ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

DEPARTMENT OF MEDICAL PHYSIOLOGY

Hematological Indices of Adult Cancer Patients Exposed to Chemotherapy, in Ayder Comprehensive Specialized Hospital, Mekelle, Northern Ethiopia, 2020.

By: Asgele Tsehaye (BSc)

A Thesis Submitted to the College of Health Sciences, School of Medicine, and Department of Medical Physiology at Addis Ababa University in Partial Fulfillment of the Requirements for a Master's Degree in Medical Physiology.

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SCHOOL OF GRADUATE STUDIES

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List of abbreviations and acronyms

ACSH ---------- Ayder Comprehensive Specialized Hospital

AOR ---------- Adjusted Odds Ratio

B.C. ---------- Before Christ

CBC ---------- Complete Blood Count

CI ---------- Confidence Interval

CIT ---------- Chemotherapy-Induced Thrombocytopenia

COR ---------- Crude Odds Ratio

CTX/CTx ---------- Chemotherapy

DNA ---------- Deoxyribonucleic Acid

ECAS ---------- European Cancer Anemia Survey

EDTA ---------- Ethylene Diamine Tetra Acetic acid

GLOBOCAN ---------- Global Burden of Cancer

Hb ---------- Hemoglobin

Hct ---------- Hematocrit

HDAC ---------- Histone Deacetylase

IARC ---------- International Agency for Research on Cancer

IL ---------- Interleukin

MCH ---------- Mean Corpuscular Hemoglobin

MCHC---------- Mean Corpuscular Hemoglobin Concentration

MCV ---------- Mean Corpuscular Volume

NCDs ---------- Non-Communicable Diseases

NSCLC ---------- Non-Small Cell Lung Cancer

OR ---------- Odds Ratio

RBC ---------- Red Blood Cell

RDW ---------- Red cell Distribution Width

SD ---------- Standard Deviation

SPSS ---------- Statistical Package for Social Science

TNF ---------- Tumor Necrosis Factor

WBC ---------- White Blood Cell

WHO ---------- World Health Organization

Abstract

***Background**: Cancer is one of the fastest-growing diseases throughout the world and it is an emerging public health issue in Africa. Cancer and chemotherapy can directly result in or exacerbate myelosuppression by suppressing the process of hematopoiesis.*

***Objective**: This study was designed to determine haematological indices of adult cancer patients who were exposed and not exposed to chemotherapy, in Ayder Comprehensive Specialized Hospital (ACSH), Mekelle, Northern Ethiopia, 2020.*

***Methods**: Institutional-based comparative cross-sectional study design was conducted using a convenient and quota sampling method to assess haematologic indices among patients attending the oncology clinic who were exposed and not exposed to chemotherapy, in ACSH, Mekelle, Ethiopia from January to June 2020. The socio-demographic and clinical characteristics of 72 cancer patients were assessed. Structured questionnaires, hospital medical records of study subjects, and Sysmex XT-4000i automated hematology analyzer for CBC analysis were considered. Independent-sample T-test was used to compare the mean values of variables. Binary logistic regression analysis was considered to identify determining factors.*

***Results**: Nearly one-half of the study subjects (45.8%, n=72) were found to have anemia in unclassified cancers (exposed group: 58.3%; non-exposed group: 33.3% with $P<0.05$). There was a significant difference in the mean values of Hb ($P<0.001$) between the two groups. Around one-third of the study subjects (30.6%, n=72) were found to be neutropenic (exposed group: 44.4%; non-exposed group: 16.7% with $P<0.05$). There was a significant mean difference in neutrophil count between the two groups ($P<0.001$). More than one-fifth of the study subjects (22.2%, n=72) had experienced thrombocytopenia (exposed group: 33.3%; non-exposed group: 11.1% with $P<0.05$). There was a significant difference in the mean values of platelet between the two groups ($P<0.001$). The absence of regular income & advanced-stage cancer were the factors associated with anemia in the exposed group. On the other hand, advanced-stage cancer was the only factor found to be associated with the occurrence of anemia in the non-exposed group. The occurrence of neutropenia was significantly linked with the absence of regular income, advanced-stage cancer, and chemotherapy treatments of ≥ 5 cycles in chemotherapy exposed group.*

***Conclusion**: This study found that a higher prevalence of anemia, neutropenia, and thrombocytopenia was documented among patients who were exposed to chemotherapy. The absence of regular income advanced-stage cancer, and chemotherapy treatments of ≥ 5 cycles were also revealed as risk factors; indicating further studies on the evaluation of patients with cancer, management protocols, and follow-up to find out causes & manage accordingly.*

Keywords: Haematological indices, Chemotherapy, Duration of treatment, Cycles of treatment

1. Introduction

1.1. Background of the study

1.1.1. Natural History and Pathogenesis of Cancer

Cancer is a class of disorders distinguished by uncontrolled cell growth and the capacity to directly invade other tissues or to spread through the blood and lymphatic systems. Hippocrates first used the word "cancer"—which is Latin for "crab"—in the fifth century B.C. to refer to illnesses in which tissues develop and spread out of control throughout the body until they inevitably suffocate life (1).

A tumor (or neoplasm), which is a mass of growing tissue, develops as a result of an abnormal type of tissue growth in which some cells multiply and accumulate in a loose, largely independent manner, progressively increasing the number of dividing cells. Although normal restrictions on cell proliferation have been sidestepped by tumors, tumor cells don't necessarily divide more quickly than normal cells. What matters most is the equilibrium between cell division and cell differentiation or cell death rather than the rate of cell division (2).

Cell differentiation is the process by which cells develop the specific characteristics that set certain cell types apart from one another. As cells have these specialized features, they typically lose their ability to divide, where new cells continuously replace aging cells. From the progenitor cell, which divides into two cells with distinct fates, come the new replacement cells. One cell remains and can continue to divide, whilst the other cell can no longer divide and differentiates as it moves on. The cell eventually dies and is eliminated. So, in response to growth signals, growth-inhibiting signals, and death signals, complex genetic control mechanisms balance cell birth and death during normal development and throughout adult life (2, 3).

This delicately balanced system is disrupted in tumors, causing cell division to become independent of cell differentiation and death. Because of this, some cell divisions give rise to two cells that continue to divide, gradually increasing the total number of dividing cells. The tumor will continue to grow regardless of how quickly or slowly the cells divide since more new cells

are being made than are required. As the number of proliferating cells increases, the tissue's regular structure and functionality become deteriorated steadily (2).

Failures of the cellular regulatory mechanisms, which typically regulate the growth and proliferation of cells, result in cancer. It develops as a result of many somatic modifications to the DNA of target cells, which cause unregulated cellular proliferation. The majority of these variations entail mutations, which are actual sequence changes in DNA. Cancer development can start with the majority of known etiological agents as a result of random replication errors, exposure to carcinogens (such as radiation and chemicals), or flawed DNA repair mechanisms. While most cancers develop randomly, some families with a germline mutation in a cancer gene have familial clustering of tumors (3-5).

The two types of genes whose mutations have been associated with the development of cancer are proto-oncogenes and tumor suppressor genes. By increasing mutations that make the gene overly active in encouraging amplification, proto-oncogenes are turned on to become oncogenes. Incorrect growth is made possible by distraction to tumor suppressor genes, which typically control growth. Numerous genes in both categorizations help govern cell birth (i.e., entry into and progression through the cell cycle) or cell death by apoptosis; other genes help repair DNA damage (3).

With most natural etiologic agents, the development of CANCER is a very long process that takes years (10 to 40 or more) and involves several distinct phases. Although it is natural to think of the prevention of any disease process as primarily removing, avoiding, or neutralizing the initial etiological agent that starts the entire chain of events, this perspective is too restrictive and limited in the development of efficient ways to prevent many chronic diseases, including cancer (5).

1.1.2. Emergence of Chemotherapy

There are four basic categories of cancer treatment: surgery, radiation therapy (including photodynamic therapy), chemotherapy, and biological therapy (including gene and immunotherapy). Although they can affect how a tumor behaves in distant areas, surgery, and radiation therapy are regarded as local treatments. Chemotherapy and biological therapy, however, are typically systemic treatments (4).

Chemotherapy, often known as CTX or CTx, is a type of cancer treatment that involves administering one or more anti-cancer medications (also known as chemotherapeutic agents) as a prescribed course of treatment. Palliative chemotherapy is provided to extend life or reduce symptoms as opposed to curative chemotherapy, which nearly often involves medication combinations. One of the main subspecialties of the medical field known as medical oncology, which is dedicated to pharmacotherapy for cancer, is chemotherapy (6).

Chemotherapy is the use of potent cytotoxic medications to treat serious illnesses like cancer. Latin's prefix cyto-, meaning "cell," denotes that a substance is cytotoxic and it kills cancer cells that are dividing quickly. The premise behind cytotoxic chemotherapy for cancer is that cancer cells multiply quickly. Rapidly proliferating cells are preferentially killed by cytotoxic chemotherapy due to differential effects on them. This is also the reason why cytotoxic chemotherapy's common side effects arise (7).

The concept that systemically administered drugs may have a useful effect on cancers was historically derived from three sets of observations. Paul Ehrlich in the 19th century observed that different dyes reacted with different cell and tissue components. He hypothesized the existence of compounds that would be “magic bullets” that might bind to tumors, owing to the affinity of the agent for the tumor. A second observation was the toxic effects of certain mustard gas derivatives on the bone marrow during World War I, leading to the idea that smaller doses of these agents might be used to treat tumors of marrow-derived cells. Finally, the observation that certain tumors from hormone-responsive tissues could shrink after oophorectomy led to the idea that endogenous substances promoting tumor growth might be antagonized. Chemicals achieving

each of these goals are actually or intellectually the forbearers of the currently used cancer chemotherapy agents (4).

The introduction of chemical weapons by Germany during World War I marked the beginning of the modern era of cancer chemotherapy. The most severe and lethal chemical weapon deployed was mustard gas, an alkylating agent created at the beginning of the 20th century. Ironically, it was the use of mustard gas, a chemical warfare agent, as a successful method of slowing the growth of cancer cells by destroying their DNA that led to the discovery of chemotherapy utilizing nitrogen mustard-like medicines (7, 8).

Soon after the discovery of nitrogen mustard, Sidney Farber of Boston demonstrated in his important work that folic acid antagonists, such as 4-amino pteroylglutamic acid (aminopterin), produced brief remissions in young children with acute undifferentiated leukemia. These discoveries led to the development of other chemotherapy medicines, which are now being used to treat juvenile and adult cancers in various patients. That drug served as the forerunner to the cancer therapy drug methotrexate today. In 1956, choriocarcinoma and chorioadenoma, a rare tumor, were successfully treated with methotrexate. This marked the beginning of the therapeutic management of metastatic cancer (9-11).

After World War II, the U.S. government sponsored a large-scale screening program in search of anticancer drugs. Out of more than 500,000 compounds screened, 45 anticancer drugs were discovered, a great boon to cancer treatment. To date, more than 100 nitrogen mustards have been used alone or in combination with other drugs to treat cancer, saving thousands of lives (7).

Most forms of chemotherapy can be subdivided into four major categories. (a) Antimetabolites inhibit metabolic pathways required for DNA synthesis by acting as competitive inhibitors that bind to enzyme-active sites in place of normal substrate molecules. Examples include fluorouracil, methotrexate, fludarabine, pemetrexed, and gemcitabine. (b) Alkylating agents inhibit DNA function by chemically crosslinking the DNA double helix. Examples include cyclophosphamide, chlorambucil, and cisplatin. (c) Antibiotics are substances made by microorganisms that inhibit DNA function by either binding to DNA or inhibiting topoisomerases required for DNA replication. Examples include doxorubicin and epirubicin. (d)

Plant-derived drugs either inhibit topoisomerases or disrupt the microtubules of the mitotic spindle. Examples include the topoisomerase inhibitor etoposide and the microtubule-disrupting drug, taxol (2).

1.1.3. Impact of Chemotherapy

Tumors frequently develop mutations that render them resistant to the medications being used, which is a frequent side effect of pharmacological therapy. Even when only one treatment is used, tumors frequently develop resistance to both the drug that is provided and the combined effects of numerous unrelated drugs. Generally speaking, chemotherapy is dangerous to both healthy and cancerous cells that are dividing normally. Almost always, the common cytotoxic chemotherapy drugs have an impact on bone marrow function. Myelosuppression complications arise from the expected effects of the absent cells' function. Chemotherapy frequently causes myelosuppressive conditions commonly anemia, neutropenia, and thrombocytopenia. Other typical adverse effects of chemotherapy include diarrhea, alopecia, mucous membrane inflammation, nausea, and vomiting (2, 4).

1.2. Statement of the Problem

Cancer is one of the fastest-growing diseases globally. It comes in as the second-largest cause of morbidity and mortality, right behind cardiovascular disease. Cancer death is more common among Blacks than Whites. Rates of occurrence and mortality vary by racial and ethnic group. It is not known what led to the difference. In 2010, there were 1.53 million new instances of invasive cancer reported, and 569,490 people died from cancer, according to the National Cancer Institute's database. The two most prevalent kinds of cancer worldwide are lung cancer and breast cancer. Globally, stomach cancer is second following lung cancer in terms of mortality rates (1, 4).

In 2018, there were 9.6 million cancer-related deaths worldwide, and there were 18.1 million new cases, according to the IARC report. 1 in 5 men and 1 in 6 women will experience a cancer diagnosis at some point in their life, and 1 in 8 men and 1 in 11 women will succumb to the illness. The number of individuals surviving within five years of a cancer diagnosis is used to estimate the global 5-year prevalence, which is predicted to be 43.8 million (12).

The global report of 2012 revealed there were an estimated 14.1 million new cancer cases (7.4 million cases in men and 6.7 million in women). This number may increase to 24 million by 2035. Cancers of the lung and female breast were the leading types in terms of new cases for each of these types, with approximately 2.1 million cases by 2018. Lung cancer was also responsible for the largest number of deaths (1.8 million deaths, 18.4% of the total) because of the poor prognosis for this cancer type worldwide (12).

The provision of services for the prevention and treatment of cancer has had a low priority with African governments and development agencies, which have focused on the more common health issues, such as communicable diseases and maternal and child mortality, which have been largely solved in the developed world. Unfortunately, in Africa, these older, more common diseases co-exist with newer ones, most evidently AIDS, and also with some of the non-communicable diseases, including cancer (13).

Cancer is an emerging public health issue in Africa, with estimates of 715,000 new cases and 542,000 cancer deaths in the continent in 2008. According to 2018 GLOBOCAN estimates of cancer incidence and mortality produced by IARC, the proportion of cancer deaths in Africa accounts for 7.3% of the total death worldwide. A third of cancer deaths in Africa are potentially preventable; many are caused by chronic infection and tobacco use. An aging and growing population, together with the adoption of lifestyle habits such as smoking, physical inactivity, and unhealthy high-calorie Western diets all contribute to the rise of the cancer burden in Africa. Projections suggest that cancer incidence and mortality will double to 1.28 million new cases and 970,000 deaths per year by 2030. The most common cancers in Africa are cervical, breast, and liver cancers (12, 14).

In Ethiopia, the Annual incidence and mortality of all cancer types reported by GLOBOCAN in 2008 were 51,700 and 41,600 respectively. For people under the age of 75 years, the risk of being diagnosed with cancer is 11.3%, and the risk of dying from the disease is 9.4%. 5-year prevalence for 2003–08 was 224.2 per 100,000 people (14).

Myelotoxicity in cancer patients including anemia, neutropenia, and thrombocytopenia is the result of complex processes as a result of the disease, the approach to treatment, and the characteristics of the individual patient (15).

Cancer can directly cause or exacerbate anemia either by suppressing hematopoiesis through bone marrow infiltration or production of cytokines that lead to iron sequestration, inhibit the release and synthesis of endogenous erythropoietin, reduce the response of Erythroid progenitor cells to erythropoietin, which ultimately impair erythropoiesis. Blood loss can result from hemorrhage of the tumor and organ damage can further exacerbate anemia from cancer (16-19).

The overall incidence of chemotherapy-induced neutropenia and thrombocytopenia are frequent in patients with certain hematologic neoplasms where marrow is infiltrated with tumors. Chemotherapy is routinely used in conventional dose regimens. In general, these doses produce reversible acute side effects, primarily consisting of transient myelosuppression. High-dose chemotherapy regimens can produce markedly increased therapeutic effects that require intensive support, usually in the form of hematopoietic stem cell support (4).

1.3. Significance of the study

Myelosuppression is one of the most frequent side effects of chemotherapy, and depending on the type and intensity of treatment; repeated cycles of chemotherapy may have cumulative toxic effects on hematopoiesis. Many patients develop anemia, neutropenia, and thrombocytopenia during treatment and a considerable number of patients require RBC transfusions. Some cytotoxic agents appear to produce more frequent and severe anemia related either to more severe myelosuppression or additional mechanisms, such as impairment of renal function and erythropoietin production. In recent years, cancer-related or chemotherapy-induced anemia, neutropenia, and thrombocytopenia have been shown to have an enormous impact on the physical well-being, functional capacity, and quality of life of patients. In addition, anemia is a negative prognostic factor for the outcome of treatment and survival of patients with various types of malignant diseases (20, 21).

Chemotherapy-treated patients had an increased risk of anemia, neutropenia, and thrombocytopenia. These complications can potentially lead to bleeding disorders, opportunistic infections, and significant morbidity in patients (22).

The emergence and growing magnitude of non-communicable diseases (NCDs) such as cancer have become current challenges to developing countries like Ethiopia. In addition to this, there are no previously published and documented studies in Ethiopia that compare hematologic indices among cancer patients who are exposed and not exposed to chemotherapy.

Considering all the above aspects in cancer and the fact that the consequences of chemotherapy could be treated successfully in a considerable number of patients by the use of hematopoietic stimulating factors and minimized by lifestyle modifications, it is of particular clinical interest to have reliable data on the magnitude and clinical significance of anemia, neutropenia, and thrombocytopenia in cancer patients who are exposed and not exposed to chemotherapy.

2. Literature review

The commonly used cytotoxic chemotherapeutic agents such as direct DNA-interacting agents (Alkylators, antitumor antibiotics & topoisomerase poisons), indirect DNA-interacting agents (antimetabolites and antimitotic agents) have myelosuppression as a common side effect, causing anemia, leukopenia (prominently neutropenia) and thrombocytopenia by damaging the DNA of hematopoietic cells (4).

Neutropenia occurs from an uncontrolled neoplasm involving the bone marrow or, more usually, in a patient undergoing treatment with cytotoxic agents. Chemotherapy predisposes patients with cancer to infections both by suppressing the production of neutrophils and by cytotoxic effects on the cells that line the alimentary tract. Mortality from uncontrolled infection varies inversely with the neutrophil count, with a markedly increased risk of death when the neutrophil count is <500/μL (4, 23).

Chemotherapeutic agents can affect platelet production through different mechanisms, including DNA synthesis, DNA repair, platelet shedding, and clearance of platelets. Some chemotherapeutic agents may act to increase the rate of platelet destruction (24). CIT is frequently observed in both solid tumors and hematologic malignancies with different chemotherapeutic agents, which is dependent upon tumor type and specific chemotherapy (25).

The myelosuppressive effect of chemotherapy is a significant contributing factor to anemia in patients undergoing cytotoxic treatment. Chemotherapeutic agents induce anemia by directly impairing hematopoiesis, including the synthesis of RBC precursors, in the bone marrow. In addition, the nephrotoxic effects of particular cytotoxic agents (e.g., platinum-containing agents) commonly used in lung, ovarian, and head and neck cancers are well known to induce anemia through decreased renal production of erythropoietin. The myelosuppressive effects of particular cytotoxic agents are likely to accumulate throughout repeated cycles of therapy, resulting in a steady increase in the rate of anemia with additional chemotherapy cycles (21, 26).

Anemia is one of the most common side effects among patients with cancer. It has been estimated that 30 percent to 90 percent of all cancer patients are anemic (27), a figure that varies depending on a variety of parameters such as the type of cancer, stage of disease, type of

chemotherapy regimen provided, presence of concomitant illnesses, and definition of anemia used (28, 29).

Medical record review for 331 patients who received adjuvant chemotherapy for breast cancer at Toronto Cancer Centre, Canada showed that 221 patients received 2200 cycles (complete data) of chemotherapy. 6 (3%) patients were anemic at the start of the study, compared with 55 (25%) at the final cycle of chemotherapy (30).

The Turkish study found a statistically significant difference in hemoglobin levels before and following chemotherapy treatment. The decrease in Hb levels was statistically significant in the cisplatin and anthracycline groups. 17 patients (20.7%) had Hb levels under 11.0 g/dl before chemotherapy, and this proportion was increased to 31 patients (37.8%) after chemotherapy (31).

Using a global definition of anemia as Hb < 12 g/dL, a large, prospective survey of European cancer patients (n = 15,367) showed that anemia rates were 75% in all types of cancer patients receiving chemotherapy and 39.7% in patients who received no cancer treatment during the 6 months of follow-up. The incidence of anemia (Hb < 12 g/dL) was found to increase from 19.5% in cycle 1 to 46.7% by cycle 5 (26, 32).

According to the study conducted in Tikur Anbessa Specialized Hospital, the prevalence of anemia at diagnosis of cancers was 23.0% in unclassified cancers, and higher anemia prevalence was noted in gynecologic (37.7%) and colorectal cancers (26.7%). The majority of the anemia (83.5%) was a mild-moderate type, whereas 11.3% and 5.2% were a severe and life-threatening type (33).

Based on the report of the study conducted on Japanese cancer patients, 44% of the study subjects were anemic before the initiation of chemotherapy. After the initiation of treatment, chemotherapy further increased the number of anemic patients to 84% at some point during the treatment course (34).

According to a study in Athens, Greece, a retrospective analysis was conducted on a total of eight hundred fifty-eight patients. Grade I/II (mild) and grade III/IV (severe) neutropenia were observed in 176 (20.5%) and 197 (23%) patients, respectively (35).

The finding of chemotherapy-induced neutropenia among patients of advanced non-small-cell lung cancer conducted in Italy unveiled the occurrence of mild and severe neutropenia in 32 percent and 21 percent of study subjects respectively (36).

A study conducted in Japan in patients with NSCLC revealed that chemotherapy-induced neutropenia was available from 387 patients and 80% had chemotherapy-induced neutropenia; 5% had grade 1, 10% had grade 2, 25% had grade 3, and 40% had grade 4 neutropenia (37).

The report of grade 4 chemotherapy-induced neutropenia varies widely from 3 percent to 100 percent of patients depending on the type of cancer, stage of disease, functional status of patients, and chemotherapy cycles & regimens provided (38).

According to the study conducted in the USA, 43% of study subjects experienced severe neutropenia events during 1290 cycles of primary chemotherapy(39).

The report of a study conducted in Japan revealed the occurrence of chemotherapy-induced neutropenia in 50.5% of study subjects with gynecologic malignancies (40).

A study conducted in France reported that neutropenia prevalence of 71.2% in the whole population. 36.1% of the experienced mild neutropenia and 35.1% had experienced severe neutropenia (41).

A report from solid tumor and lymphoma patients treated with pulsed chemotherapy at Hurlingham Oncology Clinic, Nairobi Hospital revealed WHO grade 3 and grade 4 neutropenia prevalence of 51.8 percent (42).

The severity and emergence of thrombocytopenia varies based on the type of cancer, stage of disease, and type of chemotherapy treatment/s provided. The prevalence of platelet counts less than 100,000 per μL can vary widely ranging from about 100% of patients with acute leukemia to less than 5 percent in patients treated for head malignancies (43).

3. Hypothesis

3.1. Null Hypothesis (H0)

There is no significant difference in haematologic indices among cancer patients exposed and not exposed to chemotherapy.

3.2. Alternative Hypothesis (H1)

There is a significant difference in haematologic indices among cancer patients exposed and not exposed to chemotherapy.

4. Objective

4.1. General Objective

- ✓ To assess haematologic indices among patients with cancer attending an oncology clinic who are exposed and not exposed to chemotherapy, in Ayder Comprehensive Specialized Hospital (ACSH), Mekelle, Northern Ethiopia, 2020.

4.2. Specific Objective

- ✓ To compare the level of anemia in cancer patients exposed and not exposed to chemotherapy.
- ✓ To determine the level of neutropenia in cancer patients exposed and not exposed to chemotherapy.
- ✓ To compare the magnitude of thrombocytopenia in cancer patients exposed and not exposed to chemotherapy treatment.
- ✓ To identify the determinant factors of anemia, neutropenia, and thrombocytopenia.

5. Methods and materials

5.1. Study area

The study was conducted in ACSH, Mekelle City, Northern Ethiopia. ACSH provides diagnosis, treatment, care, and support for cancer patients visiting oncology clinic. In this hospital, there were around 1,000 adult cancer patients receiving different healthcare services in 2020. It is a teaching hospital and provides comprehensive health services for patients that come from all directions of the region and neighboring regions. ACSH was selected taking into account that, there were no previously published and documented reports on hematologic indices in cancer patients exposed and not exposed to chemotherapeutic treatments.

5.2. Study period

The study was conducted from January to June 2020.

5.3. Study design

Institution-based comparative cross-sectional study design was conducted.

5.4. Population

5.4.1. Source population

All cancer patients attending regular follow up at the oncology clinic of ACSH.

5.4.2. Study population

All adult cancer patients who met the inclusion criteria, had voluntarily consented to participate in the study and attending regular follow-up at the oncology clinic of ACSH during the study period.

5.5. Sample size determination and sampling technique

5.5.1. Sample size determination

The total sample size was calculated using double population proportion formula considering the following assumptions: 2-sided confidence level at 95%, standard margin of error (power of 80%), and 1:1 ratio of non-exposed group and exposed group adults. The prevalence of anemia in all types of adult cancer patients who were not exposed to chemotherapy and exposed to chemotherapy was 39.7% and 75% respectively, as per a study of ECAS (32). Then sample size was calculated using StatCalc-Epi-info data for a cross-sectional study to get the required sample size. Accordingly, a total of 72 adults with cancer (36 from the non-exposed group and 36 from the exposed group) had included in the study.

5.5.2. Sampling technique

A convenient and quota sampling method was used in which, all adult cancer patients, who visited the oncology clinic during the study period, had consented to take part in the study, and who met the inclusion criteria had been involved until the necessary sample size was fulfilled.

5.6. Eligibility Criteria

5.6.1. Inclusion Criteria

- ✓ All adult cancer patients aged 18 years and above

5.6.2. Exclusion Criteria

- ✓ Critically ill, admitted cancer patients
- ✓ History of blood transfusion in the last 3 months
- ✓ Pregnant and lactating women
- ✓ Malaria attack in the last 2 weeks
- ✓ Bleeding history from other causes such as trauma in the last 2 weeks
- ✓ Patients with Aplastic anemia
- ✓ Patients with other chronic co-morbidities like renal failure

- ✓ Other therapies that suppress bone marrow

5.7. Study variables

5.7.1. Dependent variables

- ✓ Hematologic indices (RBC, Hb, Hct, MCV, MCH, MCHC, RDW, WBC & differentials, platelet count)

5.7.2. Independent variables

- ✓ Age, gender, marital status, educational status, residence, tumor type and stage of disease, duration of disease, occupation, chemotherapy usage, type of chemotherapy used, schedule, and cycles of chemotherapy.

5.8. Operational definitions

- ✓ Anemia: a decrease in Hb (<13g/dL for men aged ≥15 years and <12g/dL for non-pregnant women aged ≥15 years) due to cancer or chemotherapy, which was coded as mild, moderate, or severe.
- ✓ Mild anemia: Hb level of 11-11.9g/dL for women and 11-12.9g/dL for men.
- ✓ Moderate anemia: Hb level of 8-10.9g/dL irrespective of sex difference
- ✓ Severe anemia: Hb level of less than 8g/dL for men and women.
- ✓ Neutropenia: a decrease in neutrophil count (<2,000 cells/µL) due to cancer or chemotherapy irrespective of sex difference, which was coded as grade 1, grade 2, grade 3, or grade 4 neutropenia.
- ✓ Grade 1 neutropenia: absolute neutrophil count of ≥1,500 to <2,000 cells/µL.
- ✓ Grade 2 neutropenia: absolute neutrophil count of ≥1,000 to <1,500 cells/µL.
- ✓ Grade 3 neutropenia: absolute neutrophil count of ≥500 to <1,000 cells/µL.
- ✓ Grade 4 neutropenia: absolute neutrophil count of <500 cells/µL.
- ✓ Thrombocytopenia: clinical condition of decreased platelet count (<150,000 cells/µL) that was classified as grade 1, grade 2, grade 3, or grade 4 ± with an effect of bleeding from the nose, gum, and other sites of the body spontaneously.

- ✓ Grade 1 thrombocytopenia: absolute platelet count of ≥75,000 to <150,000 cells/μL
- ✓ Grade 2 thrombocytopenia: absolute platelet count of ≥50,000 to <75,000 cells/μL
- ✓ Grade 3 thrombocytopenia: absolute platelet count of ≥25,000 to <50,000 cells/μL
- ✓ Grade 4 thrombocytopenia: absolute platelet count of <25,000 cells/μL
- ✓ Pancytopenia: a decrease in all of three blood cell lines (RBCs, WBCs, and platelets).
- ✓ Chemotherapy: a drug or combination of drugs given to cancer patients to eradicate/lessen the size of the rapidly growing cancerous cells.
- ✓ Chemotherapy exposure status: one who had taken chemotherapeutic treatment at least one dose.

5.9. Data collection tools and Procedures

5.9.1. Data collection tools

Instruments for data collection were

- ✓ Structured questionnaire
- ✓ Hospital medical records of the study subjects
- ✓ Alcohol swab, gauze, 5ml disposable syringe with needle, tourniquet
- ✓ Thermometer
- ✓ EDTA-coated test tube, sharp box
- ✓ Sysmex XT-4000i automated hematology analyzer for CBC analysis

5.9.2. Data collection procedures

Subjects exposed to chemotherapy and those not exposed to chemotherapy were allocated into two groups for the study based on their exposure status. The data collectors evaluated each client who came to the clinic throughout the study period to see if they met the requirements to be included in the study. These eligible subjects were consecutively enrolled in the study. The selection and inclusion of patients continued until the required number of subjects was fulfilled. Structured and pretested questionnaires were used to collect the data.

I. Questionnaires

A standardized semi-structured pretested questionnaire was used during face-to-face interview and review of documented medical records.

Socio-demographic variables (age, gender, occupation, income status, marital status, educational status, residence) were collected using face-to-face interview questions by the data collectors.

Variables including duration of disease, type and stage of cancer, type of medication, and duration of treatment were taken from patients' database/ medical records.

II. Blood sample collection

Once a subject's enrollment in the study had been verified, 4 ml of venous blood was aseptically taken into an EDTA tube from their left brachial vein. The qualified laboratory technician collected the samples in accordance with the standardized operational procedures (44). The collected blood sample was transported to the laboratory center for analysis by trained laboratory technicians.

The Sysmex XT-4000i automated hematology analyzer, which uses fluorescence flow cytometry and hydrodynamic focusing technology, was used to determine the hematologic laboratory values, including total RBC count, Hb, Hct, RDW, MCV, MCH, MCHC, total and differential leukocyte counts, and platelet counts. The Sysmex XN series delivers the following information: WBC from optical/fluorescent, RBC by impedance, Hb and HCT from measurements of RBC pulse heights, MCV, MCH, and MCHC (calculated), RDW-SD and platelet by impedance (45). The reagents CELLPACKTM (diluent), STROMATOLYSER-FBTM(lyse), STROMATOLYSER-4DLTM(lyse), STROMATOLYSER-4DSTM (Stain), SULFOLYSER (lyse), RET-SEARCH II (diluent), and RET-SEARCH II (stain) are used by the Sysmex XT-4000i hematology analyzer (45).

5.10. Data quality control

The data collectors were instructed on the goal of the study and each step of the data collection process to maintain the quality and reproducibility of the data. Through the use of quality control samples that were performed in accordance with the laboratory's protocol, the operation of the automated machines was externally monitored (44, 46) before the analysis of the collected blood sample.

The validity of the questionnaire was kept by conducting a pretest in 5% of the sample size using the local language Tigrigna in the study area and essential improvements were undertaken on the questions after the pretest. Data from pretested subjects was not included in the actual study result. Each completed questionnaire was checked each day by the principal investigator to be sure that all the questions were answered consistently and incomplete data was discarded and/or corrected. The data was entered into SPSS version 25.0 statistical software and rechecked carefully.

5.11. Data Analysis and Interpretation

Data was manually checked for its clarity and completeness and then coded, cleaned, and entered into the SPSS version 25.0 software package for analysis. The data was analyzed for its descriptive statistics and the independent-sample T-test was used to compare the mean values of variables between the two groups. Binary logistic regression analysis was also considered to identify determinant factors of anemia, neutropenia, and thrombocytopenia. P-value <.05 was considered statistically significant.

5.12. Ethical consideration

The study was conducted after ethical clearance and approval obtained from the Research and Value Ethical Review Committee of the Department of Medical Physiology, College of Health Sciences, Addis Ababa University. Once again, the proposal was further assessed concerning the ethical standards, and a permission letter was obtained from Ayder Comprehensive Specialized Hospital research head office.

The study participants were informed of the objective and procedures of the study. Thereafter, both verbal and written informed consent was obtained from those volunteers that were selected for the study. No personal identifiers were attached/recorded to the interview. The data provided was kept strictly confidential by using only code numbers.

6. Result

6.1. Socio-demographic characteristics of study subjects

A total of 72 study subjects who met the inclusion criteria (36 exposed and 36 non-exposed to chemotherapy) with a median age of 50 years (ranging from 18-74 years) were included in the study. 39 of them were male, which accounts for 54.2% (n=72) of the study subjects. The mean age of the study subjects was 46.7 and 47.8 years for exposed and non-exposed groups respectively.

Of the total study subjects, more than three-fourth of them (83.3%, n=72) achieved elementary school education and above. Almost all (94.4%, n=72) of them were Orthodox Christian followers, and the remaining Muslims. Less than half (47.2%, n=72) of them had regular income and were employed in private and government organizations. Around three-fourth (73.6%, n=72) of them live in urban areas. Most socio-demographic characteristics of both study groups were comparable (table 2). The report from the Chi-square test result showed the socio-demographic characteristics of study subjects and chemotherapy exposure statuses were not associated with one another at a statistically significant level (P-value: > .05) (table 1).

Table 1: Chi-Square test table for the socio-demographic characteristics of adult cancer patients with chemotherapy exposure status in ACSH, Mekelle, Northern Ethiopia, 2020

Variables	Chemotherapy exposure status
	Asymptotic Significance (2-sided)
Sex of study subjects	0.813
Age group of subjects	0.696
Marital status	0.954
Residence	0.181
Educational status	0.072
Religion	0.303
Income status	0.157
Stage of cancer	1.00

Table 2: Assessment of socio-demographic characteristics of adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

Variables	**Exposed group (n=36)**		**Non-exposed group (n=36)**	
	Frequency	**Valid percent**	**Frequency**	**Valid percent**
Sex				
Male	19	52.8	20	55.6
Female	17	47.2	16	44.4
Age group (in years)				
18-49	16	44.4	18	50
50-79	20	55.6	18	50
Mean age	46.7		47.8	
Median age	50		49	
Mode age	50		28	
Marital status				
Single	6	16.7	7	19.4
Married	29	80.6	28	77.8
Widowed	1	2.8	1	2.8
Residence				
Rural	12	33.3	7	19.4
Urban	24	66.7	29	80.6
Educational status				
Unable to read & write	8	22.2	4	11.1
Elementary	9	25	14	38.9
Secondary	13	36.1	6	16.7
Diploma and above	6	16.7	12	33.3
Religion				
Orthodox Christian	35	97.2	33	91.7
Muslim	1	2.8	3	8.3
Regular income				
Yes	14	38.9	20	55.6
No	22	61.1	16	44.4

6.2. Clinical characteristics of study subjects

6.2.1. General clinical characteristics

Of the total study subjects, 20 (27.8%, n=72) had anorectal and or colorectal cancer followed by lung cancer, which accounts for 13.9%. Around two-third of the study subjects (63.9%) had stage II & III cancer in both study groups. The stage of cancer in both study groups was comparable.

6.2.2. RBC Indices

Independent-sample T-test statistical analysis for mean comparison revealed a significant mean difference in Hb between the exposed group & non-exposed group (P-value: < .001, 95% CI: (-2.56, -.91)) (table 3).

Table 3: Independent-sample T-test statistical analysis for the comparison of mean levels of RBC indices among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

Variables	**Exposed group**	**Non-exposed group**	**95% CI of the mean difference**	**P-value**
	Mean (SD)	Mean (SD)		
RBC number (millions/µL)	4.10±.62	4.59±.52	(-.76, -.23)	.000*****
Hb (g/dL)	11.26±1.95	12.99±1.55	(-2.56, -.91)	.000*****
Hct (%)	34.53±5.64	39.58±4.39	(-7.42, -2.67)	.000*****
MCV (fL)	84.22±4.51	86.32±4.70	(-4.27, .07)	.057
MCH (pg/cell)	27.44±1.95	28.34±1.78	(-1.78, -.03)	.044*****
MCHC (g/L)	326.06±9.82	328.50±8.66	(-.68, .19)	.266
RDW SD%	13.71±1.14	13.30±1.09	(-.11, .94)	.123
***** indicates for significant mean difference among the two study groups at 5% level.				

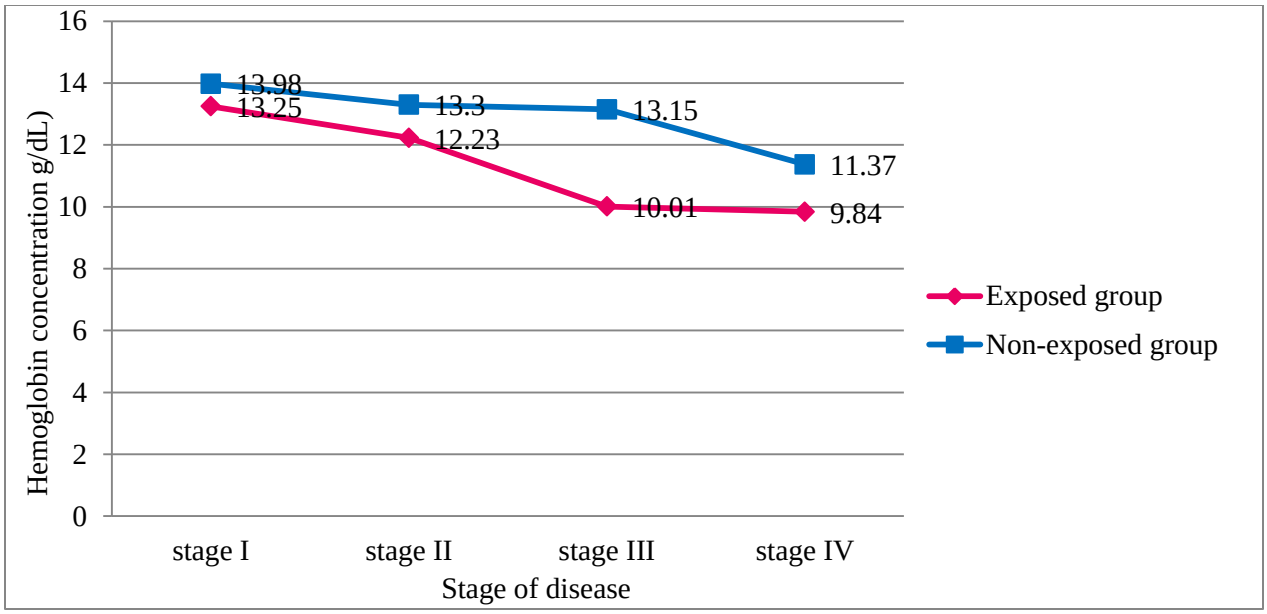

Figure 1: Trends of mean hemoglobin (g/dl) concerning the stage of disease among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

6.2.3. Prevalence and Characteristics of Anemia

Of the total study subjects, nearly one-half (45.8%, n=72) of them were found to have anemia in unclassified cancers. Higher anemia prevalence was recorded in anorectal and or colorectal cancers (70%, n=20) followed by lung cancer (60%, n=10) and breast cancer (57.1%, n=7).

The prevalence of anemia was 21 (58.3%, n=36) and 12 (33.3%, n=36) among patients exposed and not exposed to chemotherapy respectively. Around two-thirds of the total anemic patients (63.6%, n=33) were found to have anemia associated with chemotherapy. From the total study subjects (n=72), the majority (25%) were found to have moderate anemia, 19.4% mild anemia, and 1.4% severe anemia. Mild anemia (25%) was dominant among study subjects not exposed to chemotherapy. On the other hand, moderate anemia (41.7%) was the dominant form among study subjects exposed to chemotherapy (figure 2). The Hb level for the total study subjects ranged from 7.9 g/dL to 15.7 g/dL with a mean value of 12.13 g/dL and SD of 1.96.

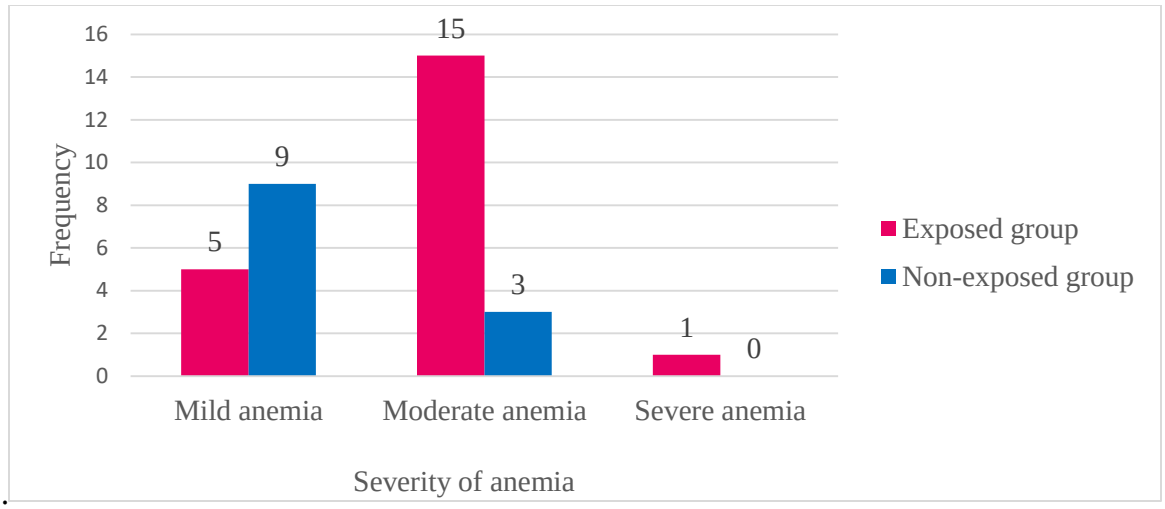

Figure 2: Severity of anemia among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

Binary logistic regression analysis suggested that the exposed group (OR: 2.80) was more likely to be anemic compared to the non-exposed group. In this study, the association between the exposed group and anemia was statistically significant (P-value: < .05, 95% CI: (1.07, 7.30)).

The prevalence of anemia generally increased with increasing chemotherapy cycles. In cycle 1, the prevalence of anemia was 28.6%. Prevalence increased to 40% in cycle 3, 50% in cycle 5, 71.4% in cycle 6, and 100% in cycle 8. The prevalence of anemia also increased along the stage of the disease. In stage I, the prevalence of anemia was 16.7%. This value has increased to 20.8% in stage II, 63.6% in stage III, and 85.7% in stage IV cancers.

6.2.4. White blood cells and differential

Of the total study subjects, 13 (18.1%, n=72) of them were found to have leukopenia. The prevalence of leukopenia was 11 (30.6%, n=36) and 2 (5.6%, n=36) among patients exposed and not exposed to chemotherapy respectively. Binary logistic regression revealed the association between the exposed group and leukopenia was statistically significant (P-value: < .05, 95% CI: (1.52, 36.78)).

Independent-sample T-test analysis for comparison of mean showed a significant difference in the mean value of total WBCs between the exposed group & non-exposed group (P-value: < .001, 95% CI: (-1.48, -0.58)) (table 4).

Neutropenia has been recorded in 16 (44.4%, n=36) and 6 (16.7%, n=36) among patients exposed and not exposed to chemotherapy respectively. Binary logistic regression showed that the exposed group (OR: 4.00) was more likely to be neutropenic as compared to the non-exposed group. The association between the exposed group and neutropenia was statistically significant (P-value: < .05, 95% CI: (1.34, 11.97)). Overall, grade 1-2 (mild) neutropenia occurred in 15 (41.7%, n=36) and grade 3-4 (severe) neutropenia in 1 (2.8%, n=36) among patients exposed to chemotherapy (figure 3).

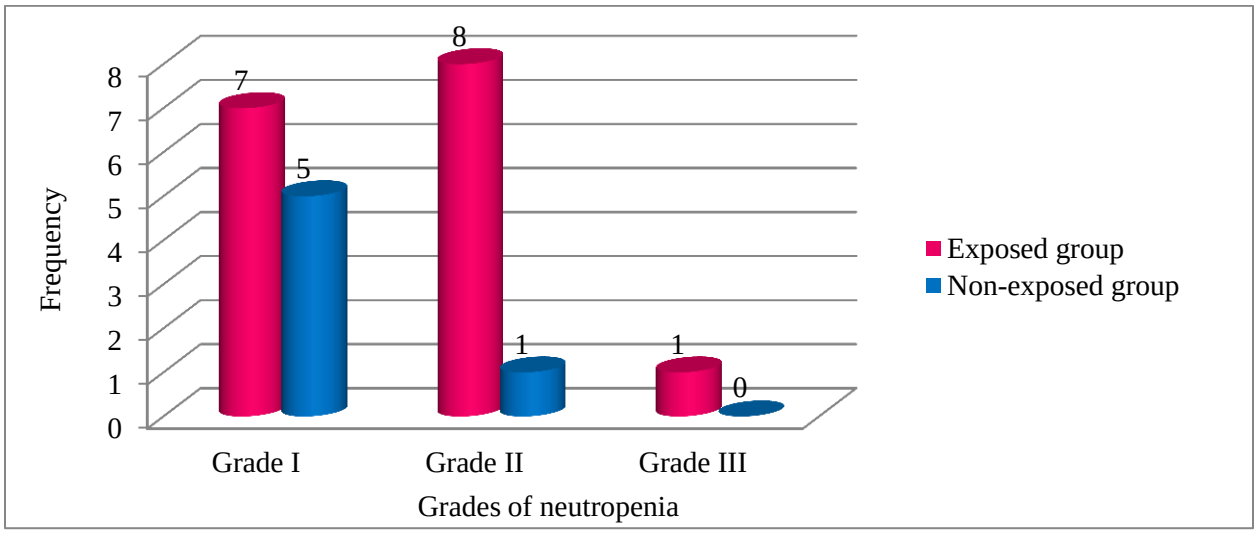

Figure 3: Severity of neutropenia among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

Independent-sample T-test for mean comparison indicated a significant mean difference in neutrophil count between exposed & non-exposed groups (P-value: < .001, 95% CI: (-1.04, -.33)) (table 4).

Table 4: Independent-sample T-test analysis for the comparison of mean levels of white blood cells and differential among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

Variables	**Exposed group**	**Non-exposed group**	**95% CI of the mean difference**	**P-value**
	Mean (SD)	Mean (SD)		
WBC number (10^3 per µL)	4.12±.84	5.15±1.05	(-1.48, -.58)	.000*****
Neutrophil count (10^3 per µL)	2.06±.66	2.74±.84	(-1.04, -.33)	.000*****
Eosinophil count (10^3 per µL)	.12±.08	.15±.09	(-.07, .01)	.205
Basophil count (10^3 per µL)	.03±.02	.04±.02	(-.01, .00)	.120
Lymphocyte count (10^3 per µL)	1.50±.36	1.84±.41	(-.52, -.15)	.000*****
Monocyte count (10^3 per µL)	.40±.20	.39±.13	(-.06, .09)	.707
***** indicates for significant mean difference between the two study groups at 5% level.				

6.2.5. Platelets

Of the total study subjects, 16 (22.2%, n=72) had experienced thrombocytopenia. The prevalence of thrombocytopenia was 12 (33.3%, n=36) and 4 (11.1%, n=36) patients exposed and not exposed to chemotherapy respectively (figure 4). Binary logistic regression suggested that the exposed group (OR: 4.00) was more likely to be thrombocytopenic as compared to the non-exposed group. The association between the exposed group and thrombocytopenia was statistically significant (P-value: < .05, 95% CI: (1.15, 13.95)).

Independent-sample T-test analysis for mean comparison indicated a significant mean difference in platelet count between the exposed group (with mean ± SD of 175.4±60.55) and non-exposed group (with mean ± SD of 243.28±72.37) (P-value: < .001, 95% CI: (-99.24, -36.51)).

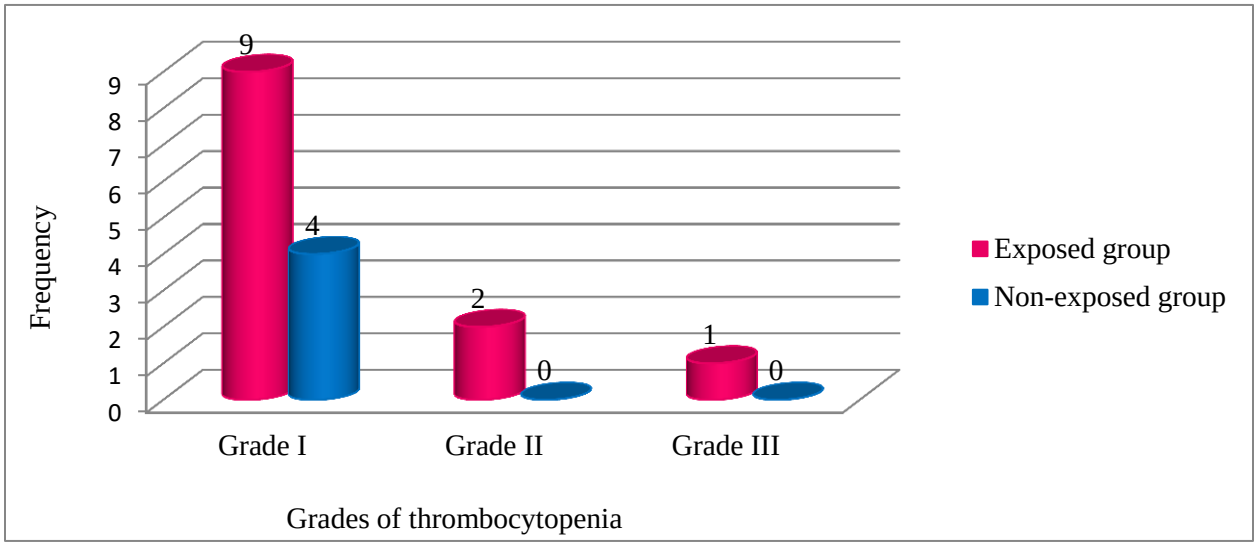

Figure 4: Severity of thrombocytopenia among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

6.2.6. Determinants of anemia

From a total of 9 variables initially considered to be associated with anemia; binary logistic regression analysis identified 5 variables fulfilling the criteria for the exposed group and 4 variables for the non-exposed group (P-value: < .25).

In both study groups, the odds of being anemic were significantly associated with rural residence and advanced-stage cancer. Absences of regular income and chemotherapy treatments of ≥ 5 cycles were also significantly associated with the odds of having anemia in the exposed group (P-value: < .05) (table 5).

Table 5: Binary logistic regression statistical analysis for the independent determining factors of anemia among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

Variables	**Category**	**Exposed group (n=36)**			**Non-exposed group (n=36)**		
		P-value	**COR**	**95% CI**	**P-value**	**COR**	**95% CI**
Age group	≥ 50 years < 50 years	.821 (ref.)	1.167	.31-4.42	.481 (ref.)	1.655	.41-6.71
Gender	Female Male	.464 (ref)	1.650	.43-6.31	.636 (ref.)	1.400	.35-5.64
Residence	Rural Urban	.043***** (ref.)	5.909	1.06-32.92	.029***** (ref.)	7.857	1.24-49.83
Regular income	No Yes	.001***** (ref.)	16.50	3.09-88.03	.065 (ref.)	4.00	.92-17.40
Type of cancer	Ano/colorectal cancer All other types of ca.	.071 (ref.)	4.875	.87-27.26	.112 (ref.)	3.571	.74-17.19
Duration of cancer	≥6 months <6 months	.303 (ref.)	2.133	.51-9.01	____	____	_____
Stage of cancer	Advanced [a] Early [b]	.001***** (ref.)	20.8	3.45-125.3	.009***** (ref.)	10.00	1.76-56.93
Type of chemotherapy	Combination of alkylators and antimetabolites Other chemotherapy	.252 (ref.)	2.462	.53-11.50	____	____	_____

	agents						
Chemotherapy cycles	5-8 cycles 1-4 cycles	.028***** (ref.)	5.00	1.20-20.92	____	____	_____
***** indicates for significant difference among the grouping variables at 5% level. [a] = stage III & IV cancers, [b] = stage I & II cancers							

According to the multivariate logistic regression study, the exposed group's odds of being anemic were considerably increased by both the absence of a regular income and advanced-cancer stages. The only variable statistically linked to an increased risk of anemia in the non-exposed group, however, was advanced-stage cancer (table 6).

Table 6: Multivariate logistic regression statistical analysis for the determining factors of anemia among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020

Variables	**Category**	**Exposed group (n=36)**			**Non-exposed group (n=36)**		
		P-value	**AOR**	**95% CI**	**P-value**	**AOR**	**95% CI**
Residence	Rural Urban	.626 (ref.)	.493	.03-8.49	.234 (ref.)	6.085	.31-119.23
Regular income	No Yes	.048***** (ref.)	13.302	1.03-172.69	.179 (ref.)	5.018	.48-52.86
Type of cancer	Anorectal & colorectal cancer All other types of cancer	.141 (ref.)	6.687	.53-83.85	.237 (ref.)	4.431	.38-52.26
Stage of cancer	Advanced [a] Early [b]	.038***** (ref.)	11.502	1.15-115.29	.017***** (ref.)	16.989	1.67-172.77
Chemotherapy cycles	5-8 cycles 1-4 cycles	.211 (ref.)	3.753	.47-29.76	____	____	____
***** indicates for significant difference among the grouping variables at 5% level. [a] = stage III & IV cancers, [b] = stage I & II cancers							

6.2.7. Determinants of neutropenia and thrombocytopenia

9 variables were initially considered to be associated with neutropenia. Binary logistic regression analysis identified 7 variables fulfilling the criteria for the exposed group and 1 variable for the non-exposed group (P-value: < .25).

The odds of being neutropenic were significantly associated with the absence of regular income, advanced-stage cancer, and chemotherapy treatments of ≥ 5 cycles in the exposed group. On the other hand, no variable was significantly associated with the odds of being neutropenic in the non-exposed group (P-value: < .05) (table 7).

The odds of being thrombocytopenic were associated with rural residence, anorectal & colorectal cancer, and advanced-stage cancer in the exposed group (P-value: < .25). But no variable was found to be significantly associated with the odds of being thrombocytopenic.

Multivariate logistic regression analysis revealed no variable was significantly associated with the odds of being neutropenic in the non-exposed group and being thrombocytopenic in both study groups.

Table 7: Multivariate logistic regression statistical analysis for the determining factors of neutropenia among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

Variables	**Category**	**Exposed group (n=36)**			**Non-exposed group (n=36)**		
		P-value	**AOR**	**95% CI**	**P-value**	**AOR**	**95% CI**
Age group	≥ 50 years < 50 years	.455 (ref.)	1.667	.44-6.36	1.00 (ref.)	1.00	.17-5.77
Gender	Female Male	.709 (ref.)	.778	.21-2.91	.765 (ref.)	1.308	.23-7.57
Residence	Rural Urban	.240 (ref.)	2.333	.57-9.60	.357 (ref.)	2.50	.36-17.57
Regular income	No Yes	.033***** (ref.)	5.296	1.14-24.55	.765 (ref.)	1.308	.23-7.57
Type of cancer	Anorectal & colorectal cancer Other types of cancer	.132 (ref.)	3.111	.71-13.60	.608 (ref.)	1.643	.25-10.95
Duration of cancer	≥ 6 months < 6 months	.177 (ref.)	2.889	.62-13.50	___	___	____
Stage of cancer	Advanced [a] Early [b]	.010***** (ref.)	7.00	1.59-30.80	.104 (ref.)	6.538	.68-62.99
Type of chemotherapy	Combination of alkylators and antimetabolites Other chemotherapy agents	.132 (ref.)	3.111	.71-13.60	____	____	_____
Chemotherapy cycles	5-8 cycles 1-4 cycles	.041***** (ref.)	4.50	1.06-19.04	___	___	_____

***** indicates for significant difference among the grouping variables at 5% level.

[a] = stage III & IV cancers, [b] = stage I & II cancers

From the total study subjects, six cases were found to have pancytopenia. Overall, anemia was the major cytopenia in both study groups (figure 5).

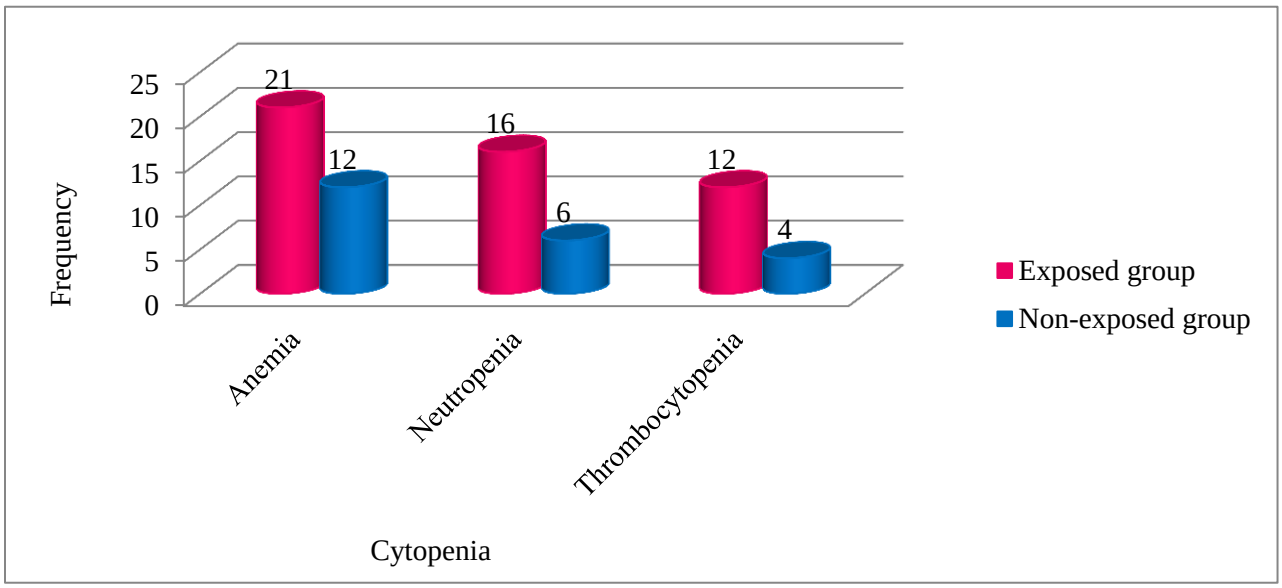

Figure 5: Types of cytopenia among adult cancer patients exposed and not exposed to chemotherapy in ACSH, Mekelle, Northern Ethiopia, 2020.

7. Discussion

This study was conducted to assess hematological indices among adult cancer patients exposed and not exposed to chemotherapy. Most socio-demographic characteristics of the two groups were comparable. This makes it easier to compare hematological parameters between the groups and interpret the results without allowing obvious differences to affect the outcome.

This study used the WHO cut-point for Hb level to assess the prevalence and scale of anemia. Based on this, study subjects with Hb levels < 13 g/dL for males and < 12 g/dL for females were considered as having anemia (5, 47).

According to the current study, the prevalence of anemia was 58.3% (n=36) for study subjects exposed to chemotherapy and 33.3% (n=36) for study subjects not exposed to chemotherapy. The report on the prevalence of anemia varies from 30%-90% of patients with cancer depending on the type of cancer, stage of disease, type of chemotherapy regimens provided, presence of comorbid conditions, and definition of anemia used. The finding of this study was similar to the previous report made by other researchers (27).

The prevalence of anemia among patients not exposed to chemotherapy was higher than the reports made by other researchers which showed 23% anemia prevalence in newly diagnosed cancers in Ethiopia (33). The present result was also higher than the studies conducted in Canada (30), and Turkey (31). On the other hand, the finding of this study was lower than the results from ECAS which revealed 75% of patients who received chemotherapy and 39.7% of patients who didn't receive cancer treatment at any time during the survey (32). The present finding was also lower than the reports from other researchers which showed 84% of anemia at some point during chemotherapy treatment and 44% of anemia at the start of chemotherapy (34). The probable explanation for the variation in the prevalence of anemia in the present study could be due to the difference in the study period, type & stage of diseases, and type & dose of chemotherapy cycles provided.

The result of this study showed that the prevalence of anemia was found to increase from 28.6% in cycle 1 to 50% by cycle 5, which was similar to a large multinational prospective survey conducted in Europe (32). The possible explanation for this increase could be, depending on the type and intensity of treatment, repeated cycles of chemotherapy may have cumulative toxic effects on hematopoiesis (24, 25). This study demonstrated that the majority of patients (25%) had moderate anemia followed by 19.4% mild anemia and 1.4% severe anemia. The findings of this study contrast with other studies conducted in Ethiopia (33), Europe (32), and Japan(34), in which the majority of patients had mild anemia followed by moderate and severe anemia. The variation could be explained by the difference in the definition of anemia.

As the result of this finding showed, higher anemia prevalence was noted in anorectal and or colorectal cancer (70%) followed by lung cancer (60%). This finding was not in line with the report made by ECAS, where gynecological cancer (81.4%) scored higher in anemia prevalence followed by lung cancer (77%). This report also differs from the study conducted in Ethiopia, where 37.7% of gynaecologic and 26.7% of colorectal cancer patients had anemia (32, 33). The observed variation could be attributed to the types of cancer included in the sample.

When other factors were taken into account as confounders in this study's multivariate logistic regression analysis, it became clear that the absence of regular income and advanced-stage cancer were the two main factors strongly related to the probabilities of developing anemia in the exposed group. In contrast, the sole predictor related to anemia in the group that had not been exposed to chemotherapy was advanced-stage cancer (P-value < .05).

The absence of regular income was substantially correlated with the occurrence of anemia, according to demographic and health surveys from 32 countries, which agreed with the findings of the current study (48). The possible reason could be low income is often connected with a lack of access to proper and timely health care, including frequent checkups and advice on iron supplements, food fortification for appropriate nutrition consumption, and anthelminthic therapy (48, 49). The plausible explanation for advanced-stage cancer to cause anemia could be, cancer cells can invade the bone marrow and decrease hematopoiesis directly. Furthermore, cancer cells produce cytokines that cause iron sequestration, limiting red blood cell synthesis. Tumor cells

can also cause chronic blood loss at the tumor site, leading to cancer-related anemia and organ damage (50).

The current study used National Cancer Institute Toxicity Criteria for the diagnosis and grading of neutropenia. Considering this, study subjects with a neutrophil count of < 2000 per µL were defined as having neutropenia.

The result of this study noted a neutropenia prevalence of 44.4% (n=36) for study subjects exposed to chemotherapy and 16.7% (n=36) for study subjects not exposed to chemotherapy. The result of this finding was lower than the studies conducted among patients of NSCLC, gynecologic malignancy, and metastatic colorectal cancer, which showed neutropenia prevalence of 53%, 50.5%, and 71.2% respectively (36, 40, 41). The possible justification for the discrepancy could be the present study had included study participants with unclassified cancers. In addition, it could be explained by the difference in the severity of the disease, and the type & duration of chemotherapy treatment provided.

The result of this study revealed a mild (grade 1-2) neutropenia prevalence of 41.7% (n=36) and a severe (grade 3-4) neutropenia prevalence of 2.8% (n=36) in the exposed group. The finding on the prevalence of severe neutropenia was similar to another study conducted by the American Society of Clinical Oncology (38). On the other hand, the finding of the current study contradicted the result of another study conducted in Kenya (42), which showed 51.8% prevalence of severe neutropenia. It was also contrary to other studies conducted in Greece (35), Japan (37), USA (39), and Italy (36). The possible explanation for the variations could be due to the difference in study design, severity of disease, and number of chemotherapy cycles provided.

This study used National Cancer Institute Toxicity Criteria for the diagnosis and grading of thrombocytopenia. Accordingly, study subjects with platelet count below 150,000 per µL were considered thrombocytopenic.

The result of this finding revealed a thrombocytopenia prevalence of 33.3% (n=36) for study subjects exposed to chemotherapy and 11.1% (n=36) for study subjects not exposed to chemotherapy. The prevalence of platelet counts less than 100,000 per µL can vary widely

ranging from nearly 100% of patients with acute leukemia to less than 5% in patients treated for head malignancies (43). The finding on the prevalence of all grade thrombocytopenia in the exposed group was higher than the report of the study conducted in Kenya (42), which reported 11.3%. One possible explanation for this difference could be, the frequency and degree of CIT is dependent upon chemotherapy regimens, dose of the drugs, and number of chemotherapy cycles provided. Furthermore, depending on the chemotherapeutic regimen, the time of platelet nadir and the kinetics of platelet recovery may differ dramatically (43).

The present finding revealed a severe thrombocytopenia prevalence of 2.8% (n=36) in study subjects exposed to chemotherapy. This was similar to the studies conducted among patients of colon cancer (51), metastatic colorectal cancer (52), and pulmonary adenocarcinoma (53). However, it was somewhat lower than the report in cancer patients treated with sunitinib (54). The possible reason for the difference could be, targeted therapies for hematologic malignancies are frequently linked with a considerable incidence of high-grade thrombocytopenia, as one might expect, albeit the causes behind thrombocytopenia can differ (55).

8. Conclusion

Anemia was present in 45.8% of the unclassified tumors in the current investigation. Compared to other cancer types, anorectal and/or colorectal cancer had the highest prevalence of anemia (70%), followed by lung cancer (60%) and breast cancer (57.1%). It was discovered that chemotherapeutic treatment-related anemia affected almost two-thirds of all anemic individuals. It was statistically significant that the exposed group had a higher incidence of anemia.

Based on the finding of multivariate logistic regression analysis, the absence of regular income and advanced-stage cancer were the key factors significantly associated with the occurrence of anemia in the exposed group. In the non-exposed group, however, the occurrence of anemia was significantly associated with advanced-stage cancer.

According to this finding, the overall prevalence of neutropenia was stated to be 30.6%. The exposed group (OR: 4.00) was more likely to be neutropenic as compared to the non-exposed group. The association between the exposed group and neutropenia was statistically significant.

Among the study subjects who were exposed to chemotherapy, the occurrence of neutropenia was significantly linked with the absence of regular income, advanced-stage cancer, and chemotherapy treatments of ≥5 cycles. Multivariate logistic regression analysis however identified no variable was significantly associated with being neutropenic in the non-exposed group.

Overall, 22.2% of the study subjects had experienced thrombocytopenia. The association between the exposed group and thrombocytopenia was statistically significant. The exposed group (OR: 4.00) was more likely to be thrombocytopenic as compared to the non-exposed group. This finding also revealed that there was a significant difference in the mean values of platelets between the study groups.

Based on the result of this finding, anemia was the major cytopenia in both study groups.

9. Limitation of the study

- ✓ The number of reticulocytes was not assessed. Because it was expensive to purchase the specific reagent needed to determine the reticulocyte count.
- ✓ This study used a cross-sectional study design, which gives a snapshot of data at one point in time making it less reliable than other study designs like case-control or cohort studies.
- ✓ This study used a non-probability sampling method, which makes it difficult to draw an inference.
- ✓ Even though it was calculated using the double population proportion formula, the sample size was small making it difficult to analyze predicting factors.
- ✓ A variation in cut-off points for defining anemia and other blood cell parameters among different studies was challenging to compare with the results of the present study.

10. Recommendation

- ✓ More reliable study designs should be conducted to identify determining factors for the occurrence of anemia, neutropenia, and thrombocytopenia in cancer patients.
- ✓ A cross-sectional (snapshot) study in this finding should be confirmed using more reliable studies such as case-control and cohort studies to draw a justifiable inference on the cause and effect.
- ✓ In addition to the study of haematologic indices, further studies on the diagnosis of anemia, neutropenia, and thrombocytopenia such as iron study, bone marrow examination, and organ function tests should be considered especially for those under chemotherapy to find out the causes of anemia, neutropenia, and thrombocytopenia and take appropriate management protocol accordingly.
- ✓ Anemia control strategies should be sustainable at the population level by the relevant government and nongovernment health and other institutions with special emphasis on home dietary fortifications and healthcare-seeking behavior.

11. References

1. Naaz F, Ahmed S. Integration of unani medicine in cancer management. WJPR. 2017;6(6):450-61.
2. Hardin J, Bertoni G, Kleinsmith L. Becker's world of the cell, eBook. Egypt: Pearson Higher Ed. 2017.
3. Lodish H, Berk A, Kaiser CA, Kaiser C, Krieger M, Scott MP, et al. Molecular cell biology: Macmillan; 2008.
4. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's principles of internal medicine2012. 7122 p.
5. Farber E. Cancer development and its natural history a cancer prevention perspective. Cancer. 1988;62(S1):1676-9.
6. Johnstone RW, Ruefli AA, Lowe SW. Apoptosis: a link between cancer genetics and chemotherapy. Cell. 2002;108(2):153-64.
7. Li JJ. Laughing gas, Viagra, and Lipitor: the human stories behind the drugs we use: Oxford University Press; 2006.
8. Weisse AB. Medical odysseys: the different and sometimes unexpected pathways to twentieth-century medical discoveries: Rutgers University Press; 1991. 127 p.
9. Farber S, Diamond LK, Mercer RD, Sylvester Jr RF, Wolff JA. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). New England Journal of Medicine. 1948;238(23):787-93.
10. Miller DR. A tribute to Sidney Farber–the father of modern chemotherapy. British journal of haematology. 2006;134(1):20-6.
11. Li MC, Hertz R, Spencer DB. Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma. Proceedings of the Society for Experimental Biology and Medicine. 1956;93(2):361-6.
12."Cancer"(https://www.who.int/en/news-room/fact-sheets/detail/cancer). World Health Organization. 12 September 2018. Retrieved 28 October 2019.
13. Parkin DM, Sitas F, Chirenje M, Stein L, Abratt R, Wabinga H. Part I: Cancer in Indigenous Africans—burden, distribution, and trends. The lancet oncology. 2008;9(7):683-92.
14. Woldeamanuel YW, Girma B, Teklu AM. Cancer in Ethiopia. The Lancet Oncology. 2013;14(4):289-90.
15. Kurtin S. Myeloid toxicity of cancer treatment. Journal of the advanced practitioner in oncology. 2012;3(4):209.
16. Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. American Journal of Health-System Pharmacy. 2007;64(3_Supplement_2):S5-S13.
17. Birgegård G, Aapro MS, Bokemeyer C, Dicato M, Drings P, Hornedo J, et al. Cancer-related anemia: pathogenesis, prevalence and treatment. Oncology. 2005;68(Suppl. 1):3-11.

18. Aapro M, Österborg A, Gascón P, Ludwig H, Beguin Y. Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of iv iron. Annals of Oncology. 2012;23(8):1954-62.
19. Zarychanski R, Houston DS. Anemia of chronic disease: a harmful disorder or an adaptive, beneficial response? Cmaj. 2008;179(4):333-7.
20. Nowrousian M. Prevalence, pathophysiology, predictive factors, and prognostic significance of anemia in cancer chemotherapy. Recombinant human erythropoietin (rhEPO) in clinical oncology: Springer; 2002. p. 63-100.
21. Rodgers GM, Blinder M, Cella D, Cleeland C, Coccia PF, Djulbegovic B, et al. Cancer- and Chemotherapy- Induced Anemia. Journal of the National Comprehensive Cancer Network. 2014.
22. Schutz FA, Je Y, Choueiri TK. Hematologic toxicities in cancer patients treated with the multi-tyrosine kinase sorafenib: a meta-analysis of clinical trials. Critical reviews in oncology/hematology. 2011;80(2):291-300.
23. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. 2004;100(2):228-37.
24. Cairo MS. Dose reductions and delays: limitations of myelosuppressive chemotherapy. Oncology (Williston Park, NY). 2000;14(9 Suppl 8):21-31.
25. Wu Y, Aravind S, Ranganathan G, Martin A, Nalysnyk L. Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: a descriptive study of a large outpatient oncology practice database, 2000-2007. Clinical therapeutics. 2009;31 Pt 2:2416-32.
26. Rodgers GM, Becker PS, Blinder M, Cella D, Chanan-Khan A, Cleeland C, et al. Cancer-and chemotherapy-induced anemia. Journal of the National Comprehensive Cancer Network. 2012;10(5):628-53.
27. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. The American journal of medicine. 2004;116 Suppl 7A:11s-26s.
28. Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2007;64(3 Suppl 2):S5-13; quiz S28-30.
29. Calabrich A, Katz A. Management of anemia in cancer patients. Future oncology (London, England). 2011;7(4):507-17.
30. Dranitsaris G, Clemons M, Verma S, Lau C, Vincent M. Chemotherapy-induced anaemia during adjuvant treatment for breast cancer: development of a prediction model. The Lancet Oncology. 2005;6(11):856-63.
31. COŞKUN HŞ YO, Aydin O, ALANOĞLU G, ŞAHİN M, Özlem E, et al. CHEMOTHERAPY ASSOCIATED ANEMIA IN PATIENTS WITH SOLID TUMOR. TURKISH JOURNAL OF ONCOLOGY.20(2).
32. Ludwig H, Van Belle S, Barrett-Lee P, Birgegård G, Bokemeyer C, Gascón P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining

the prevalence, incidence, and treatment of anaemia in cancer patients. European journal of cancer. 2004;40(15):2293-306.
33. Kifle E, Hussein M, Alemu J, Tigeneh W. Prevalence of Anemia and Associated Factors among Newly Diagnosed Patients with Solid Malignancy at Tikur Anbessa Specialized Hospital, Radiotherapy Center, Addis Ababa, Ethiopia. 2019;2019:8279789.
34. Kitano T, Tada H, Nishimura T, Teramukai S, Kanai M, Nishimura T, et al. Prevalence and incidence of anemia in Japanese cancer patients receiving outpatient chemotherapy. International journal of hematology. 2007;86(1):37-41.
35. Pallis AG, Agelaki S, Kakolyris S, Kotsakis A, Kalykaki A, Vardakis N, et al. Chemotherapy-induced neutropenia as a prognostic factor in patients with advanced non-small cell lung cancer treated with front-line docetaxel-gemcitabine chemotherapy. Lung cancer (Amsterdam, Netherlands). 2008;62(3):356-63.
36. Di Maio M, Gridelli C, Gallo C, Shepherd F, Piantedosi FV, Cigolari S, et al. Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of three randomised trials. The Lancet Oncology. 2005;6(9):669-77.
37. Kishida Y, Kawahara M, Teramukai S, Kubota K, Komuta K, Minato K, et al. Chemotherapy-induced neutropenia as a prognostic factor in advanced non-small-cell lung cancer: results from Japan Multinational Trial Organization LC00-03. British journal of cancer. 2009;101(9):1537-42.
38. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24(19):3187-205.
39. Laskey RA, Poniewierski MS, Lopez MA, Hanna RK, Secord AA, Gehrig PA, et al. Predictors of severe and febrile neutropenia during primary chemotherapy for ovarian cancer. Gynecologic oncology. 2012;125(3):625-30.
40. Hashiguchi Y, Kasai M, Fukuda T, Ichimura T, Yasui T, Sumi T. Chemotherapy-induced neutropenia and febrile neutropenia in patients with gynecologic malignancy. Anti-cancer drugs. 2015;26(10).
41. Rambach L, Bertaut A, Vincent J, Lorgis V, Ladoire S, Ghiringhelli F. Prognostic value of chemotherapy-induced hematological toxicity in metastatic colorectal cancer patients. World journal of gastroenterology: WJG. 2014;20(6):1565.
42. Othieno-Abinya NA, Waweru A, Nyabola LO. Chemotherapy induced myelosuppression. East African medical journal. 2007;84(1):8-15.
43. Liebman HA. Thrombocytopenia in cancer patients. Thrombosis research. 2014;133:S63-S9.
44. Tuck MK, Chan DW, Chia D, Godwin AK, Grizzle WE, Krueger KE, et al. Standard operating procedures for serum and plasma collection: early detection research network consensus statement standard operating procedure integration working group. Journal of proteome research. 2009;8(1):113-7.
45. George T. Automated hematology instrumentation. Up to Date. 2019.

46. Lehto T, Leskinen P, Hedberg P, Vaskivuo T. Evaluation of the Sysmex XT-4000i for the automated body fluid analysis. International Journal of Laboratory Hematology. 2014;36(2):114-23.
47. Labpedia.net. Anemia - Part 1 - Anemia Classification, Thalassemia, Sickle cell anemia, Megaloblastic anemia, Iron-Deficiency anemia Sep 14, 2020 [cited 2020 Nov 2]. Available from:https://www.google.com/search?sxsrf=ALeKk00rUJB7xkZHtty6oKe2jPRdTvpwYA%3A1604298363183&ei=e6afX9LaCoWW1fAPwLi1oAI&q=wintrobe+classification+of+anemia&oq=wintrobe+classification+of+anemia&gs_lcp=CgZwc3ktYWIQARgAMgUIABDJA1AAWABgrqMEaABwAHgAgAH1AYgB9QGSAQMyLTGYAQCqAQdnd3Mtd2l6wAEB&sclient=psy-ab.
48. Alderman H, Linnemayr S. Anemia in low-income countries is unlikely to be addressed by economic development without additional programs. Food and nutrition bulletin. 2009;30(3):265-9.
49. Pasricha S-R, Drakesmith H, Black J, Hipgrave D, Biggs B-A. Control of iron deficiency anemia in low-and middle-income countries. Blood. 2013;121(14):2607-17.
50. Rodgers GM, 3rd, Becker PS, Blinder M, Cella D, Chanan-Khan A, Cleeland C, et al. Cancer- and chemotherapy-induced anemia. Journal of the National Comprehensive Cancer Network : JNCCN. 2012;10(5):628-53.
51. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. New England Journal of Medicine. 2004;350(23):2343-51.
52. Van Cutsem E, Köhne C-H, Hitre E, Zaluski J, Chang Chien C-R, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. New England Journal of Medicine. 2009;360(14):1408-17.
53. Mok TS, Wu Y-L, Thongprasert S, Yang C-H, Chu D-T, Saijo N, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. New England Journal of Medicine. 2009;361(10):947-57.
54. Funakoshi T, Latif A, Galsky MD. Risk of hematologic toxicities in cancer patients treated with sunitinib: a systematic review and meta-analysis. Cancer treatment reviews. 2013;39(7):818-30.
55. Dy GK, Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. CA: a cancer journal for clinicians. 2013;63(4):249-79.

12. Annexes

12.1. Annex I: Information sheet and consent form (English version)

Information sheet

My name is Asgele Tsehaye. I am an MSc student at Addis Ababa University, College of Health Sciences, Department of Medical Physiology, and currently, I am researching the assessment of hematologic profiles among cancer patients who are exposed and not exposed to chemotherapy in Ayder Comprehensive Specialized Hospital. This study has been approved by the Ethical and Review Committee of the Department of Medical Physiology at Addis Ababa University and the College of Health Science Research Directorate Office in ACSH. The objective of the study is to assess the hematologic profile among two groups of cancer patients (one group exposed to chemotherapy and another group not exposed to chemotherapy).

Dear participants, your participation in the study is on a purely voluntary basis and no payment will be given for your participation. You will have face to face interview for no more than 30 minutes to accomplish the questionnaire. You will also be requested to give a 4ml blood sample from your left upper arm by an experienced laboratory technician. You may have minor discomfort and pain during blood drawing and there may also be mild redness, or swelling on the site where blood is drawn. But this is minor and will resolve in the next couple of minutes. The outcome of the result will help to generate the information necessary to alert health professionals about cancer and chemotherapy-related hematologic effects and to solve the consequences timely.

No personal identifiers will be attached/ recorded to the interview. The data you provided will be kept strictly confidential by using only code numbers and will aggregated with the responses of others to establish common voices. During the interview, if you feel inconvenienced, you can interrupt and clarify the inconvenience, appoint to another time, or even withdraw any time after you get involved in the study. Dear respondent, below are some questions that are designed to assess the hematologic profile among those exposed and not exposed to chemotherapy. Your honest and genuine participation in this study is very important & highly appreciated.

Consent form

Information about the study has been explained to me by the data collector. I understood the objective of this study. I also understood the risk and benefits of participation in this study. I agree to participate in the study and I here approve my agreement with my signature.

Participant's signature_____ Date_____

Investigator's signature_____ Date____ _____ questionnaire code_____

Thank you for your invaluable support!

If you need further information, you can contact me using the following address.

Investigator: Asgele Tsehaye

Phone: +251914285023

Email: 12talex21@gmail.com

12.2. Annex II: Questionnaire (English version)

Addis Ababa University College of health science, department of medical physiology

Questionnaire to assess hematologic profile among cancer patients exposed and not exposed to chemotherapeutic treatment in Ayder Comprehensive Specialized Hospital, Northern Ethiopia.

Questionnaire identification code_____, Site_____, Date of interview_____

S.No	Variables	Response	Remark
Part I: Socio-demographic characteristics			
101	Age (years)	_____	
102	Sex	1. Male 2. Female	
103	Marital status	1. Single 3. Divorced 2. Married 4. Widowed	
104	Residence	1. Rural 2. Urban	
105	Educational status	1. Illiterate 3. High school 2. Elementary 4. Diploma & above	
106	Religion	1. Orthodox 4. Protestant 2. Muslim 5. others 3. Catholic _____	
107	Occupation	1. Employed 2. Unemployed	
108	Regular income	1. Yes 2. No	
Part II: Clinical characteristics			
201	Type of cancer	_____	
202	Duration of cancer	_____	
203	Stage of cancer	1. Stage I 3. Stage III 2. Stage II 4. Stage IV	
204	Chemotherapy usage	1. Yes 2. No	If no, skip to Q.207
205	Type of chemotherapy	_____	
206	Treatment duration and number of chemotherapy cycles	_____ _____	
207	RBC indices Total RBC Hb (g/dL) Hct (%) MCV	 _____ _____ _____ _____	

	MCH MCHC RDW	_____ _____ _____	
208	Total WBC Neutrophil count Eosinophil count Basophil count Lymphocyte count Monocytes	_____ _____ _____ _____ _____ _____	
209	Platelet count	_____	

12.3. Annex III: Information sheet and consent form (Tigrigna version)

<u>መብርሂ ቅጥዒ</u>:

ኣብ ክልል ትግራይ ዓይደር ሪፈራል ሆስፒታል ዝካየድ ኣብ መንነ መድሓኒት ዝወስዱን ዘይወስዱን ሕማም መንሽሮ ዘለዎም ሰባት ኣድሂቡ ዝግበር መፅናዕቲ ንምክያድ ዝተዳለወ መሕተት

ሰላም ጥዕና ይሃበለይ ሽመይ ኣስገለ ፀሃየ ይበሃል። ናይ ኣዲስ ኣበባ ዩኒቨርሲቲ ጥዕና ሳይንስ ኮሌጅ ካልኣይ ዲግሪ ተምሃራይ ኮይነ ነዚ ፅንዓት ንምክያድ ማለት እውን መድሓኒት ዝወስዱን ዘይወስዱን ብሕማም መንሽሮ ዝተጠቕዑ ተሓከምቲ ሓፈሻዊ ኩነታት ደሞም ሳይንሳዊ ብዝኾነ መንገዲ መፅናዕቲ ንምክያድ ካብ ዘለዎ ጥቕሚ ብምብጋስ ካብ 30 ደቂቓ ብዘይበልፅ ግዜ ቃለ-መሕተት ብምጥቃምን 4 ሚሊ ሊትር ናሙና ደም ብምውሳድን መንነቶም/ተን ምስጢራዊ ብዝኾነ መንገዲ ተሓልዩ ኣብዚ ፅንዓት ንኽሳተፉ/ፋ ፍቓዶም/ደን ብትሕትና ይሓትት። ኣብ ግዜ ምውሳድ ናሙና ብጣዕሚ ውስን ዝኾነ ቃንዛ ክስመዖም ይኽእል እዩ። ይኹን እምበር ተሎ ዝሓውን ጎናዊ ሳዕቤን ዘይብሉን ብምኺኑ ከየተሓሳስቦም። እዚ መፅናዕቲ ንምክያድ ካብ ኣዲስ ኣበባ ዩኒቨርሲቲ ጥዕና ሳይንስ ኮሌጅ ፊዝዮሎጂ ክፍሊ ትምህርትን ካብ ዓይደር ሆስፒታል ምርምር ዳይሬክቶሬት ቢሮን ፍቓድ ተዋሂቡዎ እዩ።

ኣብዚ ፅንዓት ምስታፎም ዝረኽብዎ ቐጥታዊ ጥቕሚ የለን። ድሕሪ እዚ ፅንዓት ግን ዘለዉ ጎናዊ ሳዕቤናት እቲ ሕማምን እቲ መድሓኒትን ብኣግባቡ ብምፍላይ ኣብ ፅሬት ክትትል ሕክምና ጠቓሚ ዝኾነ ለውጢ ከምፀኣሎም እዩ። ብተወሳኺ እውን ኣብ ግዜ ምእካብ እቲ ሓበሬታ ንዝተነፀሩ ሃንደበታዊ ናይ ጥዕና ፀገማት ምስ ዝምልከቶም ሰብ ሞያ ጥዕና ብምርኻብ ኣድለይቲ ምርመራታት ፣ ሕክምናዊ ሓገዝን ምኽራዊ ኣገልግሎትን ክረኽቡ እዮም። እዚ ቓለ-መሕተት እዚ ምሉእ ብምሉእ ኣብ ሰናይ ድሌቶም ዝተመስረተ ስለዝኾነ እንተዘይተመችዩዎም እቲ ቃለ-መሕተት ንኻሊእ እዋን ናይ ምዝውዋርን ኢሉ እውን ኣብ ዝኾነ እዋን ናይ ምቁራፅን መሰሎም ሕልው እዩ። ዝተኽበሩ ተሳታፋይ እዚ መፅናዕቲ ኣብቲ ቀፂሉ ዘሎ ገፅ ኣብ መድሓኒት ዝወስዱን ዘይወስዱን ተሓከምቲ ሕማም መንሽሮ ዘሎ ኩነታት ደም

ንምፍታሽ ዝተወሰኑ ሕቶታት ተዳልዮም ኣለው። ተገዳስነት ዝተመልኦ ተሳትፈኦም ኣብዚ መፅናዕቲ እዚ ኣዝዩ ወሳንን ዝነኣድን እዩ።

ንዝህልዎም ዝኾነ ይኹን ሕቶ በዚ ዝስዕብ ኣድራሻ ሓበሬታ ክረኽቡ ይኽእሉ እዮም።

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ክብረት ይሃበለይ!

ናይ ተሳተፍቲ ውዕሊ ስምምዕነት ቅጥዒ፡

ብዛዕባ እቲ መፅናዕቲ ዕላማን ጥቅምን ብዝግባእ ተሓቢሩለይን ተረዲአን ንኽሳተፍ ብዝተሓተትኩዎ መሰረት ብዓርሰ ፍቓደይ ንኽሳተፍ ብፌርማይ ኣረጋጊፀ ኣለኹ።

ናይ ተሳታፊ ፌርማ _____ ዕለት _____

ናይ መተሓባበሪ ፌርማ _____ ዕለት _____

12.4. Annex IV: Questionnaire (Tigrigna version)

ኣብ ኣዲስ ኣበባ ዩኒቨርሲቲ ጥዕና ሳይንስ ኮሌጅ ፊዝዮሎጂ ክፍሊ ትምህርቲ

ኣብ ዓይደር ሆስፒታል መድሓኒት ኣብ ዝወስዱን ዘይወስዱን ሕሙማት መንሽሮ ዘሎ ኩነታት ደም ንምፍታሽ ዝተዳለወ ቃለ-መሕተት።

ናይዚ ፅንዓት መፍለዪ ቁፅሪ _____ ቃለ-መሕተት ዝተገበረሉ ቦታ_____ዕለት _____

<u>ቀዳማይ ክፋል፡ ማሕበራዊ ኩነታት</u>

101. ዕድመ _____

102. ፆታ ሀ) ተባዕታይ ለ) ኣንስታይ

103. ኩነታት ሓዳር ሀ) ዝተመርዐወ/ት ለ) ዘይተመርዐወ/ት ሐ) ዝተፋተሐ/ት መ) ብሞት ዝተፈለየቶ/ያ

104. ዝነብርሉ ቦታ ሀ) ገጠር ለ) ከተማ

105. ደረጃ ትምህርቲ ሀ) ዘይተምሃረ/ት ለ) ክሳብ 8ይ ሐ) 9ይ - 12 መ) ዲፕሎማን ልዕሊኡን

106. ሃይማኖት ሀ) ኦርቶዶክስ ለ) ሙስሊም ሐ) ካቶሊክ መ) ፕሮቴስታንት ረ) ካሊእ _____

107. ኩነታት ስራሕ ሀ) ዝተቐፀረ/ት ለ) ዘይተቐፀረ/ት

108. ቀዋሚ ኣታዊ ኣለዎም/ወን ዶ? ሀ) እወ ለ) ኣይፋል

<u>ካልኣይ ክፋል፡ ኩነታት ሕክምናን ባህርያትን</u>

201. ዓይነት ሕማም መንሽሮ _____

202. ምስ ሕማም መንሽሮ ንኽንደይ እዋን ፀኒሑም? _____

203. ደረጃ ሕማም መንሽሮ ሀ) 1ይ ደረጃ ለ) 2ይ ደረጃ ሐ) 3ይ ደረጃ መ) 4ይ ደረጃ

204. ፀረ ሕማም መንሽሮ መድሓኒት ይወስዱ ዶ? ሀ) እወ ለ) ኣይፋል መልሶም ኣይፋል እንተኾይኑ ናብ ሕቶ ቁፅሪ 207 ይዝለሉ።

205. ዓይነት ዝወስድዎ መድሃኒት አንታይ እዩ? _____

206. ንኽንደይ እዋንን ንኽንደይ ዙርን መድሓኒት ወሲዶም? _____

207. ላባራቶሪ ዓቕን ቀያሕቲ ዋህዮታት ደም

- ✓ ጠቕላላ ቁፅሪ ቀያሕቲ ዋህዮታት ደም _____
- ✓ ሄሞግሎቢን ብ (ግ/ደሊ) _____
- ✓ ሄማቶክሪት ብሚኢታዊ _____
- ✓ MCV _____
- ✓ MCH _____
- ✓ MCHC _____
- ✓ RDW _____

208. ላባራቶሪ ዓቕን ፃዕዱ ዋህዮታት ደም

- ✓ ጠቕላላ ቁፅሪ ፃዕዱ ዋህዮታት ደም _____

- ✓ ቁፅሪ neutrophil _____
- ✓ ቁፅሪ eosinophil _____
- ✓ ቁፅሪ basophil _____
- ✓ ቁፅሪ lymphocyte _____
- ✓ ቁፅሪ monocyte _____

209. ላባራቶሪ ዓቐን ፕላትሌት _____

ደጊመ የቐንየለይ!!!