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DEPARTMENT OF MEDICAL LABORATORY SCIENCES

Assessment of Chemotherapy induced Leukopenia and its determinants among solid cancer patients attending St. Paul Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia

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This is to certify that the thesis prepared by **Mekonnen Dessalegn**, entitled: **Assessment of Chemotherapy induced Leukopenia among solid cancer patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia** and submitted in partial fulfillment of the requirements for Master of Science degree in Clinical Laboratory Sciences (Hematology and Immunohematology) complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Chairman of the Department or Graduate Program Coordinator

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Abbreviations

AAU	Addis Ababa University
ANC	Absolute neutrophil count
CBC	Complete blood count
CIL	Chemotherapy-induced leukopenia
CSF	Colony stimulating factor
DM	Diabetes Millets
ECOG	Eastern Corporation Oncology Group
EDTA	Ethylene Diamine Tetra Acetic Acid
FN	Febrile neutropenia
GM-CSF	Granulocyte macrophage colony stimulating factor
Ht	Height
HTN	Hypertension
IL	Interleukin
MBC	Metastatic Breast Cancer
MoH	Ministry of Health
NCI	National Cancer Institute
NHL	Non Hodgkin Lymphoma
PCP	Pneumocystis pneumonia
QoL	Quality of life
RDI	Relative dose intensity

SPHMMC	St Paul's Hospital Millennium Medical College
SPSS	Statistical Package for Social Sciences
WBC	White blood cells
Wt.	Weight

Abstract

Background: Chemotherapy is among the standard treatments for cancer and leukopenia, neutropenia, febrile neutropenia and lymphopenia are the most common side effects. These side effects have been reported to be associated with substantial morbidity, mortality and healthcare costs.

Objectives: To assess the prevalence of chemotherapy induced leukopenia (CIL) in solid cancer patients at St Paul's Hospital Millennium Medical College Oncology unit, Addis Ababa, Ethiopia.

Methods: An institution based cross sectional study was performed at St Paul's Hospital Millennium Medical College Oncology unit from February 1st 2020 to May 2020. Using convenient sampling technique, 92 patients, who were diagnosed for any type of solid cancer, were recruited in this study. EDTA whole blood was collected before each cycle of treatments and analyzed for complete blood count (CBC) using Beckman coulter analyzer before and after the initiation of chemotherapy. The laboratory analysis was done for five times Data were entered; cleared and analyzed to match the objectives. Chi-square statistics were employed and p values less than 0.05 were taken as statistically significant.

Results: Among the 92 patients who participated in this study, the following adverse effects were observed after the use of various chemotherapy regiments in the five cycles. The most common adverse effects of Chemotherapy Are Leukopenia 80.4%, Neutropenia 70.7 %, Febrile Neutropenia 50% and Lymphopenia 88%. occupation and ECOG have a significant association with the occurrence of hematological toxicities with (p=0.011) and (*P*=0.013) respectively. Also majority of hematological toxicities are caused by Adriamycin + cyclophosphamide.

Conclusion: Even though chemotherapy is the standard treatment for cancer patients, it causes leukopenia, neutropenia, febrile neutropenia and lymphopenia which may cause delaying of treatment, morbidity and mortality.

Keywords: Cancer, Chemotherapy, Leukopenia, Neutropenia, Lymphopenia, Febrile Neutropenia

1. Introduction: -

1.1 Background Cancer is a term for diseases in which abnormal cells divide without control and can invade other tissues (1-3) _Cancer is a significant and major health problem all over the world with an incidence of 10 million new cases per years (3). There were 18.1 million incident cases of cancer and 9.6 million deaths globally from cancer. Currently, cancer is the second cause of death globally next to cardiovascular illness. Of all these new cases and deaths, about 2/3 occurred in LMICs 2018 (4).

The human immune system has its own roles in cancer suppression and has several mechanisms for identifying cancer cells and removing them from the body. Most of these mechanisms involve leukocytes, which comprise about 45%-70% of Neutrophils (5) and 30% of lymphocytes of the normal human white blood cell population and are essential effector cells in the immune response to cancer (6).

Chemotherapy is the standard treatment for cancer and leukopenia is the most common side effect (7-12). Chemotherapy-induced leukopenia (CIL) has been reported to be associated with substantial morbidity, mortality, and healthcare costs (13).

In many centers, cancer patients undergoing high-dose chemotherapy frequently receive antibiotics and antifungal agents, prophylactically or during periods of drug-induced leukopenia-(14). Moreover, chemotherapy‑induced leukopenia may be a biological measure of drug activities, disease control and a predictor of treatment efficiency (10,15).

Leukopenia is characterized by a decrease in the number of circulating white blood cells (WBCs), below to a level of approximately $4.0X10^{9}$/l. Leukopenia can be caused either by primary factors or secondarily, for example, following radiotherapy or chemotherapy as part of cancer treatment regimens (11).

If an absolute neutrophil count (ANC) is below 1.5×10^9/l (1500/mm3), then the term is known as neutropenia (16). The Common Toxicity Criteria of the National Cancer Institute of America established a scale of four grades for neutropenia, according to the absolute neutrophil count (ANC): grade 1, ANC 1.5 to -$2x10^9$/l; grade 2, ANC 1.0 to -$1.5x10^9$/l; grade 3, ANC 0.5 to -$1x10^9$/l; grade 4, ANC <$0.5x10^9$/l (17,18).

The functional consequences depend largely, but not exclusively, on the severity of neutropenia: ANC of 1.0–1.5×10^9/l does not impair host defense, but may warrant investigation of the underlying cause; ANC of 0.5-1.0×10^9/l may slightly increase the risk of infections, but only if other arms of the immune system are impaired; ANC of 0.2–0.5×10^9/l is associated with an increased risk of infections in most patients. ANC of 0.2×10^9/l or less (often referred to as "a granulocytosis") carries a risk of severe, life-threatening infections with susceptibility to opportunistic organisms (16).

Lymphopenia is defined as a lymphocyte count below 1.5 x 10^9/L (19) and grading of lymphopenia is as follows: 1. Mild lymphopenia: 1-1.5 x 109/L; 2. Moderate lymphopenia: 0.5-1 x 109/L; 3. Severe lymphopenia < 0.5 x 10^9/L, which may predispose the patient to opportunistic infections such as *Pneumocystis pneumonia (PCP)*, esophageal candidiasis, herpes zoster and systemic cytomegalovirus infection (20).

One of the major complications in cancer treatment is neutropenia, which is caused by chemotherapy. Neutropenia is one of the major dose-limiting toxicities in clinical trials and is a common complication in cancer treatment. Morbidity, mortality, and treatment costs are associated with febrile neutropenia. Febrile neutropenia is clinically relevant problem and it also affects the patient's quality of life (21).

Leukopenia has a significant adverse effect observed during chemotherapy, and can lasts 5-10 days. Most patients develop fever during leukopenia (16, 22) directly affecting the continuity of the chemotherapeutic treatment and leading to possible complications in tumor immune defense. As many authors consider leukopenia secondary to chemotherapy as one of the main causes of the anticancer treatment discontinuation, it emphasizes the need to monitor the immune competence of the patient through (CBC) during the course of treatment (7).

1.2. Statement of the problem

The development of multi-chemotherapy protocols in the treatment of cancer patients enhances the chances of survival in cancer patients. However, many patients are faced with treatment-complications. This can lead to delay or dose reduction of chemotherapeutic drugs which in turn affects the outcome (23).

Hematopoietic system, impairing of host protective mechanisms and the dose limiting of chemotherapy that can be tolerated is caused by cytotoxic chemotherapy (24).CIL is one of the major dose limiting toxicities seen in clinical oncology practice. Leukopenia is a clinically relevant issue with a negative impact on patients 'clinical care, quality of life (QoL) leads to increased morbidity and mortality, as well as causes increased treatment costs (13,24) .

Neutropenia is the other main danger hematological toxicity, which related to life the risking worsening infection plus chemotherapy dose reductions and delays that may compromise treatment outcomes. Despite its importance as the primary dose-limiting toxicity of chemotherapy its impact and consequences remained largely unknown (24).

As a result of chemotherapy around 33% of cancer patients faced an infection, of them 57% are associated to neutropenia(25) and it has been shown that 1–5% of patients receiving chemotherapy die within 1 month after the administration of chemotherapy, mostly as a consequence of febrile neutropenia. The risk of infection is dramatically increased if the neutrophil count falls to below 1×10^9/l (26).

The incidence of febrile neutropenia, severe anemia, thrombocytopenia, and early death after chemotherapy are also associated with lymphopenia. However, the nature of the depleted lymphocyte subpopulation remains unclear (27).

Febrile neutropenia (FN) is characterized by a low absolute neutrophil count (ANC; generally < 0.5×10^9 cells/l or expected to fall below 0.5×10^9 cells/ l) together with fever (oral temperature >38.3°Cor two consecutive oral temperatures >38°C during 2 h). The incidence of FN is mainly dependent on the chemotherapy regimen (28).

Even though chemotherapy has a Serious of effects in terms of the patient's Immune system, QoL, cost of treatments and patient's day to day activity, there is a scarcity of researches and gaps in this area in our country. Therefor this research is conducted to minimize the gaps by showing the incidence of chemotherapy induced hematological toxicities and to generate data by demonstrating consequences for the responsible stake holders.

1.3. Significance of the study

Identifying patients who develop leukopenia particularly febrile neutropenia, which has a substantial risk of mortality, decreased QOL and increased cost of treatment after chemotherapy, is of great importance. Such information will help clinicians to improve patients care. They can monitor the leukocyte count or CBC in general as the major determinant of severity of myelosuppression.

Therefore, this study will provide evidence on the determinants of CIL. Moreover, it will give a motive for future studies in the area and help policy makers to make evidence based decisions.In our country, there is limited data about chemotherapy induced leukopenia. Therefore, this study will add more evidence for researchers and will be additional input for Ministry of Health (MoH) and Policy makers.

2. Literatures Review

Cancer is a significant and major health problem and the leading cause of mortality globally (3, 4). Chemotherapy-induced leukopenia is one of the major dose-limiting toxicities seen in clinical oncology practice (13). Several studies have attested this observation. For example, a retrospective research was conducted by Isabelle Ray-Coquard *et al* to determine the prognostic value of lymphopenia for progression-free and overall survival in patients treated with chemotherapy. The patients were treated for metastatic Breast Cancer (MBC), Non Hodgkin Lymphoma (NHL), and advanced sarcoma in 2009 by the, American Association for Cancer Research, America. The incidence of lymphopenia in the three types of cancers was 27%, 25%, and 24%, respectively (19).

A retrospective cohort study was undertaken by Derek Weycker *et al*.To assess incidence, treatment, and consequences of chemotherapy-induced febrile neutropenia. Participants were recruited from both inpatient and outpatient settings. Data was extracted from Humedica's National Electronic Health Record-Derived Longitudinal Patient-Level Database (2007–2010) in USA. The result showed that risk of febrile neutropenia during the chemotherapy regimen course was 16.8% (29)

Bogani Giorgio *et al*, in their retrospective study investigated chemotherapy related leukopenia as a biomarker predicting survival out- comes in locally advanced cervical cancer at IRCCS National Cancer Institute – Milan Italy, in 2016._Their finding showed that 71.4% of the patients developed leukopenia (30).

The incidence and the severity of chemotherapy-associated oral mucositis were determined in a retrospective study by J.E. Raber-Durlacher during 1994 in Netherlands and in some cases through 1995.In this study which was conducted in the total of 150 patients with various solid tumors were included. The result showed that most patients (n=109, 79%) had one or more episodes of leukopenia during their treatment (14).

A retrospective analysis was conducted by Aimi Huang, *etal*, china in 2016, to investigate chemotherapy-induced leukopenia as a prognostic factor in 309 patients with metastatic non-small cell lung cancer treated with platinum-based chemotherapy. The study showed that, Grade I/II (mild)leukopenia was seen in37.9% of the patients while grade III/IV (severe) leukopenia was observed in 29.4%) of them (31) .

Another retrospective study was conducted in China in 2016by Hongyan Jin*et al*, to determine risk factors for chemotherapy-induced leukopenia in patients with lung Cancer at the Department of Oncology, puren Hospital. A total of 358 patients participated in the study. Among 358 cases of lung cancer who received chemotherapy, a total of 240 patients (67%) experienced CIL (13).

A retrospective study was conducted by Yunwei Han • *et al*. to assess Prognostic value of chemotherapy-induced neutropenia in early-stage breast cancer in Tianjin Medical University Cancer Institute and Hospital in china between April 2005 and April 2007.The result shows that mild neutropenia (grades 1–2) occurred in 42% patients and severe neutropenia (grades 3–4) occurred in (11%)(32).

Randomized research was conducted in Japan by Y Kishida *et al*, to assess Chemotherapy-induced neutropenia as a prognostic factor in advanced non-small-cell lung cancer, between March 2001 and April 2005.from Japan Multinational Trial Organization LC00-03.A total of 387 chemotherapy- naïve patients were enrolled in this randomized controlled trial .the result shows that 308 patients (80%) had chemotherapy-induced neutropenia (33).
A retrospective study was conducted by Yasunori Hashiguchi *et al*, using the available Electronic medical record data between January 2009 and December 2011._,The study was based on the recorded results of 152 cancer patients in Department of Obstetrics and Gynecology, Graduate School of Medicine, Osaka City University, Osaka, Japan. The result shows that Chemotherapy-induced neutropenia occurred in 147 (50.5%) patients (7).

A prospective study was carried out by Choi *et al*. on cancer patients who received cytotoxic chemotherapy at Guro Hospital, Korea University, from September 2001 to February 2002._A total of 82 patients were enrolled in the study period. The result showed that the incidence of febrile neutropenia was 18% (34).

With the aim of evaluating the incidence of chemotherapy-induced neutropenia and febrile neutropenia in patients with solid tumors, an observational study was conducted by Bhavik D. Doshi*et al*. The study was carried out at Shyam Hem-Onc Clinic, Ahmedabad and Medisurge Hospitals, Ahmedabad, Gujarat, India in 2012. A total of 100 patients participated in the study. The incidence of febrile neutropenia was 15% (17).

A cross-sectional study was carried out by Shahrasbi A,*et al*, in Booali university hospital and Tehran private hospital, to investigate the Hematologic Adverse Effects following Systemic Chemotherapy in Tehran, Iran in 2017. In this research a total of 200 cancer patients were participated. The result concluded that 9.4% in BUH and 8.3% in TPH were Neutropenia (8).

Mohamed Badr*et al.* conducted a prospective cohort study to determine Chemotherapy-induced neutropenia among pediatric cancer patients in Egypt: Risks and consequences at Department of Pediatrics, Faculty of Medicine, Zagazig University, Zagazig, Sharqia, Egypt.A total of 50 pediatric cancer patients were admitted to the Pediatric Oncology Unit of the Zagazig University Children's Hospital (Zagazig, Egypt) in the period from the 1st of June, 2013 to the 1st of June, 2014.The result showed that febrile neutropenia was the leading complication among the cases (73.5%) (35).

A prospective cohort study was conducted by Ahmed *et al*. with the aim to determine the incidence and predictors of chemotherapy induced hematologic toxicities and reduced received dose intensity (RDI).The study recruited Ethiopian Breast Cancer Patient at the radiotherapy center of Tikur Anbessa specialized hospital, Addis Ababa University, Addis Ababa, Ethiopia between mid-June 2014 to mid-June 2015. The result showed that Forty nine (19.7%) and six (2.4%) patients initiated their chemotherapy at baseline absolute neutrophil count of 1,500–2,500/m2 (grade 1 neutropenia) and 1,000–1,500 /m2 (grade 2 neutropenia), respectively and the overall incidence of chemotherapy induced grade 3 or 4 hematological toxicity was 51.0% [95% confidence interval (CI) = 44.54–57.46%]. Most of the hematologic toxicity events were neutropenic toxicities, 50.2% (95% CI = 43.83–56.56%) (36).

Despite cancer is one of the major public health issues in Ethiopia, enough researches were not conducted and published data about the consequence of chemotherapy were not found .Most of the literature reviews above implied chemotherapy induced leukopenia particularly febrile neutropenia as a common consequence of chemotherapy. Both leukopenia and neutropenia are common even in healthy Ethiopians (37).Thus, how chemotherapy further aggravates the situation is a research concern, which this study tries to contribute.

3. Objectives

3.1 General Objective

- To assess the prevalence of Chemotherapy induced leukopenia (CIL) among cancer patients at St. Paul's Hospital Millennium Medical College unit of oncology from February 2020 to May2020, Addis Ababa, Ethiopia.

3.2 Specific Objectives

- To assess the prevalence of Chemotherapy induced leukopenia among solid cancer patients at St. Paul's Hospital Millennium Medical College unit of oncology for five cycles from February 2020 to May2020, Addis Ababa, Ethiopia.

- To assess the determinants of CIL among solid cancer patients at St. Paul's Hospital Millennium Medical College unit of oncology from cycle one to cycle five from February 2020 to May2020, Addis Ababa, Ethiopia.

- To determine the prevalence of Chemotherapy induced neutropenia, febrile neutropenia and lymphopenia of cancer patients in oncology unit from cycle one to cycle five from February 2020 to May2020, Addis Ababa, Ethiopia.

4. Hypothesis of the study

There is a relationship between chemotherapy and leukopenia in cancer patients.

5. Materials and Methods

5.1 Study area

This study was conducted in SPHMMC oncology unit which is located in Addis Ababa, the capital city of Ethiopia. St Paul's Hospital Millennium Medical College was established through a decree of the Council of Ministers in 2010, although the medical school opened in 2007 and the hospital was established in 1968 by the late Emperor Haile Selassie. The College initiated Ethiopia's first integrated modular and hybrid problem-based curriculum for its undergraduate medical education. The college has more than 2800 clinical, academic, and administrative and support staffs that provide: medical specialty services to patients who are referred from all over the country. The hospital has 800 beds and gives diagnostic and treatment services for about 370,000-400,000 patients per year. SPHMMC offers the lowest cost for these services.

SPHMMC Oncology Unit was established in August 1, 2018.It was the second hospital offering cancer treatment in the country next to Black Lion Hospital. Currently there are two oncologists, 12 general practitioners, 14 nurses one medical physicist, 3 clinical pharmacists, 2 cleaners and 2 porters, and around 800 cancer patients are served in the unit since its establishment

5.2. Study design and Period

5.2.1 Study design

An institution based cross sectional study was conducted at SPHMMC oncology unit

5.2.2. Study Period

The study was conducted from February 2020 to May2020.

5.3 Population

5.3.1 Source Population

All solid cancer patients who visited SPHMMC oncology unit was the source population.

5.3.2 Study Population

All solid cancer patients, who were receiving chemotherapy at SPHMMC oncology unit between February 2020 to May2020, and who fulfill the eligibility criteria were the study population.

5.4 Inclusion and Exclusion criteria

5.4.1 Inclusion Criteria

- All cancer patients who receiving chemotherapy for five cycles at SPHMMC oncology unit between February 2020 to May2020 and
- Whose base-line WBC was not leukopenic.

5.4.2 Exclusion criteria

- Patients who started chemotherapy before the study period.
- Patients who were suffered from mental health and hearing problems.
- Patients who were not voluntary to participate in the study.
- Patients who have had radiotherapy in addition to chemotherapy.

5.5 .Study Variables

5.5.1 Dependent Variables

Chemotherapy induced leukopenia, neutropenia, febrile neutropenia and lymphopenia

5.5.2 Independent Variables

- Demographic variables: Sex, Age, Educational level, Marital Status, Weight, Height and Body Surface Area.
- Disease related variables – type of cancer, stage, performance status (ECOG)
- Types of chemotherapy regimen

5.6. Sample Size determination and Sampling Method

5.6.1. Sample Size determination

Since the study follows patients until they finish 5 cycles, a convenient sample size of 92, recruiting those who fulfilled the eligibility criteria.

5.6.2. Sampling Method

The research was conducted by using convenient sampling technique.

5.7. Measurement and data collection

5.7.1. Data collection procedure

After obtaining consent, patients who fulfilled the inclusion and exclusion criteria were identified by oncology unit nurses. Socio-demographic data was collected by using standardized pretested questionnaire and from the patients chart.

The questionnaires included demography related questions and disease related questions obtained by interviewing the patients and from the patients charts. About 2-3 ml blood sample was collected for hematological analysis using EDTA test tube. Patients were followed until end of their 5 cycles of chemotherapy.

5.7.2. Laboratory Analysis

Using 70% denatured alcohol, the puncture site was disinfected and 2-3 ml of blood was collected by using 5cc EDTA test tubes. CBC was analyzed by using automated Beckman coulter analyzer in the laboratory of SPHMMC.

Coulter principle

A suspension of blood cells is passed through a small orifice simultaneously with an electric current. The individual blood cells passing through the orifice introduce an impedance change in the orifice determined by the size of the cell.

The system counts the individual cells and provides cell size distribution. The number of cells counted per sample is approximately 100 times greater than the usual microscope count to reduce the statistical error by a factor of approximately 10 times.

Coulter method

The Coulter Method accurately counts and sizes cells by detecting and measuring changes in electrical resistance when a particle (such as a cell) in a conductive liquid passes through a small aperture. Each cell suspended in a conductive liquid (diluent) acts as an insulator. As each cell goes through the aperture, it momentarily increases the resistance of the electrical path between the submerged electrodes on either side of the aperture. This causes a measurable electronic pulse. For counting, the vacuum used to pull the diluted suspension of cells through the aperture must be at a regulated volume while the number of pulses indicates particle count; the size of the electrical pulse is proportional to the cell volume.

DxH 800 Operation Principles

CBC analysis

In hematology, the complete blood count, the CBC, is the fundamental analytical test that evaluates the three main cellular components: white blood cells, red blood cells and platelets. The DxH 800 CBC analysis is based on the coulter principle. The sample preparation and data collection occurs in the SAM and CBC modules and analysis is handled by the system manager.

Specimen Preparation

The aspiration pump activates and aspirates 165 μL of sample. After the probe is removed from the specimen tube a second pull of the aspiration pump draws the blood through the BSV path way, verifying a proper aspiration at the blood detectors.

With each cycle, the BSV directs the delivery of sample and DxH Diluent to the WBC and RBC triple aperture baths. The RBC diluent and WBC diluent/Lyse dilutions enter through a port in the bath that is located at the bottom and tangential to a sloping surface for bubble free delivery and mixing. In the WBC bath, ~6.0 mL of DxH diluent and ~28 μL of sample are combined with ~1.08 mL of DxHCell Lyse for a final dilution of 1:251. In the RBC bath, ~10 mL of DxH diluent and ~1.6 μL of sample are combined for a final dilution of 1:6250.

5.8. Data Quality Assurance

Standard operational procedures were followed during collection and analysis of each blood sample. All the materials used for sample collection and analysis were checked for proper functioning. The completeness of the questionnaire was checked daily.

The quality assurance includes three phases. Such as

Pre analytical. The main processes that were taken into account in the study of the pre-analytical phase were:

- Firstly i gave unique identification for the patient, and then i prepare the Patients, after that I Selects the right vein then i collect the right quantity of Specimen from the patients. Then I registered the date and time of primary sample collection at the same time I gave unique labeling for each specimen. Finally I try to avoiding interferences by handling the Specimen Properly, by using right transportation system and right storage

Analytical: The main processes that were taken into account in the study of the analytical phase were:

- Firstly I collect all the proper Equipment's, reagents and proper test –SOP, and then the Laboratory professionals run the sample by using Bio-Safety.

Post analytical: The main processes that should be taken into account in the study of the analytical phase are:

- Finally I Record all the result by using SPSS Version 23 and I interpret the results for my research purpose.

5.9. Data analysis and interpretation

Data was entered, cleaned and analyzed by using SPSS version 23 software. The result was presented in table. Paired sample T-test was used to compare the pre and post treatment results. Level of statistical significance was determined at p value less than 0.05.

5.10. Operational definition

Leukopenia is a decrease in the number of white blood cells (WBCs),which is down to a level of approximately 4.0 X 10^9/l

Neutropenia is a decrease in the absolute number of neutrophils in the blood.

Based on the NCI Neutropenia has four grades according to the (ANC):

- Grade 1, ANC 1.5 -2x10^9/l
- Grade 2, ANC 1.0 to -1.5x10^9/l
- Grade 3, ANC 0.5 to -1x10^9/l and
- Grade 4, ANC <0.5x10^9/l

Febrile neutropenia is characterized by, ANC generally fall below 0.5 × 10^9 cells/ l) together with fever (oral temperature >38.3°Cor two consecutive oral temperatures >38°C during 2 h.

Lymphopenia is a decrease in lymphocyte count below 1,500/l, and grading of lymphopenia, Lymphocyte count < 1.5 x 10^9/L

- Mild lymphopenia: 1-1.5 x 10^9/L
- Moderate lymphopenia: 0.5-1 x 10^9/L and
- Severe lymphopenia < 0.5 x 10^9/L

Solid Tumor is an abnormal mass of tissue that usually does not contain cysts or liquid areas.

5.11. Ethical consideration

This MSc Research proposal was approved by the Department of Research and Ethical Review Committee of the department of Medical Laboratory Science, college of health science, of Addis Ababa University. Official permission from the study site was obtained. Written informed consents were obtained from study participants after explaining aim of the study, risk, benefits, confidentiality and their right not to participate in the study and withdraw anytime. Privacy was maintained during data collection, and confidentiality of the data was assured.

5.12. Dissemination of the results

The thesis will be presented at the Department of Medical Laboratory Sciences. The findings will be communicated in different conferences for the responsible stakeholders and the final result will be published on peer reviewed journals.

6. Results:

6.1. Socio-demographic and clinical characteristics:

A total of 101 newly diagnosed solid cancer patients participated during the study period. Because of the incomplete information, three patients were excluded. Of the total participants, 98 were eligible per inclusion criteria. Six (6.1%) patients died during the study period. The age of participant ranged from 16-84 years with the mean age of 45.From the total patients 48(49%) were young in the age group of 16-44 years old and most 42.9% attained primary education. From the total patients73 (74.5%) were females and 66 (67.3%) were married.(Table 1).

Table 1: Base-line socio-demographic characteristics of solid cancer Patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Variables		Number	%
Age (Years)	16-44	45	48.9
	45-64	39	42.4
	65-74	5	5.4
	>/=75	3	3.3
Mean ±SD	45±7		
Sex	Male	24	26.1
	Female	68	73.9
Residence	Urban	73	79.3
	Rural	19	20.7
Educational Status	Cannot read &write	15	16.3
	Primary1-8	41	44.6
	Secondary"9-12"	10	10.9
	Diploma/Degree	24	26.1
	MSc and above	2	2.2
Marital status	Married	60	65.2
	Unmarried	20	21.7
	Divorced	5	5.4
	Widowed	7	7.6
Occupation	Employee	35	38.00
	Merchant	14	15.2
	House wife	32	34.8
	Student	2	2.2
	Farmer	9	9.8

The baseline clinical characteristic of patients is shown in Table 2. Accordingly, the baseline performance status PS/ECOG of patients were distributed as follows 0 in 43(43.9%), 1 in 30, (30.6%), 2 in 15 (15.3%), 3 in 7 (7.1%) and 4 in 3 (3.1%). Of 98, 85(86.7%) patients have no history of any chronic diseases and 83 (84.7%) do not have history of using substances. Regarding the stage of cancer, majority (54.1%) were not mentioned while 27.6% were in stage 2. (Table 2).

- PS/ECOG
  - ✓ 0-Fully active, able to carry on all pre disease performance without restriction
  - ✓ 1-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
  - ✓ 2-Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
  - ✓ 3-Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
  - ✓ 4-Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
  - ✓ 5-Dead (38)

Table 2. Baseline Clinical characteristics of cancer patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February2020 to May 2020.

Variable		Number	%
ECOG/PS-Eastern Corporation Oncology Group/Performance Status	.00	41	44.6
	1.00	27	29.3
	2.00	15	16.3
	3.00	7	7.6
	4	2	2.2
Stage of Cancer	stage one	4	4.3
	stage two	24	26.1
	stage three	12	13.1
	stage four	2	2.2
	not mentioned	50	54.3
Body Mass Index	< 18.5 under weight	19	20.7
	18.5-24.9 normal	53	57.6
	25-29.9 over weight	11	12
	>/=30 obese	9	9.7
Other chronic disease	Yes	13	14.1
	No	79	85.9
Substance	Yes	14	15.2
	No	78	84.8

6.2. Chemotherapy Induced Hematological toxicities

The study included patients who were newly diagnosed of cancer and with no abnormalities in leukocytes and subset counts prior to commencement of chemotherapy. After the initial chemotherapy, the incidence of leukopenia (p=0.011) neutropenia (p=0.014), were recorded through the five cycle (Table 3). The abnormalities have significant association with occupation and BSA respectively (p<0.05).

Of the total 98 patients enrolled in the study, 6 of them died and hence were excluded from the final analysis. Hence, the study followed 92 patients throughout the five cycles. During the study period the incidence of hematological toxicities from the total of 92 cancer patients, 74 (80.4%) developed leukopenia, 65(70.7%) developed neutropenia, 46(50%) developed Febrile neutropenia and 81(88%) lymphopenia (Table 3). Generally G-CSF was used as a prophylaxis from cycle 1 to cycle 5 for those who developed Febrile Neutropenia.

Table 3.Incidence of chemotherapy Induced Hematological toxicities in the five cycles attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Hematological Toxicities	Number	%
Leukopenia	74	80.4
Neutropenia	65	70.7
Febrile-Neutropenia	46	50
Lymphopenia	81	88

Chi-square test results (Table 4) showed that the occurrence of leukopenia was more likely in patients who were female (*P*=0.063), with age rang 16-44(p=0.573), who lives in Urban (p=0.929), who are married (p= 0.495) and whose occupation are employee (p=0.011) as well as in those with ECOG /PS <2 (*P*=0.013), in the stages of 2 and 3 (*P*=0.301)

The table also shows that, the incidence neutropenia, febrile neutropenia and lymphopenia do not have any significant with determinants through the five cycle ,except leukopenia which has significant association with occupation and ECOG with P=0.011 and P=0.013 respectively. (p<0.05)(Table 4).

Table 4.Characteristics of hematological toxicities with its determinants in 92 patients following five cycles attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Variables		Leukopenia N(%)	P-Value	NeutropeniaN(%	P-Value	F.NeutrpeniaN(%)	P-Value	Lymphopenia N(%)	P-Value
Age (Years)			0.573		0.216		0.194		0.745
	16-44	37(50)		34(52)		25(54.3)		41(51)	
	45-64	30(41)		26(40)		18(39.1)		32(39)	
	65-74	4(5)		2(3.1)		1(2.2)		5(6)	
	>/=75	3(4.05)		3(4.6)		2(4.3)		3(4)	
Mean± SD	45±7								
Sex			0.063		0.264		0.543		0.742
	Male	18(24.3)		17(26.2)		12(26.1)		21(26)	
	Female	56(75.7)		48(73.8)		34(73.9)		60(74)	
Residence			0.929		0.209		0.169		0.690
	Urban	60(81%)		50(77)		35(76.1)		64(79)	
	Rural	14(18.9)		15(23.1)		11(23.9)		17(21)	
Educational Status			0.927		0.340		0.292		0.345
	Cannot read &write	11(15)		10(15)		7(15.2)		14(17)	
	Primary1-8	34(46)		29(45)		22(47.8)		36(44)	
	Secondary" 9-12"	6(8.1)		8(12.3)		6(13.0)		8(10)	
	Diploma/Degree	22(30)		17(26.)		10(21.7)		21(26)	
	MSc and above	1(1.4)		1(1.5)		1(2.2)		2(2.5)	
Marital status			0.495		0.546		0.688		0.698
	Married	46(62)		42(65)		30(65.2)		53(65)	

	Unmarried	18(24.)		15(23)		11(23.9)		17(21)	
	Divorced	4(5.4)		4(6)		2(4.3)		5(6.2)	
	Widowed	6(8.1)		4(6)		3(6.5)		6(7.4)	
Occupation			0.011		0.115		0.148		0.135
	Employee	31(42)		27(42)		20(43.5)		31(38)	
	Merchant	12(16)		10(15)		4(8.7)		13(16)	
	House wife	26(35)		22(34)		18(39.1)		29(36)	
	Student	1(1.4)		1(1.5)		0		2(2.5)	
	Farmer	4(5.4)		5(8)		4(8.7)		6(7.4)	
ECOG/PS			0.013		0.823		0.876		0.446
	.00	29(39)		31(48)		22(47.8)		35(43)	
	1.00	23(31)		17(26)		14(30.4)		25(31)	
	2.00	13(18)		9(13.8)		6(13.0)		12(15)	
	3.00	7(9.5)		6(9.2)		3(6.5)		7(8.6)	
	4	2(2.7)		2(3.1)		1(2.2)		2(2.5)	
SoCa			0.301		0.416		0.399		0.454
	stage one	3(4.1)		2(3.1)		2(4.3)		4(4.9)	
	stage two	21(28)		21(32)		15(32.6)		21(26)	
	stage three	10(13)		9(14)		7(15.2)		9(11.1)	
	stage four	2(3)		2(3.1)		1(2.2)		2(2.5)	
	not mentioned	38(51)		31(48)		21(45.7)		45(56)	
BMI			0.129		0.134		0.981		0.966
	< 18.5 under	16(22)		14(22)		11(23.9)		18(22)	
	18.5-24.9 normal	40(54)		36(55)		26(56.5)		43(53)	
	25-29.9 over	12(16)		9(14)		6(13.0)		13(16)	
	>/=30 obese	6(8)		6(9)		3(6.5)		7(8.6)	

During the study period from the total of 92 cancer patients, 32 (34.8%) developed leukopenia in the first cycle. In the second cycle, leukopenia was seen in 24 (26.1%) patients, 33 (35.9%) patients in the third cycle, 25 (27.2%) patients in the fourth cycle and 38, (41.3%) patients in the fifth cycle.

The magnitude of neutropenia in the five cycles were, 23 (25%), 25 (27.2%), 29 (31.5 %), 26(28.3%), and 33 (35.9 %), respectively. Febrile neutropenia was seen in 8(8.7%), 11(12%), 14(15.2%), 20(21.7%), and 17(18.5%) patients, in the five cycles, respectively. Generally G-CSF was used as a prophylaxis from cycle 1 to cycle 5for those who developed Febrile Neutropenia.

From 92 patients, 47(51.1%) developed lymphopenia in the first cycle while 58 (63%), 61(66.3%), 62(67.4%), and 68(73.9%) patients were found to have lymphopenia in the 2^{nd}, 3^{rd}, 4^{th}, and 5^{th} cycles respectively (Table 6).

Table 5.Distribution of chemotherapy induced Hematological toxicities in the five cycle in patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Treatment-Cycle	1 (n=92)	2 (n=92)	3 (n=92)	4 (n=92)	5 (n=92)
Variables	N (%)	N (%)	N (%)	N (%)	N (%)
Leukopenia	32(34.8)	24(26.1)	33(35.9)	25(27.2)	38(41.3)
Neutropenia	23(25)	25(27.2)	29(31.5)	26(28.3)	33(35.9)
Febrile-Neutropenia	8(8.7)	9(9.8)	14(15.2)	19(20.7)	17(18.5)
Lymphopenia	47(51.1)	60(65.2)	61(66.3)	62(67.4)	68(73.9)
Mean duration in days	5.875	6	6.57	6.5	5.94
Minimum	3	3	3	4	2
Maximum	14	9	9	12	9

6.3. Grading of Neutropenia and Lymphopenia

The rate of neutropenia grading in the whole study (cycle 1- cycle 5) were, 24 (26.1%) patients developed grade 1 and 2 neutropenia, 12 (13%) developed grade 3 and 4 neutropenia in the first cycle. In the 2nd cycle, 21 (22.83%) patients developed grade 1 and 2 neutropenia and 3(3.3%) patients developed grade 3 and 4 neutropenia. In the 3rd cycle, 26(28.3%) patients developed grade 1 and 2 neutropenia and 3(3.3%) patients developed grade 3 and 4 neutropenia. In the4th cycle, 17(18.5%) patients developed grade 1 and 2 neutropenia while 10(10.87%) patients developed grade 3 and 4 neutropenia. In the 5th cycle 27 (29.35%) patients developed grade 1 and 2 neutropenia while 8(8.7%) patients developed grade 3 and 4 neutropenia. The remaining patients in each cycle had neutrophil count within the normal range.

With regards to Lymphopenia, overall 40 (43.5%) patients in the first cycle,55 (59.78%) patients in the second cycle ,57 (61.95%) patients in the third cycle,58(63.04%) patients in the fourth cycle and 63(68.48%) patients developed mild to moderate lymphopenia. sever lymphopenia were developed by, a total of 7(7.6%) ,5(5.4%) 6(6.5%) ,4(4.3%) and 6(6.5%) patients from cycle one to cycle five, respectively(Table 4).

Table 6: Grading of Neutropenia and Lymphopenia in patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Treatment cycle	1	2	3	4	5
Neutropenia grading	N (%)	N (%)	N (%)	N (%)	N (%)
within normal range	56(60.9)	68(73.9)	63(68.5)	65(70.7)	57(62.0)
grade one	14(15.2)	11(12.0)	15(16.3)	11(12)	14(15.2)
grade two	10(10.9)	10 (10.9)	11(12)	6(6.5)	13(14.2)
Grade three	11(12.0)	3(3.3)	3(3.3)	8(8.7)	5(5.4)
grade four	1(1)	0%	0%	2(2.2)	3(3.3)
Lymphopenia grading					
within normal range >/=1500 cells/uL	46(50.0)	32(34.8)	29(31.5)	30(32.6)	23(25.0)
mild lymphopenia, 1000-1500 cells/uL	27(29.4)	31(33.7)	34(37)	37(40.2)	35(38)
moderate lymphopenia, 500-1000 cells/uL	12(13)	24(26.1)	23(25)	21(22.8)	28(30.4)
sever lymphopenia,< 500 cells/uL	7(7.6)	5(5.4)	6(6.5)	4(4.3)	6(6.5)

6.4. Incidence of chemotherapy induced toxicities with respective regimens in the five cycle

During the study period, it was observed that the majority of chemotherapy induced toxicities were caused by Adriamycin + cyclophosphamide (AC) in the five cycles.

In the five cycle 24 (32.4%) leukopenia, 24 (36.9%) neutropenia, 16(34.8%) Febrile neutropenia and 27(33.3%) lymphopenia were occurred because of AC (Adriamycin + cyclophosphamide). 10(13.5%) leukopenia, 10 (15.4%) neutropenia, 8(17.4%) Febrile neutropenia and 12(14.8%) lymphopenia were occurred because of Adriamycin + cyclophosphamide + paclitaxel (ACP) and also 10(13.5%) leukopenia, 9(13.8%) neutropenia, 8(17.4%) Febrile neutropenia and 10 (12.3%) lymphopenia were occurred because of cisplatin + paclitaxel (Table 5).

Table 7: Distribution of chemotherapy induced toxicities with respective regimens in the five cycle in patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May2020.

Chemotherapy induced toxicities	Leukopenia		Neutropenia		F.Neutropenia		Lymphopenia	
Type of Regimen	N	%	N	%	N	%	N	%
Adriamycin + cyclophosphamide	24	32.4	24	36.9	16	34.8	27	33.3
ACP	10	13.5	10	15.4	8	17.4	12	14.8
cisplatin + paclitaxel	10	13.5	9	13.8	8	17.4	10	12.3
capecitabine + oxaliplatin	7	9.5	5	7.7	2	4.3	6	7.4
cisplatin + gemicitabine	6	8.2	4	6.2	3	6.5	8	9.9
cisplatin + capacitabine	6	8.2	6	8.2	5	10.8	7	8.6
Others	11	14.8	7	10.8	4	8.8	11	13.7
Total	74	100	65	100	8	100	81	100

ACT=Adriamycin + cyclophosphamide + paclitaxel, CMF=cyclophosphamide + methotrexate + fluorouracil.

6.5. Distribution of chemotherapy induced toxicities with respective regimens in each cycle

In the first cycle 13 (40.63%) leukopenia, 11 (47.83%) neutropenia, 4(50%) Febrile neutropenia and 19(41.3%) lymphopenia were occurred because of AC (Adriamycin + cyclophosphamide). In this cycle the mean duration of febrile neutropenia was 5.875 (with the range of 3-14days) (Table 5).

Table 8. Distribution of chemotherapy induced toxicities with respective regimens in cycle 1 in patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Chemotherapy induced toxicities	Leukopenia		Neutropenia		F.Neutropenia		Lymphopenia	
Type of Regimen	N	%	N	%	N	%	N	%
Adriamycin + cyclophosphamide	13	40.6	11	47.83	4	50	19	41.3
cisplatin + gemcitabine	1	3.13	0	0	0	0	3	6.5
ACT	7	21.9	5	21.74	0	0	6	13.0
CMF	1	3.13	0	0	0	0	2	4.3
cisplatin + paclitaxel	3	9.38	2	8.69	1	12.5	4	8.7
cisplatin + capacitabine	2	6.25	1	4.35	1	12.5	4	8.7
carboplatin + paclitaxel	0	0	0	0	0	0	3	6.5
capacitabine + oxaliplatin	3	9.38	2	8.69	0	0	3	6.5
bleomycin + etoposide + cisplatin	2	6.25	2	8.69	2	25	2	4.3
Total	32	100	23	100	8	100	46	100

ACT=Adriamycin + cyclophosphamide + paclitaxel, CMF=cyclophosphamide + methotrexate + fluorouracil.

In the second cycle, 9(37.5 %) leukopenia, 9(37.5%) neutropenia, 4(44.44%) Febrile neutropenia and 24(40.7%) lymphopenia Occurred because of AC. In this cycle the mean duration febrile neutropenia was 6 (with the range of 3-9days) (Table 6).

Table 9.Distribution of chemotherapy induced toxicities with respective regimens in cycle 2 in patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Chemotherapy induced toxicities	Leukopenia		Neutropenia		F.Neutropenia		Lymphopenia	
Type of Regimen	N	%	N	%	N	%	N	%
Adriamycin + cyclophosphamide	9	37.5	9	37.5	4	44.44	24	40.7
cisplatin + gemcitabine	3	12.5	2	8.33	0	0	6	10.2
ACT	4	16.67	5	20.83	2	22.22	7	11.9
CMF	1	4.17	1	4.17	1	11.11	2	3.4
cisplatin + paclitaxel	1	4.17	0	0	1	11.11	6	10.2
cisplatin + capacitabine	3	12.5	3	12.5	0	0	6	10.2
carboplatin + paclitaxel	1	4.17	1	4.17	0	0	1	1.7
capacitabine + oxaliplatin	1	4.17	2	8.33	0	0	6	10.2
bleomycin + etoposide + cisplatin	1	4.17	1	4.17	1	11.11	1	1.7
Total	24	100	24	100	9	100	59	100

In the third cycle 13 (40.63%) leukopenia, 13(44.83%) neutropenia, 6(42.86%) Febrile neutropenia and 22(39.29%) lymphopenia occurred because of AC. In this cycle the mean duration of febrile neutropenia was 6.57 (with the range of 3-9days) (Table 7).

Table 10.Distribution of chemotherapy induced toxicities with respective regimens in cycle 3 in patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Chemotherapy induced toxicities	Leukopenia		Neutropenia		F.Neutropenia		Lymphopenia	
Type of Regimen	N	%	N	%	N	%	N	%
Adriamycin + cyclophosphamide	13	40.63	13	44.83	6	42.86	22	39.29
cisplatin + gemcitabine	4	12.5	2	6.89	3	21.43	4	7.14
ACT	6	18.75	6	20.69	1	7.14	9	16.07
CMF	1	3.13	1	3.45	0	0	2	3.57
cisplatin + paclitaxel	3	9.38	0	0	1	7.14	8	14.29
cisplatin + capacitabine	2	6.25	3	10.34	1	7.14	5	8.93
capacitabine + oxaliplatin	2	6.25	2	6.89	1	7.14	5	8.93
bleomycin + etoposide + cisplatin	1	3.13	2	6.89	1	7.14	1	1.79
Total	32	100	29	100	14	100	56	100

In the fourth cycle 6(24%) leukopenia, 9(40.9%) neutropenia, 4(21.05%) Febrile neutropenia and 23(38.98%) lymphopenia occurred because of AC. In this cycle the mean duration of febrile neutropenia was 6.5 (with the range of 4-12days) (Table 8).

Table 11.Distribution of chemotherapy induced toxicities with respective regimens in cycle 4 in patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Chemotherapy induced toxicities	Leukopenia		Neutropenia		F.Neutropenia		Lymphopenia	
Type of Regimen	N	%	N	%	N	%	N	%
Adriamycin + cyclophosphamide	6	24	9	40.9	4	21.05	23	38.98
cisplatin + gemcitabine	2	8	2	9.1	3	15.79	6	10.17
ACT	5	20	5	22.7	3	15.79	8	13.56
cisplatin + paclitaxel	2	8	0	0	3	15.79	6	10.17
cisplatin + capacitabine	4	16	3	13.65	4	21.05	6	10.17
carboplatin + paclitaxel	3	12	1	4.55	2	10.53	3	5.08
capacitabine + oxaliplatin	3	12	2	9.1	0	0	7	11.86
Total	25	100	22	100	19	100	59	100

In the fifth cycle 14(40%) leukopenia, 10(30.3%) neutropenia, 5(31.25%) Febrile neutropenia and 24(39.34%) lymphopenia occurred because of AC. In this cycle the mean duration of febrile neutropenia was 5.94 (with the range of 2-9days) (Table 8).

Table 12.Distribution of chemotherapy induced toxicities with respective regimens in cycle 5 in patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit, Addis Ababa, Ethiopia from February 2020 to May 2020.

Chemotherapy induced toxicities	Leukopenia		Neutropenia		F.Neutropenia		Lymphopenia	
Type of Regimen	N	%	N	%	N	%	N	%
Adriamycin + cyclophosphamide	14	40	10	30.3	5	31.25	24	39.34
cisplatin + gemcitabine	3	8.57	3	9.09	3	18.75	5	8.2
ACT	4	11.43	3	9.09	2	12.5	9	14.75
cisplatin + paclitaxel	7	20	7	21.21	4	25	10	16.39
cisplatin + capacitabine	3	8.57	5	15.15	1	6.25	5	8.2
capacitabine + oxaliplatin	2	5.71	3	9.09	0	0	6	9.84
bleomycin + etoposide + cisplatin	2	5.71	2	6.06	1	6.25	2	3.28
Total	35	100	33	100	16	100	61	100

7. Discussion

In cancer chemotherapy, the most important issue is how to gain the maximal pharmacologic effect; at the same time, the appearance of adverse effects should be considered. Adverse effects of anticancer agents may lead not only to the patients' pain and anxiety but also to death in some Cases. The development of G-CSF has greatly improved the therapeutic efficacy of anticancer chemotherapy. In particular, the development of G-CSF analogues as medicines has facilitated more potent cancer chemotherapy than before. However, leukopenia, is still a dose-limiting factor (39)

The current study aimed at assessing the distribution of chemotherapy induced leukopenia and it's determinants in solid cancer patients at St Paul's Hospital Millennium Medical College Oncology unit in Addis Ababa, Ethiopia. A total of 92 newly diagnosed patients aged 16-84 years; predominantly (93.88%) fulfilled the eligibility criteria. The magnitude of chemotherapy induced cytopenias in the five cycles was as follows: 74(80.4%) had Leukopenia, 65(70.7%) Neutropenia, 46(50%) Febrile Neutropenia and 81(88%) Lymphopenia.

The present study showed that the occurrence of leukopenia was more likely in patients whose occupation are employee (p=0.011) as well as in those with ECOG /PS <2 (*P*=0.013).But the research conducted by Wei Liu *et al*, showed that the occurrence of leukopenia was more likely in patients who were female (*P*=0.042), as well as in those with ECOG PS ≥2 (*P*=0.04) (10).

The present study showed that the greater risk of leukopenia were introduced in cycle three 33(35.9%) and cycle five 38(41.3%) patients. Similarly a research conducted by Hongyan Jin *et al.* showed that more than or equal to 3 cycles of chemotherapy have a greater risk of chemotherapy-induced leukopenia (10). Environmental change, life style and other unknown factors may cause the difference.

Many factor analysis shows, patients who have had taken three or more cycles of chemotherapy, developed 3.1 times CIL as much as the patients who had received less than 3 cycles of chemotherapy. The boosting risk of CIL after three cycles could be associated to intact toxicity and toxic storage of chemotherapy drugs.

Also, chemotherapy induced bone marrow nerve injury dysfunction hematopoietic regeneration demonstrating that chemotherapy-induced nerve injury in the bone marrow is a critical lesion impairing hematopoietic regeneration. This research has similar results with the present findings (13).

The occurrence of white blood cell reduction may be related to the following reasons: _1) in the late stage of tumor, tumor cells have been spread to the myeloid hematopoietic system, which directly inhibition the bone marrow hematopoietic function._2). The patients had received multiple chemotherapy, which is at the stage of bone marrow suppression (13).

In the present study less incidence of worst grade neutropenia was seen, during the first cycle 1(1%); in the fourth cycle 2(2.2%) and fifth cycle 3(3.3%). After the initiation of chemotherapy the worst grade of neutropenia was increased. But Yunwei Han *et al 2012* reported large amount of worst grade neutropenia, which is different from the present study. In 176 patients experiencing neutropenia, the worst grade was seen during the first cycle in 32(18.18%) patients, during the second cycle in 38(21.59%), during the third cycle in 32(18.18%), during the fourth cycle in 31(17.61%) and during the fifth cycle 22(12.5%) (34).Race difference might be one of the reasons.

In the present study the incidence of febrile neutropenia was continuously increased while the patients were started to taking chemotherapy, 8.7% patients in the first cycle ,9.78 % in the second cycle, 15.22% in the third cycle, 20.7% in the fourth cycle and 18.5% in the fifth cycle developed febrile neutropenia and all of them were admitted in the SPHMMC emergency and mean duration of FN were 5.87days (range 3-14days),6 days (range 3-9 days),6.57days (range 3-9),6.5 days (range 4-12 days),and 5.94 days (range 2-9 days) for cycle 1,2,3,4 and 5 respectively.

But Studies conducted by Derek Weycker *et al* showed different results with the present study. The overall risk of FN during any myelosuppressive chemotherapy regimen course was 16.8%. Risk of FN was 8.1% in cycle 1, 4.9% in cycle 2 and 3.8% in subsequent cycles (33). The mean duration of neutropenia and fever was 3.6 days (range 1–12 days), 3.4 days (range 1–9 days) and 8.4 days respectively.

The source of fever was unexplained by examination in 14 (56.0%) cycles (33). Based on this study the incidence of FN was decreased while the number of chemotherapy cycle increased but the duration of FN was more or less similar with the present study.

In the present study from 92 patients, 7(7.6%) patients in the first cycle, 5(5.4%) in the second cycle, 6(6.5%) in the third cycle, 4(4.3%) in the fourth cycle and 6(6.5%) in the fifth cycle developed sever (</= 500 cells/dl) lymphopenia. A study conducted by Athanasios Kotsakis *et al* founds a different result with the present finding, from 33 patients treated every 3 weeks were evaluated on Day 0 and 21 before the administration of the first and second cycle of chemotherapy respectively of these ,7(21%) patients presented severe lymphopenia on Day 21 (i.e. in the second cycle) (40).

In the present study the most common chemotherapy regimen was AC (Adriamycin + cyclophosphamide) and it also causes large amount of hematologic toxicities. The reason is the most cancer seen in the unite was breast cancer and the most common regimen used was AC. But research conducted by *Yasunori Hashiguchi et al* showed that, the most common chemotherapy regimen was paclitaxel and carboplatin (TC) therapy and the most common hematologic toxicities were caused by docetaxel+ nedaplatin and cyclophosphamide + Adriamycin + cisplatin (7).In-terms of common chemotherapy regimen usage the present study is different from this study. But in-terms of causing large hematologic toxicities both of them have similar results.

8. Strength and limitation of the study

8.1. Strength

- Data was collected for five cycles
- In Ethiopia there is no published research in this area following patients for five cycles: so the study serves as the baseline for other researchers.

8.2. Limitation

- Only the baseline characteristics of ECOG, BMI and Weight were evaluated.
- The influences of other prognostic factors are not evaluated.

9. Conclusion and Recommendation

9.1. Conclusion

- Even though chemotherapy is the standard treatment for cancer, it might cause leukopenia, neutropenia, febrile neutropenia and lymphopenia. In the present study it was demonstrated that hematologic toxicities are common in cancer patients who were taking chemotherapy. The main hematologic toxicities include Leukopenia (80.4%), Neutropenia (70.7%), Febrile-Neutropenia (50%) and Lymphopenia (88%). The majority of hematologic toxicities are caused by Adriamycin + cyclophosphamide and Adriamycin + cyclophosphamide + paclitaxel

9.2. Recommendation

- Further study on the predicting factors of Leukopenia, Neutropenia, Febrile neutropenia and Lymphopenia is recommended.
- Further study on the effect of chemotherapy on other components of CBC is recommended is recommended.

10. References

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11. Annex

11.1 Annex I. Participant information sheet

Addis Ababa University, collage of health sciences, department of medical laboratory sciences
E-mail: SMLT@ethionet.et
Tel. +251112-75-51-70

Title of the study: Assessment of Chemotherapy induced leukopenia in solid cancer patients attending St. Paul Hospital Millennium Medical College (SPHMMC) Oncology Unit in Addis Ababa Ethiopia.

Introduction

This information sheet and consent form is prepared by the principal investigator Mekonnen Dessalegn to clarify the study that you are asked to take part. If there is any lack of clarity you decide to participate or not you can ask freely.

What are expected from the study participant?

You will be requested to give 5 ml of blood sample. Blood will be collected from your arm using sterile tubes. If you are agree to give blood sample then you will be also asked to answer for questionnaire.

Confidentiality

Any information that we collect about you during this study will be kept confidentially. Information about your identity will be put away after recording your file; and kept in a secured place. Only the principal investigator will be able to link your identity with the code number.

Benefit

There is no direct benefit you obtain from this study, but indirectly the result of the study will be beneficial to put a new strategy for the assessment of chemotherapy induced leukopenia in cancer patients attending St. Paul hospital millennium medical college (SPHMMC) oncology unit of the cancer patients. Hence you are indirectly benefiting other cancer patients and the society in this respect.

The risk of this study

You may feel a mild pain while samples are collected except that there will be no risk.

Participation and right to refuse on the study

We are asking you and others to voluntarily participate in this study. Participation in this study is entirely voluntary. You can refuse to participate in this research at any time and your refusal to participate in this study will not affect any of the benefits you are supposed to get from the hospital.

Please direct any questions or problems you may encounter during this study to the principal investigator.

Mekonnen Dessalegn

Department of medical laboratory Sciences College of health sciences Addis Ababa University

Phone +251912 45 73 61

E-mail-ID rebuni2063@gmail.com

s

Amharic version participant information

አዲስአባባዩኒቨርሲቲጤናሳይንስኮሌጅየህክምናላብራቶሪት/ክፍል

መግለጫ

የጥናቱርእስ፡በቅ/ጳ/ሆ/ሚ/ሜ/ኮየካንሰርህክምናማዕከልበካንሰርህክምናምክንያትየሚፈጠርንየነጭደምሴልወይምህዋስየዳሰሳጥ ናትምልከታ

መግቢያ

ይህመግለጫናየጥናቱማረጋጋጫቅጽየተዘጋጀዉበዋናዉተመራማሪሲሆንበጥናቱላይለመሳተፍከመወሰኖበፊትግልጽያልሆነልዎ ትን መጠይቅ ይችላሉ.

ከጥናቱተሳታፊምንይጠበቃል

የጥናቱተሳታፊእንደመሆንዎ2-3

ሜ.ሊየሚሆንደምእዲሰጡይጠየቃሉ፡፡ደምከክንዶዎበአዲስመርፌእናስሪንጅየሚቀዳይሆናል፡፡ናሙናዉንለመስጠትፍቃደኛከ ሆኑለሚቀርብልዎጥያቄዎችመልስእዲሰጡእደገናይጠየቃሉ፡፡

የጥናቱመረጃሚስጥራዊነት

በጥናቱዉስጥየተሰበሰቡማናቸዉምግላዊመረጃዎችሚስጥራዊነታቸዉየተጠበቀይሆናል፡፡ከማንነትዎጋርበቀጥታተያያዥነትያላ ቸዉመረጃዎችበሙሉበዋናዉተመራማሪሚስጥራዊበሆነየመረጃጥንቅርዘዴከተቀየሩበኋላብቻለምርምርሂደቱየሚዉሉይሆናሉ ፡፡ዋናዉተመራማሪብቻየዕርሶንየመረጃጥንቅርዘዴይጠቀማል፡፡

የጥናቱጠቀሜታ

ከጥናቱበቀጥታየሚያገኙትጥቅምየለም፡፡ነገርግንበተዘዋዋሪየጥናቱዉጤትበሆስፒታሉለሚገኙየካንሰርህሙማንየነጭየደምሴል ሁኔታለማየትያስችላልበተጨማሪምእርሶበተዘዋዋሪሌሎችንህመምተኞችእናባለድርሻአካላትንእየረዱነው፡፡

የጥናቱችግር

ከክንዶላይደምበሚወሰድበትወቅትመጠነኛየሆነህምምሊሰማዎትይችላልከዚህዉጭምንምችግርበተሣታፊዎችላይአይከሰትም፡ ፡

በጥናቱላይየመሳተፍእናያለመሳተፍመብት

በዚህጥናትላይመሳተፍበሙሉፍቃደኝነትላይየተመሰረተነዉስለሆነምበጥናቱእንዲሳተፉፍቃደኝነትዎንእንጠይቃለን፡፡ ይህጥናትበፍቃደኝነትላይየተመሰረተእንደመሆኑመጠንበማንኛዉምወቅትበፍቃድዎከጥናቱመዉጣትይችላሉ፡፡ከጥናቱእራሶን ቢያገሉምከሆስፒታሉማግኘትያለቦትንእርዳታወይምጥቅምአይቀርቦትም፡፡

እባክዎይህንጥናትበተመለከተወይምከዚህጋርበተዛመደመልኩስለሚያጋጥሙማንኛዉምአይነትችግርወይምጥያቄካለዎትበሚከ ተለዉአድራሻመግለጥይችላሉ፡፡

መኮንንደሳለኝ

የህክምናላብራቶሪሳይንስት/ክፍልየጤናሳይንስኮሌጅአዲስአባባዩኒቨርስቲ

ስልክ 0912 45 73 61

ኢሜል- rebuni2063@gmail.com

11.2 Annex II. Consent form.

Name of the participant……..

Code no ……

Information about the study has been explained to me by the investigator. I have understood that the objective of this study is to assess chemotherapy induced leukopenia and its determinants in cancer patients attending St. Paul hospital millennium medical college (SPHMMC) oncology unit. Small amount of blood that I will give will not hurt my health. It has also been explained to me that I have the right to stop participation at any time in between and there is nothing I will loss if I refuse to participate.

I agree to participate in the study and here by approve my agreement with my signature.

Participant

Signature ……..

በምርምርለመሳተፍየፍቃደኝነትመዋዋያ

መለያቁጥር……

ጥናቱበሚየካሂዱሰዎችስለጥናቱበቂመረጃተሰጥቶኛል፡፡የዚህጥናትአላማምበቅ/ጳ/ሆ/ሚ/ሜ/ኮየካንሰርህክምናበማድረግላይበ
ሚገኙህሙማንላይየሚወስዱትየካንሰርመድሃኒትበነጭየደምሴሎችወይምህዋሳትላይየሚኖረውተፅዕናለማውቅየዳሰሳጥናትማ
ካሄድነው፡፡ከኔየሚወሰደዉደምምበኔላይምንምዓይነትየጤናጉዳትየማያስከትልመሆኑንተረድቻለሁ፡፡እንዲሁምበጥናቱለመሳተ
ፍፍቃደኛካልሆንኩበጥናቱለመሳተፍእንደማልገደድነገርግንበዚህጥናትበመሳተፍለወደፊትበዚህዙሪያለሚሰሩስራዎችመሰረትየ
ሚሆኑመረጃዎችንመስጠትእንደምችልተረድቻለሁ፡፡በመሆኑምበዚህጥናትላይለመሳተፍየተስማማሁመሆኔንበፊርማየአረጋግጣ
ለሁ፡፡

የተሳታፊፊርማ…… ቀን……..

የጥናትአድራጊዉፊርማ……..ቀን……

11.3 Annex III. Questioners

Addis Ababa University, college of health sciences, department of medical laboratory sciences

For data collectors: for each question please circle the answer or write in the black space don't worry if you make a mistake; simply cross out a mistake and circle the correct one.

Questionnaires

Address……..

Code…….Appointment date……/……/……..……/……/……/

I. Demography:

1.Age…….Sex…….Where do you came from ?…….

2. Educational status

A, Cannot read and write B, Primary (1-8) C, Secondary (9-12) D,College diploma/degree E, MSc and above

3. Marital Status

A, Married B, unmarried C, Divorced D, Widowed

4. Occupation

A, Employee B, Merchant C, House Wife D, Student E, Farmer F, Other

5. Where do you live? A, Urban B, Rural C, Other

II. Diseases Related:

6. Types of cancer……..

7. Stage of the cancer

A, I B, II C, III D, IV E. not staged

8. Number of cycles for chemotherapy

A, 1st B, 2nd C, 3rd D, 4th E, 5th F, 6th G, other……

9. What type of treatment do you take? A. Curative B. Palliative

10. What type of Regimens due you take……....

11. Do you have other chronic diseases? A, Yes B, No

12. If your answer is yes for the above question, what kind of diseases do you have?

A, TB B, Heart C, Kidney D, Liver E, Other ……

13. Is there any leukopenia (from the result)?

A, yes B, No

14. If the answer is yes for the above question, then duration of leukopenia ……

15. Is there any intervention for the leukopenia?

A, Yes B, No

16. If your answer is yes for the above question, what was the intervention?

A, G-CSF B, GM-CSF C, CSF D, Corticosteroid

17. Have you ever use substance?

A, yes B, No

18. If your answer is yes for the above question, what kind of substances do you use?

A, Alcohol B, Cigarette C, Chat D, other……..

19. Height……weight……..BMI……BSA……

20. ECOG……. A, 0 B, 1 C, 2 D, 3 E, 4

Amharic version questionnaire

አዲስአበባዩኒቨርሲቲየጤናሳይንስኮሌጅየላቦራቶሪትምህርትክፍል (ዲፓርትመንት)

ለመረጃስብሳቢዎች፡ለእያንዳነዱጥያቄከተሰጡትአማራጮችውስጥተገቢውንመልስያክብቡወይምበተሰጠውባዶቦታላይተገቢ ውንመልስይፃፉከምርጫዎቹውስጥየተሳሳተመልስካክበቡየ’(X)’
ምልክትበተሳሳተውምርጫላይበማድረግትክክለኛውንመልስመምረጥይችላሉ

አድራሻ ……

የሚስጥርቁጥር …… የቀጠሮቀን……

I. ተሳታፊውንየሚመለከትጥያቄ

1. እድሜ ……ፆታ ……ከየትነውየመጡት ……

2. የትምህርትደረጃ

ሀአንደኛደረጃ (1-8) ለሁለተኛደረጃ (9-12)

ሐየኮሌጅዲፕሎማወይምዲግሪመማስተሬትዲግሪሰዶክተሬትዲግሪረሌላ……

3. የትዳርሁኔታ…….

ሀ„ያገባለ„ያላገባሐ,አግብቶየፈታመ,የሞተበት/የሞተባት

4. የስራሁኔታ

ሀ,ተቀጣሪለ,ነጋዴሐ,የቤትእመቤትመ,ተማሪሰ,ገበሬረ,ሌላ……

5. የመኖረያቦታ…….. ሀ,ከተማለ,ገጠርሐ,ሌላ……

II. ከበሽታውጋርግኙኝነትያላቸውጥያቄዎች

6. የካንሰሩአይነት……

7. የካንሰሩደረጃ

ሀ I ለ II ሐ IIIመ IVሰአልተጠቀሰም

8. ስንተኛውዙርየካንሰርህክምናበመውሰድላይኖት

ሀ,1ኛለ, 2ኛሐ, 3ኛመ, 4ኛሰ, 5ኛረ, 6ኛሠ,ሌላ……

9. ምንዓይነትህክምናነውእየወሰዱያሉትሀ,የሚያድንለ,የሚያድንሳይሆንህመምየሚያሰታግስ
10. የመደሃኒቱአይነትምንአይነትነው……
11. ሌላየቆየከባድህመምአለቦት ?..... ሀ,አዎለ,የለብኝም
12. መልሶአዎከሆነምንአይነትህመምአለቦት

    ሀ,ነቀርሳ (TB)ለ,የልብህመምሐ,የኩላሊትህመምመ,የጉበትህመምሰ,ሌላ.....
13. ህክምናከመጀመራቸውበፊትባለውየታማሚውየላብወጤትላይነጭየደምሴልመቀነስአለ?

    ሀ,አዎለ,የለም
14. መልሶአዎከሆነነጭየደምሴልቀነሶየቆየውለምንያህልቀናትነው……
15. የቀነሱትነጭየደምሴሎችወደነበሩበትለመመለስየህክምናባለሙያዎችጣልቃገብነትነበር

    ሀ,አዎለ,የለም
16. ነጭየደምሴሎችቀንሰውከሆነወደነበሩበትለመመለስየህክምናባለሙያዎችምንአድርገዋል

    ሀ,ግራኖሎሳይትኮሎኒሰቲሙሌቲንግፋክተርሰጥተውኛል

    ለ,ግራኖሎሳይትማክሮፌጅሰቲሙሌቲንግፋክተርሰጥተውኛል

    ሐ,ኮሎኒሰቲሙሌቲንግፋክተርሰጥተውኛል

    መ,ኮርቲኮሰትሮይድሠጥተውኛል
17. ዕፅተጠቅመውያውቃሉ?

    ሀ,አዎለ,አላውቅም
18. መልሶአዎከሆነምንአይነትዕፅነውየሚጠቀሙትወይምይጠቀሙየነበረው?

    ሀ,አልኮልለ,ሲጋራሐ,ጫትመ,ሌላ…….
19. ቁመት…..… ክብደት ……. ቦዲማስኢንዴክስ……..ቤዝሰርፌስኤሪያ……

11.4 Annex IV. SOP for blood collection, handling and transportation

Purpose: correctly collected whole blood sample is important to produce a quality and accurate results in the medical laboratory room.

Principle: The EDTA process forms in insoluble calcium salt that prevents coagulation. EDTA is the most commonly used anticoagulant in hematology for tests such as the CBC.

Materials Supplies;

EDTA: Lavender top

Needle

Syringe (5 cc)

A tourniquet

Alcohol prep pads

Non-alcohol-based cleaner

Gauze pads, adhesive bandages, or tape (including hypoallergenic adhesives)

Gloves

Safety box/Sharps container

Personal protective equipment (lab coat)

Sample volume: 5ml

Special Safety Precautions:

Use standard precautions as outlined in the Blood borne Pathogen Plan.

Place sharps container close to the collection site.

Wear disposable gloves at all times during the procedure

Wash your hands before you put on your gloves and after you remove your gloves.

Change gloves between each study participants.

Procedure of blood collection

1. Clearing all laboratory bench and preparing all necessary laboratory material and reagents
2. Identify the participant
3. Inform the participant about the procedure
4. Assemble necessary supplies and select appropriate tubes according to test requests.
5. Make the participant in good position

6. Visually inspect both arms. Choose the arm that has not been repeatedly used for vein punctures and one that is free of bruises, abrasions, and sites of infection.

7. Applying the tourniquet

8. Put on gloves

9. Disinfect /cleanse the vane puncture site.

10. Vane puncture procedure, follow procedure is recommended:

    Gather the needle and syringe.

    Hold the patient's arm firmly distal to the intended puncture site.

    Prepare the donor/patient by informing him or her that the vane puncture is about to occur. Clean the skin area of the vane by 70% alcohol with the level up, puncture the vein with the needle at an angle of insertion of 30^{o}or less

11. Use the correct order of draw.

12. Release and remove the tourniquet.

13. Add dry cotton pad on the site of punctured vane

14. Remove the needle

15. Apply pressure to the site, making sure bleeding has stopped, and add wound plastic bandage

16. Label the test tube.

17. Clean up supplies from the work area, remove gloves, and wash hands.

Sample Handling:

In order to prevent possible exogenous contamination, concentration change due to evaporation and spillage a blood spacemen need to kept in covered

Labeling

First name and last name of the donors/participants

Identification cod which is similar with the questioner sheet time, date, month and year of blood collection

Name of the phlebotomist

Temperature: at room temperature

Storage of the sample: room temperature

Sample retention: 24 hrs.

11.5 Annex V. SOP for Hematology analyzer DxH 800 Coulter Operation

IntroductionDxH 8

Coulter series hematology analyzer can test 22 parameters such as WBC, RBC, HGB, PLT, MCV, etc. It can display WBC,RBC, and PLT histogram. It is connectable to bar code reader.

Application of DxH 800 Coulter hematology analyzer

The analyzer is an in vitro diagnostic medical device designed for professionals to get the count of WBC, RBC and PLT, and their volume distribution and HGB concentration,which will serve the clinical diagnosis.

Principle

A test is performed using the two independent measurement method: The analyzer accomplished the test by using two different measuring methods such as the electric impedance method for determining WBC, RBC and Platelet data and the colorimetric methods use for determining the Hemoglobin concentration.

Electric Impedance method

After the aspirated sample is diluted by conductive solution, it is taken to testing unit. The testing unit has a test hole. A pair of positive and negative electrodes exists near the hole. As the cells have the characteristic of a poor conductor, when the cell go through the hole under constant negative pressure, the DC resistant between the electrodes will change, resulting in the formation of a pulse change proportional to the cell volume. A series of electrical pulse is produced when the cell continuously go through the hole. The number of pulses is equivalent to the cell number through the hole. The pulse amplitude is proportional to the cell volume.

Colorimetric Method:

The hemoglobin concentration testing is conducted by Colorimetric Method. In the WBC counting pool, after adding hemolytic agent, RBC dissolve, releasing hemoglobin, which when combined with the hemolytic to form hemoglobin complex. A wavelength of 540nm monochromatic LED in one end of WBC counting pool illuminate hemoglobin complex solution, transmitted light is received through optical tube on the other end. The amplified light intensity signal is converted to voltage signal.

By comparing with the voltage produced by background transmitted light intensity before adding sample in WBC counting pool (only diluent exists), the HGB concentration of sample can be obtained. Unit: g/L the testing and calculation will be conducted by the analyzer automatically. The result will be displayed in analysis result area of counting interface.

Sample:

- Whole blood

Cause for rejection

- Hemolysis
- clotted specimen
- Tube not filled with minimum volume
- Improperly labeled specimen

Reagent

- Diluents
- Cell Lyse
- Diff.Pack
- Retic Pack
- Cleaner

Reagent stored at room temperature except Enzymatic Cleaner which should be stored between 2 and 8 degree centigrade.

Procedure

Ensure whole blood mode

Put the whole blood sample under the sampling probe

Take the result in print paper or record in the display

Quality control

Quality control checks performed daily according to the laboratory protocol. Commercial control materials are properly warmed and mixed according to the manufactures recommendations. Patient controls are handled according to the laboratory protocol.

Declaration

I, the undersigned agree to accept responsibility for the scientific ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the research publication.

MSC candidate: Mekonnen Dessalegn

Signature: _____

Date of submission: _____

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Signature: _____

Date _____

Mintewab Hussen (MSc)

Signature: _____

Date _____

Mengistu Fantahun (MSc)

Signature: _____

Date _____