with Acute myeloid leukemia (AML).The WBC count was reduced to $3.7*10^3$cells/mm^3 after a week of treatment.	Discontinue hydroxyurea	Partially accepted
4	A 7 year old male patient diagnosed with Hodgkin's lymphoma (HL) was kept on doxorubicin (adriamycin), bleomycin, vinblastine and dacarbazine (ABVD) regimen with no antiemetic. The regimen is a highly emetogenic chemotherapy.	Addition of Ondansetron and dexamethasone (no Neurokinin 1 (NK1) antagonists in our setup during the study period which should be added as a third agent.)	Accepted
5	A 9year old female AML patient weighing 24kg had electrolyte imbalances with serum electrolyte levels; K=2.51 mEq/l, Ca=5.8mEq/l and Mg= 0.8mEq/l was on Kcl 600mg po TID and Calci D-Denk (1000 mg /1000 IU tablet) 1 tab po/day.	Add MgSO4 1200mg (2.4ml of the 50% formulation) iv TID.	Accepted
6	A 4yearold male patient was diagnosed with Standard Risk- Acute Lymphoblastic Leukemia (SR-ALL) and he was on 3	All children patients are at high risk of PCP. Therefore, add TMP-	Accepted

	drugs induction regimen of the CALGB protocol. His weight is 16kg.	SMX 480mg po 3X/week.	
7	A 6 year old male patient having Non-Hodgkin lymphoma(NHL)+ Retroviral Infection(RVI)+ C.difficile diarrhea weighing 22kg was taking metronidazole 220mg iv TID as part of the C.difficile diarrhea.	Change metronidazole 220mg iv TID to metronidazole 220mg po TID	Accepted
8	Piperacillin/Tazobactam 900mg iv QID and Ceftazidime 600mg iv TID were given concomitantly for the management of neutropenic fever for a patient weighing 12kg.	Change Ceftazidime 600mg iv TID to Ciprofloxacin 120mg iv BID.	Accepted
9	A 4year old female patient weighing 18kg diagnosed with ALL+NF was on meropenem 360mg iv TID +Amikacin 200mg iv QD + cefepime 400mg iv BID and PCP prophylaxis TMP-SMX 80mg po 3x/wk.	Discontinue Cefepime and increase the dose of TMP-SMX 480mg po 3x/wk.	Accepted
10	A 2year and 2month old female patient weighing 10kg was diagnosed with wilms tumor +NF. As part of the NF regimen she was taking meropenem 200mg iv TID and Vancomycin 50mg iv TID. Her CrCl calculated was 68.8ml/min.	Increase the dose of vancomycin to 150mg iv TID.	Accepted
11	Piperacillin/Tazobactam 500mg iv TIDwas initiated for a patient whose weight is 15kgfor an indication of hospital acquired pneumonia.	Increase the dose of Piperacillin/Tazobactam to 1500mg iv TID	Accepted

12	A 5year old male patient was diagnosed with SR-ALL. His BSA was wrongly calculated to be 0.57m2.The prescribed regimen includes prednisolone 35mg po/day, vincristine 0.85mg iv, doxorubicin 14.25mg iv, L-Asparaginase 3420IU iv and intrathecal methotrexate (IT MTX)12mg to be given as per the protocol.	His weight was 19kg and height 107cm which gives a BSA of 0.75m2. Then increase the dose of prednisolone to 45mg, vincristine to 1.125mg, doxorubicin to 18.75mg and L-asparaginase to 4500IU.	All recommendations were accepted
13	A 15year old female patient diagnosed with relapsed ALL was on moderately emetogenic chemotherapy and taking ondansetron 6.75mg iv TID developed a sever hypersensitivity reaction following first dose injection.	Give diphenhydramine 40mg poevery6hrs. (her weight is 45kg.)	Accepted
14	Enalapril1mg po/day was given for a patient diagnosed with wilms tumor + hypertension + hospital acquired infection with no baseline potassium level done and thereafter.	Monitor potassium level	Accepted
15	A 2year old male patient whose working diagnosis was ALL+NF was taking ceftriaxone 675mg iv BID + gentamycin 80mg iv BID + vancomycin 275mg iv QID as part of NF management. His weight was 10kg.	Decrease the dose of ceftriaxone to 375mg iv BID, gentamycin to 50mg iv /day and vancomycin to 200mg iv TID.	Accepted
16	A 9year old male patient diagnosed with SR-ALL was on 3drug regimen induction phase with L-ASP 6600IU, VCR 1.65mg and prednisolone 35mg po BID to be	His actual BSA was 0.9m2 and decrease the dose of prednisolone 55mg in two divided	Accepted

	given as per the CALGB protocol. His weight was 23kg and height 128cm and the physician wrongly calculated his BSA (1.1m2).	doses, L-ASP to 5400IU and VCR to 1.26mg iv to be given as per the protocol.	
17	A 5year and 8month old male patient diagnosed with high grade NHL+ oral mucositis was taking miconazole oral gel before meal followed by application of chlorhexidine mouth wash.	Wash your oral cavity with chlorhexidine mouth wash after meal followed by miconazole oral gel application.	Accepted
18	A 6year old male patient diagnosed with high grade NHL needing IT MTX as per the protocol (NHL02: ALCL A phase) was not taking IT MTX because it was stock out.	Substitute with the preservative free cytarabine (cancyt 100mg/5ml which was available at that time) at a dose of 60 mg intrathecal.	Accepted

4.6. Predictors of occurrence of drug related problems

The identification of risk factors for DRPs may be helpful in finding patients at risk. Hospital stay and presence of neutropenic fever were independent determinants for occurrence of DRPs with a p-value of less than 0.25 and these were selected as potential predictors for multivariate logistic regression analysis. But variables like age and sex, which happen to be clinically important, were taken as predictors of DRPs occurrence even if the univariate analysis results were greater than 0.25. Then sex, age, presence of neutropenic fever and length of hospital stay were analyzed using multivariate logistic regression.

The result showed that only length of hospital stay was a risk factor for the occurrence of DRPs. As shown in Table 6, patients who stayed more than 10 days were 30.63 times more likely to develop DRPs as compared to patients who stayed less than or equal to 10 days (p = 000).

Table 6: Binary logistic regression analysis of predictors for occurrence of drug related problems at Pediatric Hematology/Oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 25 June-25 October, 2018.

Variable	Category	DRPs		COR (95% CI)	AOR COR (95% CI)	p value
		Yes (%)	No (%)			
Sex	Male	70 (65.4)	28 (57.1)	1.00	1.00	
	Female	37 (34.6)	21 (42.9)	0.71 (0.35-1.41)	0.89 (0.36-2.19)	0.792
Age	≤ 1years	7 (6.5)	3 (6.1)	1.00	1.00	
	>1year to≤ 5years	45 (42.1)	26 (53.1)	0.64 (0.10-4.10)	0.18 (0.02-1.86)	0.152
	>5yearsto≤10years	49 (45.8)	16 (32.7)	0.87 (0.22-3.36)	0.54 (0.08-3.45)	0.516
	>10yearsto≤15years	6 (5.6)	4 (8.2)	0.49 (0.12-1.96)	0.26 (0.04-1.75)	0.164
Hospital stay	≤10 days	44 (41.1)	47 (95.9)	1.00	1.00	
	>10 days	63 (58.9)	2 (4.1)	33.65 (7.76-145.84)	30.63 (6.72-139.63)	0.000
Neutropenic fever	No	64 (59.8)	43 (87.8)	1.00	1.00	
	Yes	43 (40.2)	6 (12.2)	4.82 (1.89-12.23)	2.23 (0.75-7.08)	0.148

5. Discussion

The goal of pharmacotherapy is to achieve definite therapeutic outcomes and improve quality of life while minimizing patient risks. The World health organization (WHO) estimated that over half of all medicines are prescribed, dispensed or sold inappropriately and that half of all patients fail to take their medicine correctly (38), which may expose patients to DRPs (9). Many studies have shown that clinical pharmacists can effectively identify and prevent clinically significant DRPs (10, 19, 21, 22, 31, 34). Therefore, this study was carried out to identify DRPs and make appropriate intervention in Pediatric Hematology/Oncology ward patients of a tertiary care teaching hospital in Ethiopia.

In the present study, the clinical pharmacists identified 257 DRPs among 107 (68.6%) of the included patients, giving an overall frequency of 1.65 DRPs per patient or an average of 2.4 DRPs in those patients with DRPs. The frequency of DRPs was higher than a study done at Toronro's Hospital for Sick Children (HSC) Pediatric Hematology/Oncology clinic which showed 0.6 DRPs per patient (39). Our result also showed higher prevalence of DRPs as compared to other studies. A DRP prevalence of 21% and 32% were reported in a study conducted in pediatric wards of Hong Kong (35) and ZMRH (26), respectively.

A DRP prevalence of 55% was also reported in a study conducted in adult cancer patients of Northern Cyprus hospital (40). In contrary, our result was lower than what was reported by Degu *et al* (41) at Kenyatta National Hospital, which showed a DRP prevalence of 93.8% with a mean of 2.83 DRPs per patient. The difference could be attributed to hospital settings such as differences in training levels of prescribers, availability of support system and composition of health care team in these hospitals. However, similar prevalence rates (66-75%) were reported in different studies (28, 31, 32, 42, 43).

According to a study conducted to assess the impact of clinical pharmacists on DRP prevalence, there was a gradual decrease in DRPs from 70% to 17.5% after incorporation of clinical pharmacists (34). Thus, we can decrease the DRP prevalence and increase the quality of healthcare by assigning clinical pharmacists in wards.

DRPs are an essential term in the world of pharmaceutical care. DRPs can originate when prescribing, dispensing or taking/administering medicines (9). Prescribing chemotherapy in

pediatrics is an error-prone medical act because it combines at the same time the risks inherent in pediatrics and those in oncology. The most frequently encountered DRPs in the present study were inappropriate dosing (dose too low and dose too high) followed by needs additional drug therapy and non-adherence to the prescribed medications.

In line with our result, dosing problems (dose too low and dose too high) were the most frequently (61.8%) reported DRPs in a study conducted at Pediatric Oncology department of French hospital (44). A study conducted at Pediatric inpatient department of Cote D'ivoire also showed that dosing problems were the most frequently (34.9%) reported DRPs, followed by noncompliance with recommendations (24.1%) (45). Dosing problems were also the leading (42.7%) DRPs in a prospective cohort study conducted in pediatric wards of seven Hong Kong hospitals (35).

In a crossectional study conducted at ZMRH, the most frequently identified DRPs were also dosing problems, with dose too low being 35% and dose too high being 7.5%. This was followed by drug–drug interactions (39%) and ADRs (8.5%) (26). Similarly, a study conducted at adult cancer patients showed that dosing problems were the most frequent (37.9%) DRPs following ADR (45.5%) (28).

The drugs more associated with dosing problems in our study include TMP/SMT, vancomycin, vincristine, metoclopramide, cimetidine, furosemide and doxorubicin. Too high dose of doxorubicin and too low dose of the rest six of the above medications were identified and intervened.

Dosing problems in pediatrics might result in ineffective treatment, due to sub therapeutic concentration, or toxicity due to over dose that may lead to mortality. Generally inappropriate doses are more common in pediatrics than adults because of weight-based dosing calculations, fractional dosing (e.g., mg vs. gm), and the need for decimal and incorrect recording of patients' weights (46). Therefore, the high prevalence of dosing problems in the present study would make this an important area requiring further attention.

Needs additional drug therapy was also common DRP type in the present study. In line with our result a study done at Australian pediatric teaching hospital also showed that need for additional drug therapy was the most common DRP in the Hematology/Oncology ward (47).

ADR and ineffective drug were the least prevalent DRP types, which accounted for 5.4% and 4.3%, respectively. In the present study only 1 clinically significant drug-drug interaction that resulted ADR was identified and intervened, though there were minor drug-drug interactions which were not clinically significant In contrast to our finding, a study done at the Pediatric Hematology-Oncology of Erasmus MC-Sophia showed that 83.5% of the patients were exposed to at least one drug-drug interaction (48). A study done in Ethiopian adult cancer patients also identified ADR as being the most frequent (45.5%) of all DRPs followed by dosing problems (37.9%) (28). Other studies also showed that ADR was the top ranking DRP in chemotherapy of cancer patients (41, 49). In cancer chemotherapy ADRs are strongly connected to the treatment itself. Because of the fact that most cytotoxic agents cannot distinguish between normal and neoplastic cells, most ADRs seem to be unavoidable and they are often accepted not only by patients but also by health care providers (11). The lower ADR prevalence in the present study might be due to the non-reporting of ADRs that were managed appropriately.

In contrast to our study, treatment effectiveness was also the major (50.2%) type of DRP, which was followed by treatment safety (24.7%) in a study conducted in Northern Cyprus (40). We have limited pharmaceutical products in the country and the study evaluated the treatment based on the available drugs in the national drug list which might justify the lower prevalence of ineffective drug use.

Methotrexate was used as a back bone and also as a central nervous system (CNS) prophylactic agent of choice in many of our protocols. But stock out of this medication was seen repeatedly in our setup and accounted for half of the DRPs related to methotrexate. Methotrexate was the second frequent (9.7%) of all drugs associated with DRPs. Shortages of essential drugs, including critical chemotherapy drugs, have become more common in developing countries. Pediatric oncology is particularly susceptible to drug shortages (50).

In order to identify the most common drug classes associated with DRPs the ATC classification system was used since it is the recommended drug classification system by the WHO for drug utilization studies (37). Based on this classification system, anti-infectives for systemic use (ATC group J) was the most common (30.7%) drug class associated with DRPs in our study.

In line with the present study, the pharmacists in France identified DRPs primarily related to anti-infective agents (ATC group J, 59.5%) followed by drugs regarding the alimentary tract and metabolism (ATC group A, 6.4%) (29). Anti-infective agents were also the major (41.1%) group of drugs associated with DRP in hospitalized patients with hematologic malignancies (51). Our result is also consistent with other studies which showed that anti-infectives were the top ranking drug classes involved in DRPs (35, 39, 43, 45, 52).

Anti-infectives are often the group of drugs most commonly prescribed in our setup and it is not surprising that they are the therapeutic group (antibiotics, antiparasitics, antifungals, and antivirals) with the largest number of drug classes associated with DRPs needing pharmaceutical interventions. Among the anti-infectives, TMP/SMX is the most frequent (13.6%) drug associated with DRPs followed by ceftriaxone (2.7%) and miconazole (2.3%). Vancomycin, gentamicin, ciprofloxacin and metronidazole also accounted for 1.9% each.

The second common drug class associated with DRPs was antineoplastic and immunomodulating agents (ATC group L, 26.5%), followed by drugs acting on alimentary tract and metabolism (ATC group A, 23.0%). In contrast to our study, clinical pharmacists in France reported only 3.9% of DRPs related to antineoplastic and immunomodulating agents (ATC group L) (29). The most identified problem in our study associated with antineoplastic and immunomodulating agents was BSA calculation error. The high prevalence of DRPs associated with antineoplastic and immunomodulating agents in the present study might be because of differences in training levels of residents and absence of clinical pharmacists assigned in our study setting.

In the present study, intervention was provided for 242 (94.2%) of all DRPs identified. For the rest 15 (5.8%) of all DRPs intervention was not made due to different reasons, such as unavailability of the proposed/substitute drug, discharge or death of the patient before the principal investigator made the recommendation.

Among the different types of recommendations provided in this study, the majority of them were regarding addition of the drug which accounted for about 31.4% of the total recommendations. Similarly, in a study done at Indian tertiary care hospital addition of the drug was the most common intervention which accounted 29.32% of all pharmacist interventions followed by cessation of the drug (24%) (32).

The second most common clinical pharmacist interventions recommended in this study was dose adjustment (30.2%). This was in close proximity with the result of the Cote D'ivoire study which showed that dose adjustment accounted 31.8% of all pharmacist interventions (45).

In the present study, full acceptance of the intervention was achieved in 223 (92.15%) of all clinical pharmacist interventions, while partially accepted 9 (3.72%) and not accepted 10 (4.13%). Only 3 of 30 measures proposed for cessation/discontinuation of drug were not accepted. Among DRPs associated with addition of drug 2 of 76 measurers were not accepted, while 74 of measures were either partially or fully accepted.

Acceptance rate of the present study is similar with a study conducted at National Cancer Centre of Singapore (93%) (53); lower than studies conducted in Cote D'ivoire (94.8%) (45) and France (96%) (29), and higher than studies conducted in Norway (75%) (31), Canada (81%) (39), India (86.6%) (54), and South Korea (88.3%) (51). The difference could be attributed to hospital settings such as differences in training levels of clinical pharmacists to give evidence based recommendations, and the already existing composition of health care team in these hospitals.

In general, clinical pharmacists' acceptance rate was high (92.15%) in our setup, which indicates the great acceptance and recognition of clinical pharmacists as active members of the healthcare team.

In the attempt to identify risk factors for the occurrence of DRPs in this study, length of hospital stay was an important risk factor for the occurrence of DRPs, while sex, age and presence of neutropenic fever were not significantly associated to DRPs. A study conducted in adult cancer patients also demonstrated that the length of hospital stay was significantly associated on the occurrence of DRPs (28). A prospective crossectional study also showed that length of hospital stay was significantly associated with the presence of DRPs. Patients whose hospital stays was greater than seven days, were 2.4 times more likely to have DRPs than patients whose hospital stay less than seven days (43).

Patients stayed for long period of time were exposed to DRPs as a result of developing different complications apart from neutropenic fever such as nausea/vomiting, mucositis and specific drug side effects that ultimately contribute for the occurrence of DRPs. On the other hand, patients exposed to DRPs will stay for a long period of time without the resolution of the clinical symptoms.

This intern results in association between length of hospital stay and occurrence of DRPs. In line with our study, age and sex were not also significantly affect occurrence of DRPs in many studies (26, 28, 35, 43, 44).

6. Limitation of the study

- ✓ The study did not show the overall incidence of DRPs for a patient in his/her hospital stay (admission to discharge) rather it shows DRPs with in the study period.
- ✓ The intervention given for the identified DRPs may to some extent affect the incidence of DRPs in the study subjects.
- ✓ The study may not be generalized due to its small sample size, the relatively high cost and long time required to enroll many patients.

7. Conclusion

DRPs are common among Pediatric Hematology/Oncology ward patients. Dosing problems are more frequent than other types of DRPs. The study also demonstrated that clinical pharmacists can effectively identify and resolve significant DRPs. Length of hospital stay an important determinant for the occurrence of DRPs in hospitalized pediatric cancer patients. In general, to decrease DRPs and improve quality of health care, the hospital requires a coordinated intervention from all concerned bodies and need to assign clinical pharmacists in wards.

8. Recommendations

- The hospital should assign clinical pharmacists in the ward. In addition to the traditional roles, clinical pharmacists should also focus to identify, solve, and prevent DRPs.
- The hospital drug and therapeutics committee (DTC) should develop pediatric dosing chart for the commonly prescribed medications.
- The health care professionals should take care of calculating doses of medications.
- Clinicians should monitor patients for signs of adverse drug effects, including doing laboratory tests as necessary.
- The drug supply management (DSM) case team should ensure uninterrupted supply of medications.
- Appropriate counseling of patient/caregivers including instruction of the prescribed medications should be given.
- Further studies with large number of patients are required.

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Annex I

I. Consent Form

Addis Ababa University

School of Pharmacy

Department of pharmacology and clinical pharmacy

Drug Related Problems identification and resolution in Pediatric Hematology/Oncology Ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Greeting:

Hello, My name is_____. I am here today to collect data to asses drug related problems in Pediatric hematology/oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. The study is being conducted by Mr. Malede Berihun from Addis Ababa University, school of Pharmacy, department of pharmacology and clinical pharmacy, post graduate program.

The objective of this study is:

- ✓ To determine the prevalence of drug related problems
- ✓ To identify drugs and drug classes involved in DRPs.
- ✓ To resolve the identified DRPs
- ✓ To determine acceptance rate of interventions
- ✓ To identify predictors for the occurrence of DRPs

This is a prospective interventional study so I request your child to take part in this study. Your cooperation and willingness is greatly helpful in assessing drug related problems in Tikur Anbessa Specialized Hospital. The study will be conducted through recording medical findings from your child medical chart and interviewing (if needed). Intervention will be given to correct any drug related problem as fast as possible.

Your child name will not be written in this form and will never be used in connection with any information we take from the chart and you tell us. There is no possible risk associated with participating in this study except the time spent to deliver information for us. All information

taken from your child medical chart or given by you will be kept strictly confidential. Your child participation is voluntary and your child is not obligated to participate in the study.

If you feel discomfort with the study, it is your right to drop out your child from the study. If you have questions regarding this study or would like to be informed of the results after its completion, please feel free to contact the principal investigator.

Address of the principal investigator:
Malede Berihun

Cell phone: +251- 966335852

E-mail: malede.berihun@aau.edu.et

Are you willing to participate your child in this study?

1. Yes - …….. Continue
2. No - …… Skip to the next participant

የአስታማሚዎች የፈቃደኝነት መጠይቅ ፎርም

በአዲስ አበባ ዩኒቨርሲቲ

ጤና ሳይንስ ኮሌጅ

የፋርማሲ ትምህርት ቤት

ጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል ውስጥ በመታከም ላይ በሚገኙ ህፃናት የካንሰር ህሙማን ላይ ከመድሃኒት ጋር የተያያዙ ችግሮችን ለመለየትና መፍትሄ ለመስጠት የሚደረግ ጥናት ነው።

<u>ሰላምታ፡</u>

ጤና ይስጥልኝ እኔ _____ እባላለሁ። አሁን የመጣሁበት ዋና ዓላማም ከመድሃኒት ጋር የተያያዙ ችግሮችን ለመለየትና መፍትሄ ለመስጠት መረጃ ለመሰብሰብ ነው።

ጥናቱ የሚካሄደው በአቶ ማለደ በሪሁን ሲሆን በአሁኑ ወቅት በአዲስ አበባ ዩኒቨርሲቲ፣ፋርማሲ ትምህርት ቤት በፋርማኮሎጅና ክሊኒካል ፋርማሲ ትምህርት ክፍል የሁለተኛ ድግሪ ተማሪ ነው።

የጥናቱ ዓላማም፡ ከመዲሃኒት ጋር የተያያዙ ችግሮችን ስርጭት ማየት፥ከመዲሃኒት ጋር ለተያያዙ ችግሮች አጋላጭ ነገሮችን መለየት፥ለተለዩ ችግሮች መፍትሄ መስጠት እና የመፍትሄዎችን አተገባበር መመዘን ነው።

በመሆኑም የእርስዎ ልጅ ከጥናቱ እንዲሳተፉ በአክብሮት እጠይቅዎታለሁ። የእርስዎ ትብብርና ፈቃደኝነት ከመድሃኒት ጋር የተያያዙ ችግሮችን ለመለየትና ለመፍታት ከፍተኛ አስተዋፆ አለው። በመሆኑም ከእርስዎ፣ ከልጅዎ ፣ከልጅዎ ካርድ ላይ እና ከከልጅዎ ሐኪም መረጃ ለመውሰድ እንፈልጋለን። ከመድሃኒት ጋር የተያያዙ ችግሮች ካሉም አስፍላጊውን መፍትሄ በተሎው እንሰጣለን።

ለጥናቱ የሚስፈልጉት መረጃዎችና ለተነሱት ጥያቄዎች የሚሰጧቸው መልሶች ሙሉ በሙሉ በምስጢር የሚጠበቁ ሲሆን የልጅዎ ስም በማንኛዉም መልኩ በጥናቱ ውስጥ አይገለጽም፤ እንዲሁም የሚሰጡት ምላሽ ከርስዎ ወይም ከልጅዎ ማንነት ጋር በማንኛውም መልኩ አይያያዝም። የልጅዎ ፍቃደኝነትም ስለሚያስፈልግ ልጅዎ በግዳጅ ሊሳተፉ አይገባም።

በዚህ ጥናት ውስጥ የልጅዎ መሳተፍም ሆነ አለመሳተፍ መወሰንዎ በሆስፒታሉ ውስጥ በሚያገኙት አገልግሎት ላይ ምንም አይነት ተጽእኖ የማይኖረው ሲሆን ተሳትፎውን በማንኛውም ሰአት ማቋረጥ ወይም ጥያቄዎችን አለመመለስ ይችላሉ።

<u>ስለ ጥናቱ የበለጠ መረጃ ለማግኘት የአጥኙ አድራሻ፡</u>

ማለደ በሪሁን

ስልክ ቁጥር- +251-966335852

ኢሜል- Malede.berihun@aau.edu.et

በጥናቱ ልጅዎ እንዲሳተፍ/እንድትሳተፍ ፈቃደኛ ነዎት?

አዎ ☐ አይደለሁም ☐

ፈቃደኛ መሆናቸውን ካረጋገጡ መረጃ መሰብሰብ ይጀምሩ

ፈቃደኛ ካልሆኑ ወደ ሚቀጥለው ተገልጋይ ይሸጋገሩ

II. Assent Form for Children Aged 12-18 years

Greeting:

Hello, My name is_____. I am here today to collect data to asses drug related problems in Pediatric hematology/oncology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. The study is being conducted by Mr. Malede Berihun from Addis Ababa University, school of Pharmacy, department of pharmacology and clinical pharmacy.

Your parent has given permission for you to be involved in this study. But first, we want to tell you all about it so you can decide if you want to be in it. If you don't understand, please ask questions. The objective of this study is to determine the prevalence of drug related problems, resolve the identified DRPs and assess acceptance rate of pharmacists' interventions and identify factors associated with DRPs. This is a prospective interventional study so I kindly request you to take part in this study.

Your cooperation and willingness is greatly helpful in assessing drug related problems in Tikur Anbessa Specialized Hospital. The study will be conducted through recording medical findings from your medical chart and interviewing (if needed). Intervention will be given to correct any drug related problems fast as possible. Your name will not be written in this form and will never be used in connection with any information we take from the chart and you tell us. There is no possible risk associated with participating in this study except the time spent to deliver information for us. All information taken from your medical chart or given by you will be kept strictly confidential. Your participation is voluntary and you are not obligated to participate in the study.

If you feel discomfort with the study, it is your right to drop out from the study. If you have questions regarding this study or would like to be informed of the results after its completion, please feel free to contact the principal investigator.

Are you willing to participate in this study?

1. Yes - …….. Continue
2. No - …… Skip to the next participant

ከ12-18 አመት ለሆኑ ህፃናት የፈቃደኝንት መጠይቅ ፎርም

በአዲስ አበባ ዩኒቨርሲቲ

ጤና ሳይንስ ኮሌጅ

የፋርማሲ ትምህርት ቤት

<u>ሰላምታ፡</u>

ጤና ይስጥልኝ እኔ _____ እባላለሁ። አሁን የመጣሁበት ዋና ዓላማም ከመድሃኒት ጋር የተያያዙ ችግሮችን ለመለየትና መፍትሄ ለመስጠት መረጃ ለመሰብሰብ ነው።

ጥናቱ የሚካሄደው በአቶ ማለደ በሪሁን ሲሆን በአሁኑ ወቅት በአዲስ አበባ ዩኒቨርሲቲ፣ፋርማሲ ትምህርት ቤት በፋርማኮሎጅና ክሊኒካል ፋርማሲ ትምህርት ክፍል የሁለተኛ ድግሪ ተማሪ ነው።

የአንተ/ቺ አስታማሚ እንድትሳተፍ/ፊ ፈቃደኛ ናቸው። ነገር ግን ጥናቱን ለማካሄድ የአንተ/ቺ ፈቃደኝነትም ያስፈልጋል። የጥናቱ ዓላማም፡ ከመዲሃኒት ጋር የተያያዙ ችግሮችን ስርጭት ማየት፥ ከመዲሃኒት ጋር ለተያያዙ ችግሮች አጋላጭ ነገሮችን መለየት፥ለተለዩ ችግሮች መፍትሄ መስጠት እና የመፍትሄዎችን አተገባበር መመዘን ነው።በመሆኑም የአንተ/ቺ ትብብርና ፈቃደኝንት ከመድሃኒት ጋር የተያያዙ ችግሮችን ለመለየትና ለመፍታት ከፍተኛ አስተዋፆ አለው። በመሆኑምከአንተ/ቺ፣ ከአስታማሚዎ ፣ከ ካርድ ላይ እና ከሐኪምህ/ሽ መረጃ ለመውሰድ እንፈልጋለን። ከመድሃኒት ጋር የተያያዙ ችግሮች ካሉም አስፍላጊውን መፍትሄ በተሎው እንሰጣለን። ለጥናቱ የሚስፈልጉት መረጃዎችና ለተነሱት ጥያቄዎች የሚሰጧቸው መልሶች ሙሉ በሙሉ በምስጢር የሚጠበቁ ሲሆን የአንተ/ቺ ስም በማንኛዉም መልኩ በጥናቱ ውስጥ አይገለጽም። ጥናቱ ምንም ጉዳት የማያመጣ ሲሆን በማንኛውም ሰአት ከጥናቱ መውጣትም ትችላለህ/ሽ።

በጥናቱ ለመሳተፍ ፈቃደኛ ነህ/ሽ? ☐ አዎ ☐ አይደለሁም

ፈቃደኛ መሆናቸውን ካረጋገጡ መረጃ መሰብሰብ ይጀምሩ

ፈቃደኛ ካልሆኑ ወደ ሚቀጥለው ተገልጋይ ይሸጋገሩ

Annex II

Data abstraction format

I. Socio demographic information

Code number _____ Sex: _____Wt.: _____Height: _____BSA: _____

Current age_____ Age at diagnosis_____

Date of admission: _____

Resident: ☐ urban ☐ rural

Family history of cancer ☐ yes ☐ no

Caregiver education ☐ No formal education ☐ Grade 1-8

☐ Grade 9-12 ☐ College and above

II. Clinical characteristics

Working diagnosis

Date					
Diagnosis					

Cancer diagnosis_____

Number of total comorbidities_____

Follow up start date _____ Follow up stop date _____
Hospital stay: _____

Past Medications: _____
_____

Immunization History: _____
_____

Review of Systems (ROS) (abnormal findings only):

Abnormal organ function tests & electrolytes by date

Pertinent investigations

CBC with differentials

Lab. Parameters	Normal Range	Date of test					
WBC							
Lymphocytes							
Neutrophils							
PLT count							
RBC							
Hgb							
Hct							
MCV							
MCHC							
ANC							

Vital sign (abnormal values, start from recent results)

Medication Registration Form

Date	Disease condition	Medication/s given	Dosage regimen	Length of therapy	Comment (DRP)

Total number of drugs prescribed during study period _____

Is there drug related problem

- ☐ **Yes**
- ☐ **No**

III. Drug related problem registration sheet

Unnecessary drug therapy ☐ Duplicate therapy ☐ No medical indication at thistime ☐ Nondrug therapy more appropriate ☐ Addiction/recreational drug use ☐ Treating avoidable adverse reaction
Needs additional therapy ☐ Preventive therapy ☐ Untreated condition ☐ Synergistic therapy
Ineffective drug ☐ More effective drug available ☐ Condition refractory to drug ☐ Dosage form inappropriate ☐ Drug not indicated for condition

Dosage too low

- ☐ Ineffective dose
- ☐ Needs additional monitoring
- ☐ Frequency inappropriate
- ☐ Drug interaction
- ☐ Incorrect storage
- ☐ Duration inappropriate

Adverse drug reaction

- ☐ Undesirable effect
- ☐ Drug interaction
- ☐ Incorrect administration
- ☐ Allergic reaction
- ☐ Dosage increase/decrease too fast

Dosage too high

- ☐ Dose too high
- ☐ Needs additional monitoring
- ☐ Frequency too short
- ☐ Duration too long
- ☐ Drug interaction

Non-adherence

- ☐ Does not understand instructions
- ☐ Cannot afford drug product
- ☐ Patient prefers not to take
- ☐ Patient forgets to take
- ☐ Drug product not available
- ☐ Cannot swallow/administer drug

Medication/s with DRP/s

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____
11. _____
12. _____

Medication/s class with DRP/s

- ☐ A, Alimentary tract and metabolism
- ☐ B, Blood and blood forming organs
- ☐ C, Cardiovascular system
- ☐ D, Dermatologicals
- ☐ G, Genito-urinary system and sex hormones
- ☐ H, Systemic hormonal preparations, excluding sex hormones and insulins
- ☐ J, Antiinfectives for systemic use
- ☐ L, Antineoplastic and immunomodulating agents
- ☐ M, Musculo-skeletal system
- ☐ N, Nervous system
- ☐ P, Antiparasitic products, insecticides and repellents
- ☐ R, Respiratory system
- ☐ S, Sensory organs
- ☐ V, Various

IV. Interventions on DRP/s

Type of intervention given

- ☐ Cessation of drug
- ☐ Addition of drug
- ☐ Change in drug dose
- ☐ Change in duration or frequency
- ☐ Substitution of drug
- ☐ Need for monitoring
- ☐ Change in dosage form
- ☐ No recommendation

Intervention outcome

- ☐ Fully accepted
- ☐ Partially accepted
- ☐ Not accepted
- ☐ Not applicable

Intervention respondent

- ☐ Physician
- ☐ Nurses
- ☐ Patients/caregiver
- ☐ Pharmacist