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Research Article

Incidence and Predictor of Anemia in Patients Diagnosed with Solid Tumors Receiving Chemotherapy in the University of Gondar Comprehensive Specialized Hospital: A Retrospective Follow up Study

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Abstract

Introduction: Chemotherapy-induced anemia is a frequent complication of systemic chemotherapy and is associated with decreased functional capacity and quality of life. Despite having debilitating problems that negatively influences their overall quality of life, high occurrence during chemotherapy, and worsens their prognosis, there is a scarce of evidence regarding the incidence and predictor of chemotherapy induced anemia among cancer patients in Ethiopia. Therefore, this study aimed to assess the incidence and predictors of chemotherapy induced anemia in patients diagnosed with solid tumors receiving chemotherapy in the University of Gondar Comprehensive specialized hospital.

Methods: An institutional-based retrospective cohort study was conducted from September 2015 and August 2021. Simple random sampling technique was employed to select a total of 400 cancer patients enrolled on chemotherapy. Data was collected and entered into EPI DATA 3.1 and analyzed using STATA version 14.1. Time-to-event distributions were estimated using Kaplan-Meier estimates. Hazards across different categories were compared using log-rank tests. Determinants were identified using the Cox proportional hazards model. The Hazard Ratio (HR) and 95% Confidence Interval (CI) were computed. Variables having P-value <0.05 from the multivariable analysis were considered as a statistically significant.

Results: Among 400 records reviewed, 398 (99.5%) were included in the final analysis. The total follow-up period was 34,149 Person-Days (PD). The incidence rate in this cohort was found to be 5.71 per 1000-person day (95% CI: 4.963-6.57). Being underweight (AHR=2.12; 95% CI: 1.12-4.00) and the presence of metastasis (AHR=2.79; 95% CI: 1.59-4.88) were found to be an independent predictor of chemotherapy induced anemia among cancer patients.

Conclusion: The incidence of chemotherapy induced anemia in patients with solid tumors receiving chemotherapy was high. The presence of metastasis and being underweight were found to increase the hazard of chemotherapy induced anemia. Therefore, regular measurement of BMI and screening for the presence of metastasis in all patients who undergo chemotherapy better to be practiced.

Keywords: Anemia; Chemotherapy; Incidence; Predictors; Gondar; Ethiopia

Abbreviations

AHR: Adjusted Hazard Ratio; BMI: Body Mass Index; CIA: Chemotherapy Induced Anemia; ECAS: European Cancer Association Survey

Introduction

A leading cause of mortality globally, cancer is expected to account for roughly 10 million deaths in 2020, with an estimated 19.3 million new cases. Breast, lung, colon, rectum, and prostate cancers are the most prevalent types of cancer [1]. The number of cancer survivors has increased over the previous ten years due to advancements in cancer diagnosis and treatment, significantly raising the relative percentages of survivors [2]. Today, chemotherapy has altered as a result of the utilization of significant molecular abnormalities in the screening of prospective new medications and targeted therapies [3]. However, chemotherapy induced comorbidities becomes a significant threat to treat cancer patients [4]. There are lots of comorbidities which happened during cancer treatment [5], among that Anemia [6], Hepatotoxicity [7], Neutropenia [8], and Acute Kidney Injury (AKI) [9] and peripheral neuropathy [10] are the commonest one. One of the most frequent side effects of myelosuppressive chemotherapy is anaemia, which lowers Quality of Life (QOL) and functional ability [4]. To determine its prevalence, several researches were done. For instance, research from Southern California found that 89.5% of patients with solid tumors experienced anemia during the course of chemotherapy, with anemia developing in individuals of all ages [11]. Another study conducted in the United States on adult cancer patients receiving outpatient oncology care found that between 46.4% to 59.0% of the 75,243 cancer patients receiving chemotherapy acquired anemia [12]. Besides, a study in European Cancer Anemia Survey (ECAS)

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revealed that the incidence of anemia in European Cancer patients was 53.7% [13]. Chemotherapy-Induced Anaemia (CIA) results from inflammation-induced functional iron deficiency, bone marrow infiltration with disruption of erythropoiesis, and malignant invasion of normal tissue that causes blood loss [14]. About 70% of patients receiving chemotherapy develop anemia [14,15]. The proportion of anemic patients increased from 17% before the first chemotherapy cycle to 35% by the sixth cycle of treatment [4]. Chemotherapeutic medicines can cause anemia either directly affecting hematopoiesis in the bone marrow or by decreasing erythropoietin synthesis in the kidneys due to nephrotoxic effects of specific cytotoxic agents [6]. Studies conducted elsewhere in the world show that anemia in chemotherapy patients is significantly influenced by the presence of metastases, advanced disease stage, tumor type, type of chemotherapy, and length of treatment [16]. Untreated anemia can lead to fatigue, drowsiness, sadness, dyspnea, tachycardia, and dizziness, which could postpone the start of following chemotherapy cycles or lower patients' quality of life [17]. There is little information about the prevalence and predictors of chemotherapy-induced anemia among cancer patients in Ethiopia, despite the fact that this condition is distressing, has a high incidence during chemotherapy, and affects patients' prognoses. The present study will, therefore, assess the incidence and predictors of chemotherapy induced anemia in patients diagnosed with solid tumors receiving chemotherapy. Moreover, the output of the present study will also be used as a baseline for further study and for the establishment of surveillance system.

Materials and Methods

Study design and period

Institution based retrospective follow up study among cancer patients on chemotherapy was conducted at University of Gondar Comprehensive specialized hospital from September 2015 and August 2021.

Study setting

The hospital was founded in 1954 and is located in the Central Gondar Zone of the Amhara National Regional State, which is far around 750 km from Addis Ababa, the capital city of Ethiopia. According to the 2015 population projection of major cities in Ethiopia, the overall population size of Gondar town was around 323,900. Gondar town has 9 public health institutions (one Comprehensive Specialized Hospital and eight Health Centers). University of Gondar Comprehensive Specialized Hospital is a teaching hospital, which serves more than 7.5 million people of the Central Gondar Zone and neighboring regions. This hospital has both pediatric and adult oncology wards. The ward serves more than 3000 cancer patients every year. The oncology unit currently has 32 beds for the treatment of patients with cancer.

Source and study population

The source populations were all adult cancer patient on chemotherapy at University of Gondar referral hospital and the study population were all adult cancer patients who were on chemotherapy between September 2015 and August 2021. However, newly diagnosed patients who had anemia at the start of the follow up, patients with hematologic malignancy, had a transfusion within 2 weeks and received radiation therapy within 4 months prior to chemotherapy initiation, and patients who had missing on the key variables will be excluded from the study.

Sample size determination

The sample size for this study was determined based on a simple rule of thumb, by taking incidence of anemia 41.1 from other study [18]. Accordingly, after adding 10% for incomplete data and the final sample size was found to be 400. A computer-generated simple random sampling technique was employed to select those sampled patients' charts from a total of 2000 patients that had been on chemotherapy treatment from September, 2015 to August, 2021.

Variables

The dependent variable was the incidence of chemotherapy induced anemia. Anemia is diagnosed using National Cancer Institute's Common Terminology Criteria for Adverse Events. Anemia was classified as grade 1: 10 g/dL to lower limit of normal (14 g/dL for men and 12 g/dL for women); grade 2: 8.0 g/dL-9.9 g/dL; grade 3: 6.5 g/dL-7.9 g/dL; and grade 4: <6.5 g/dL [4]. Type of anemia was classified using Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin (MCH) as microcytic anemia (MCV <80 fL), normocytic anemia (80 ≤ MCV ≤ 100 fL), macrocytic anemia (MCV>100 fL), hypochromic anemia (MCH<27 pg/cell), normochromic anemia (27 ≤ MCH ≤ 31 pg/cell), and hyperchromic anemia (MCH>31 pg/cell) [6]. The first group of predictors assessed was socio-demographic characteristics including age, sex, marital status, residence, level of education, and religion. The second was clinical and behavioral predictors including stage of cancer, comorbidities, metastasis, Body Mass Index (BMI), type of tumor, type of chemotherapy, smoking and alcohol intake. Anthropometric measurements such as weight and height were taken using standardized methods and adjusted equipment. Weight was measured in kilogram with light cloths and no wearing of shoes, the participants height was measured in centimeter using height board with no shoes wearing and in upright position then BMI was calculated to determine the obesity status [19].

Data collection tool and procedures

A simple random sampling technique was used to select the medical charts of the patient. A data abstraction sheet was developed in English and used for the collection of relevant variables. The information collected from patients' records filled out by hospital residents and physicians. The extraction sheet tool was consisting of socio-demographic and behavioral characteristics (sex, age, residence, occupation, smoking, alcohol consumption), clinical and cancer related factors (history of DM, HTN, type of cancer, stage of cancer, site of cancer, metastasis, type, and cycle of treatment) and outcome variables. Three oncology residents were involved in the data extraction and supervised by one oncology specialist. The medical charts to be reviewed were identified by their medical registration/card number. Then, together with the data clerk working at oncology ward of the hospital, data collectors were reviewed and extract data from patient charts and registries.

Data processing and analysis

Data was entered using EPI-DATA Version 3.1 and analyzed using STATA version 14 statistical software. The patient's follow-up characteristics were described for median, interquartile range and frequency distribution table. Separate graph of Kaplan Meier survival functions and log-rank test was estimated for each categorical variable to compare the survival between different exposure groups. The necessary assumption of Cox proportional hazard regression model was checked using Schoenfeld residual test and log [-log (survival probability) *vs.* log of survival time plot. Bivariable/Cox-proportional hazard regression model was used to screen variables for the final

model. Variables having a p-value of ≤ 0.20 in the bi-variable analysis were fitted into the multivariable Cox-proportional hazard regression model. Finally, an adjusted hazard ratio with its corresponding 95% confidence interval was reported to declare the presence of a significant association between the explanatory and outcome variables The model goodness of fit was assessed using Cox-Snell residual test.

Ethical issues

Ethical approval was obtained from ethical review committee of University of Gondar College of Medicine and Health Sciences. Besides, a permission letter was also obtained from the respective hospitals. As the study was conducted through a review of records, no informed consent was obtained. The data have been anonymized and handled confidentially during all phases of research activities.

Result

Socio-demographic characteristics

Among four hundred adult cancer patients' records reviewed, three hundred ninety-eight (99.5%) records were included in the final analysis. Of this majority of cancer patients were females 317 (79.65%). The median age of the participants was 45.5 years old (IQR: 37, 57). Of the total sample 331 (83.1%) were married and the majority 348 (87.4%) of study participants were orthodox. Concerning educational status and residency more than half of participants were illiterate and from rural areas 219 (55.3%) and 217 (54.2) respectively.

Clinical and behavioral characteristics

Of the total cancer patients more than half of cancer patients were stage IV 211 (53.02%) followed by stage III 111 (27.89). From the total study participants 209(52.02%) had metastasis and 182 (45.7%) intent of treatment were palliative. From the study participants only 40 (10%) of them smoke cigarettes. Breast cancer is the most frequently encountered tumor type followed by lung cancer which accounted for 175 (43.9) and 44 (11.06) respectively. Regarding chemotherapy regimen, near one fourth of participants were on AC 97 (24.3%). Besides, of the total study participants 138 (34.8%) were underweight.

Incidence of anemia

Three hundred ninety-eight cancer patients were followed for different periods in five years which produced 34,149 Person Days (PD) of observation. Within the follow-up period, 196 patients developed anemia during the course of chemotherapy which gives an overall incidence density of 5.71cases (95% CI: 4.963-6.57) per 1000 PD (normocytic 61.73%, macrocytic 2.55 %, microcytic 35.71%, normochromic 52.04%, hyperchromic 7.65 %, hypochromic 40.31%). Besides, the incidence of anemia in breast cancer patients was found to be 67 (34.1%) and gastrointestinal cancer 54 (27.5%).

Comparison of survival experience by different factors (non-parametric tests)

Using Kaplan-Meir survival curve, the survival experience of the patients was assessed against different categories of the predictor variables and log-rank test to check the statistically significance of the survival difference. Patients with normal BMI (above 18.5 kg/m^2) had longer survival than those adults with low BMI (<18.5 kg/m^2) and this can be Confirmed by Log-rank test which indicated that there is statistically significant difference between survival experience of low and normal BMI (Log-Rank, p<0.001). The observed difference of longer survival of patients who had no metastasis compared with those adults who had metastasis was found to be statistically significant (Log-Rank, p<0.001).

Assessing proportional hazard assumption

The proportional hazard assumption was checked both graphically and Schoenfeld residuals test (global and scaled) for all possible predictors of Anemia. Just to show for some of the variables -Ln (-Ln (survival probability) to Ln (analysis time) for sex and metastasis was demonstrated graphically. Accordingly, the hazards do not cross between categories of sex and metastasis, which means that the proportional hazard assumption was satisfied for these variables. Moreover, to test the proportional hazard assumption objectively, the Schoenfeld residuals test was done, and the global test was found to be 0.11.

Predictors of anemia

Non-parametric comparison of survival: Based on the Kaplan-Meir survival curve and log rank test, patients with normal BMI and no metastasis were found to have better survival than their counter parts.

Cox-proportional hazard model: In multivariable Cox regression analysis, BMI, and metastasis were found to be significantly associated with the outcome. The hazard of chemotherapy induced anemia among cancer patients who has metastasis was 2.34 times higher as compared with their counterpart (AHR=2.79; 95% CI: 1.59-4.88). The hazard of chemotherapy induced anemia was 2.41 times higher among participants with underweight compared to their counterparts. (AHR=2.12; 95% CI: 1.12-4.00).

Discussion

In the UoGCSH, this retrospective cohort study evaluated the prevalence and risk factors for anemia among cancer patients receiving chemotherapy. Anemia among chemotherapy patients was shown to be substantially linked with participants who had metastases and were underweight. 49.2% per 1000 person days was reported to be the overall incidence of anemia. This result is consistent with research from the European Cancer Anemia Survey (ECAS), which assessed the prevalence of anemia in European cancer patients and found that it was 53.7% [20]. However, on the one hand it's lower than the study from Kaiser Permanente Southern California revealed that the incidence of chemotherapy induced anemia in solid tumors was 89.5%. Variations in patient characteristics, disease features, and treatment characteristics can be used to explain the discrepancy in incidence rate. On the other hand, this study's anemia incidence was higher than studies done in Iran and Italy, showing anemia incidence to be 10.1% and 22.4%, respectively [21,22]. This mismatch can be caused by a difference in how the term "outcome of measurement" is defined. According to the National Cancer Institute's grading system, the current study used a cutoff value of haemoglobin levels less than 14 g/dL for men and 12 g/dL for women; in contrast, anemia was diagnosed in studies from Iran and Italy when haemoglobin levels were less than 8 g/dL and 10 g/dL, respectively.

According to this study, cancer patients who had metastases had a higher risk of developing anemia. A study carried out in the USA lends credence to this [11]. This could be explained by the fact that several malignancies, including breast and prostate cancer, can migrate to the bone marrow because it is a significant and frequently involved location of metastasis for solid tumours [23]. Once bone marrow metastasis happened, it affects the normal haemopoiesis (interfere with red blood cell production) and leading to anemia [24].

This study indicated that, compared to the control group, being underweight increased the risks of chemotherapy-induced anemia.

This conclusion is backed by a French investigation [25]. The significance of this statistic can be explained by a typical chemotherapy dose calculation that accounts for Body Surface Area (BSA), which is thought to be less accurate for patients with low BMI [25]. As a result, large chemotherapy doses that cause anaemia may result. Additionally, nutritional deficiencies in cancer patients with low BMI may be brought on by appetite loss, immune-mediated antibodies that produce hemolysis or adjustments to the body's ability to clot. As a result, anemia is common in cancer patients with low BMI.

The fact that the current study is the first of its kind in Ethiopia and includes the majority of solid tumors is one of its strengths. In addition, the authors of the current study firmly feel that it is crucial to provide evidence regarding the prevalence of chemotherapy-induced anemia and its determinants among cancer patients. Due to the retrospective nature of the study, we were unable to account for additional causes of anemia, such as chronic illness-related anemia and unmeasured confounders such patient income.

Conclusion

In patients with solid tumors receiving chemotherapy, the frequency of chemotherapy-induced anaemia was significant. Patients with metastases and underweight cancer had a higher incidence of anaemia. Therefore, it is preferable to regularly measure BMI and check all chemotherapy patients for the occurrence of metastases. To lessen the risk of anemia-related morbidity, patients with anaemia should be continuously watched, and a diligent management strategy may be used. Additionally, to identify and treat chemotherapy-induced anaemia early on, this study urges all oncologists and medical professionals to adhere to the National Comprehensive Cancer Network (NCCN) Clinical Practise Guidelines in Oncology.

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