

A Prospective Study on Chemotherapy Induced Anemia Using Serial Hemoglobin Measurement in Cancer Patients Undergoing Treatment at National Hospital Abuja, Nigeria

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Abstract

Objectives: Anemia is a common complication of myelo-suppressive chemotherapy. Severe anemia is treated with red blood cell transfusion. Mild-to-moderate anemia are managed conservatively. There is no established benchmark for hemoglobin of patients to guide a global best practice and enhance treatment outcome. This study examines the change in Hb levels of cancer patients undergoing chemotherapy measuring Hb after treatment.

Methods: About 100 voluntary patients with solid malignancies were recruited within 8 months. Baseline demographic characteristics and tumours types were documented. Pre-treatment Hb level was measured on the first day of consultation and repeated every 2 weeks during and after the therapy until after three consecutive Hb readings.

Results: Breast 68% (68) was the commonest site of tumor. Prevalence of anemia was 72% and most patients had their Hb within the range of 9.60 to 10.62 g/dl after treatment. At P-value >0.05 and SD there was no statistical significance on distribution of mean hemoglobin values, were independent of sex and type of treatment.

Conclusion: Chemotherapy has no effect on Hb level between 11 to 12 g/dl. Prevalence of anemia in the cohort of patients was 72%. We recommend a benchmark minimum of Hb of 11 g/dl for patients.

Keywords: Cancer • Patients • Chemotherapy • Haemoglobin • Anaemia • Tumour

Introduction

Anemia is a common complication of myelosuppressive chemotherapy that results in a decreased functional capacity and quality of life (QoL) for cancer patients. More than 70% of cancer patients will receive treatment especially in resource poor countries like ours where late presentation, treatment delays and lack of access to radiation oncology centres, are still a huge problem. Severe anemia is usually treated with red blood cell transfusion because of its urgency and life-threatening effect. However, mild to moderate anemia in cancer patients receiving chemotherapy has been most often managed conservatively based on the perception that it was clinically unimportant. Hemoglobin level of 10g/dl as currently used in most of the Radiation Oncology centres in Nigeria is a borderline value and administration of chemotherapeutic agents without adequate hematological support will push the patient into clinical anemia.

It has been difficult to establish a global or National benchmark for the baseline hemoglobin of patients selected for cancer therapy especially at different stages of the malignancies. This practice reflects on the relative lack of attention paid to standardized and complete reporting of various degrees of chemotherapy induced anemia. In a large multinational study by [1] dubbed European Cancer Survey (ECAS) incidence of anemia in cancer patients undergoing chemotherapy, it was found to be increasing

with each cycle of chemotherapy. In cycle 1, incidence of anemia was 19.5%, this steadily increased to 34.3% at cycle 2, 42.0% at cycle 3, and to 46.7% in cycles 4 and 5. Moreover, that patients become anemic within the first 2 cycles of chemotherapy was further demonstrated by study carried out by Barrett-Lee et al. [2] using 1,821 cancer patients who began receiving chemotherapy at Hb \geq 12g/dl and analyzed to determine relative risk for anemia. This study showed that 62% of patients experienced a Hb decrease of 1.5g/dl within a average of 6.1 to 7.2 weeks and 51% had a decrease of 2g/dl within a median value of 7.3 to 8.9 weeks. While correction of anemia is very critical to the Clinician, patient awareness is an important aspect of active anemia management. National Comprehensive Cancer network (NCCN) recommended that Hb level \leq 11g/dl or \geq 2g/dl below baseline should be promptly evaluated for anemia in order to characterize the anemia and correct any underlying comorbidities [3]. At this point, a detailed record taking, physical examination and laboratory tests which include a complete blood count with indices, onset of symptoms, comorbidities, and exposure to antineoplastic drugs and radiation needs to be ascertained. ASCO/ASH recommends that clinicians also discuss the benefits and disadvantages of the therapeutic options with patients undergoing myelotoxic chemotherapy who become anemic [4].

Symptoms of anemia are often related to the hypoxia-related effects on tissues and organ function. The signs and symptoms of anemia include pallor of the skin and mucous membranes, shortness of breath, palpitation of the heart, soft systolic murmurs, lethargy and quickly becoming tired [5,6]. The pathophysiology of cancer-related anemia have been studied and found to be multifactorial [7]. Anemia usually occurs as a result of direct inhibitory effects of inflammatory cytokines, erythropoietin deficiency, blunted erythropoietin response, blood loss, nutritional deficiencies, reduced renal function and socio-cultural factors such as avoidance of egg in some village setting. In addition, treatment associated factors may aggravate the incidence of anemia and these may compromise patient's tolerance to treatment [8]. Dose-escalation chemotherapy regimen and combined modality schedules

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of chemotherapy and radiotherapy may also result in a higher degree of anemia.

Although anemia is not well tolerated in cancer patients, aggressive treatment of anemia can be just as detrimental as no treatment. According to National Cancer Comprehensive Network NCCN, anemia is defined as inadequate circulating level of hemoglobin or red blood cells compared to those that are normal for the individual [9]. Anemia is further classified based on severity by NCCN into mild (10g/dl), moderate (8.0- 9.9g/dl), severe (6.5 – 7.9g/dl) and life threatening less than (< 6.5g/dl) [9]. In a separate study by Ludwig¹ et al using 14, 912 cancer patients in the European cancer anemia survey, a prospective observational survey found that enrolled patients regardless of the disease status or cancer treatment, showed a significant correlation between Hb level and performance status at enrolment. This observation was strengthened by a study carried out by Natacha et al using 1, 403 cancer patients. They found that there was a correlation between the severity of anemia and WHO performance status of patients [10].

The influence of tumor type on the degree of anemia has been widely examined. In a systematic review of 60 papers, Carol and Colleagues measured the survival of cancer patients according to either Hb level or the presence of anemia and found that the relative risk of death varied with cancer type [11]. This was supported by work done by Ludwig¹ et al. They examined 9,118 cancer patients using Hb level less than 12g/dl as the baseline value to study frequency of anemia in various cancer types. The results of these studies documented breast cancer 26%, lung cancer 48%, colorectal 33%, head and Neck 46%, Gynecological – 43%, Lymphoma and Myeloma- 47%, Leukemia- 53%, Urogenital- 43% and others – 37%. The frequency was 39.3% at enrollment and 67% during therapy. This was supported by work done by Hendenus and his colleagues [12] on prevalence of anemia among cancer patients at presentation and also during treatment. This was found to be in the range of 10-39% at presentation and 87% during treatment. Anemia

was also observed in approximately half of patients receiving platinum – anthracycline, taxane or gemcitabine-based chemotherapy regimen [13]. Evaluation of anemia is a very important factor in cancer patients undergoing chemotherapy as hypoxic cells are known to be 2-6 times more chemo resistance than oxic cells [14]. Although, considerable progress has been made in alleviating many of the common toxicities arising from cancer and its therapy, certain complications such as anemia are still under diagnosed, under-treated and under-reported, and yet the prevalence of chemo-induced anemia in patients undergoing treatment for cancer still remain undetected and high.

Materials and Methods

A prospective study on chemotherapy-induced anemia in cancer patients undergoing treatment using serial hemoglobin measurement was carried out. It involved 100 patients with histopathologically confirmed diagnosis of cancer (solid cancers) that were referred to the Radiation oncology unit of hospital. Patients were enrolled after obtaining informed consent and ethical approval from hospital management. Voluntary participation and confidentiality were ensured. Patients World Health organization (WHO) performance status was chosen as 0 and I. All the enrolled patients had their baseline or pre-treatment Hb levels measured on the first consultation. Those who met the inclusion criteria were followed in the course of treatment by measuring

their on-treatment Hb level once every two (2) weeks. Blood film pictures of the patients were examined during treatment. This serial on-treatment Hb measurement was terminated after three (3) consecutive determination of Hb concentration level i.e. (six (6) weeks). The chemotherapy regimen, frequency of administration, dosage, route of administration and number of cycles were recorded.

All data were analyzed using IBM statistical package for Social Science (SPSS) version 20. Continuous variables were summarized using mean and standard deviation (SD). Categorical variables were summarized as proportion and percentages. Comparison of mean Hb level based on sex was made using the student T- test at significant P- value level of ≤ 0.05.

Anemia was classified for this study into: less than 10g/dl-severe anemia, 10- 10.9g/dl-moderate anemia, 11- 11.9g/dl- mild anemia, 12g/dl and above- no anemia.

Results

Table 1 shows demographic characteristics of the studied patients. Majority of patients were aged 35-44 years and were females, 88. (88.0%)

Table 2 shows that most patients that were of status 0 were females 40(83.3%) as well those of status 1 female 48 (92.3%). Also, the table shows that there was no statistical difference between males and females Hb level (P> 0.05).

Table 3 shows Distribution Hb and blood film over week 6 chemotherapy treatment.

Figure 1 shows that majority of the patient 68 (68%) had breast cancer while 3 (3.0%) had lung cancer.

Figure 2 shows that majority of the patients (72%) had stage III disease and received chemotherapy.

Figure 3 shows that there was gradual but continuous fall in haemoglobin level during chemotherapy treatment over 6 weeks.

Discussion

In this study involving 100 cancer patients undergoing chemotherapy were followed for over 6 weeks with serial hemoglobin measurements every 2

Table 1. Demographic characteristics of the studied patients on Chemotherapy.

	N = 100
Age group (Yrs)	n(%)
25-34	17 (17.0)
35-44	36 (36.0)
45-54	22 (22.0)
55-64	21 (21.0)
65-74	3 (3.0)
75x	1 (1.0)
Sex	
Female	88 (88%)
Male	12 (12%)

Table 2. WHO performance status and relationship of Sex with MeanHaemoglobin.

WHO performance status	N = 100		
	Number	Male n = 48	Female
Status		n(%)	n(%)
0	48	8 (16.7)	40(83.3)
1	52	4(7.7)	48(92.3)
Mean Hb difference			
Mean(SD)	11.72 (0.88)		11.65 (1.21)
T test (p Value)	0.53(>0.05)*		

* Not significant

Table 3. Distribution Hb and blood film over week 6 chemotherapy treatment.

	Week 0	Week 2	Week 4	Week 6
Haemoglobin g/dl				
Mean (SD)	12.55 (0.90)	12.18 (0.93)	12.02 (1.10)	11.83 (1.50)

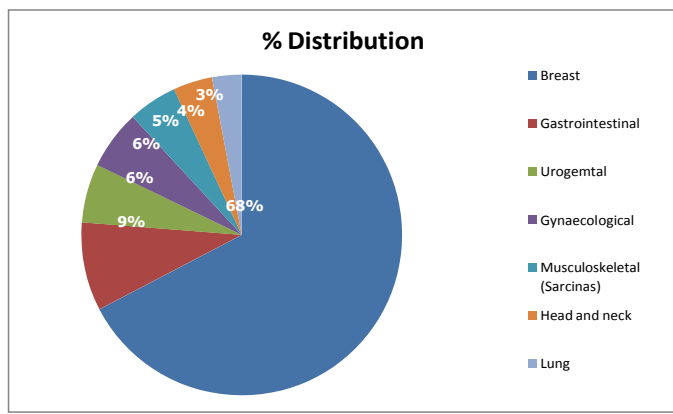


Figure 1. Percentage distribution of tumour site.

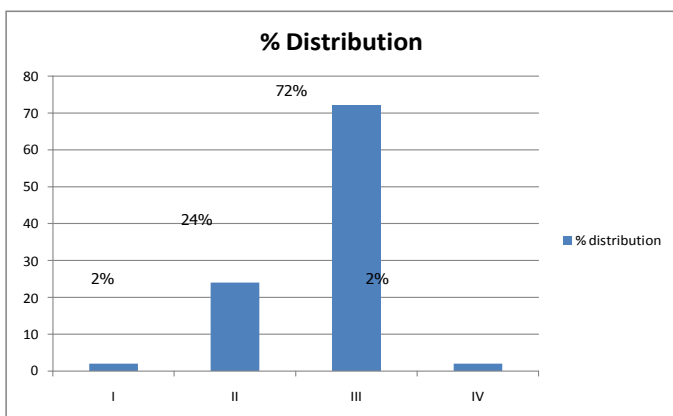


Figure 2. Shows tumour stage and treatment type percentage distribution.

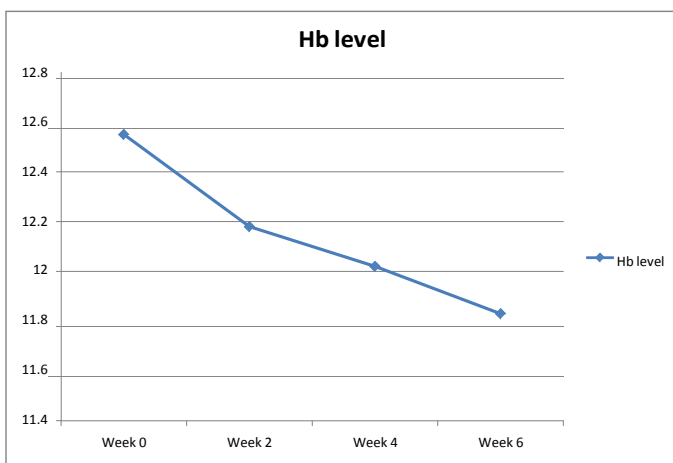


Figure 3. Shows the trend of Hb changes over weeks.

weeks, majority of the patients were female which constituted 88% of the studied group. The predominance of women of this study was in agreement with previous studies carried out by other researchers [1,15], for example Jedy-Agba et al. [16] using a population based cancer registries in Abuja and Ibadan, Nigeria also found that female were in majority among the studied group. In a separate study by Ferlay et al. [17] using GLOBOCAN 2012 estimate of cancer incidence, mortality and most common cancer in Nigeria found that among 102,100 new cases seen, 37,400 new cases occurred in males while 64,700 occurred in females. In a study carried out in Ghana, the age-standardized incidence rate (ASR) was found to be 89.1 and 104.1/100,000 for males and females respectively [18]. In another study in United Kingdom using population – based cancer registries, age- standardized incidence rate (ASR) was found to be 412 and 315/100,000

in male and female respectively within the period of 1993-1995 and 409 and 348/100,000 inmale and female respectively between 2002 and 2004 [19]. The outcome from this study was in contrast to earlier findings which showed that incidence of cancer was more common in females than males. Further studies by other researchers showed that male cancer patientswere generally ahiger proportion than female cancer patients [20-22]. Our findings may be explained that majority of the patients presented with locally advanced breast cancer and required neoadjuvant chemotherapy due to the stage of the tumor. Also, females tend to express health concern more readily than male patients and are more willing to see the Physician than their male counterparts.

In this study the age range of the cancer patients analyzed was between 25-75 years with a median value of 50 years. Majority of the patients were in age range 35-44 years which constituted 36% of the 100 patients. This early age at which cancer is diagnosed in our study group may be an opportunity for early cancer screening test among the Nigerian population. This group is an active work force and also within reproductive age group which is detrimental to economic growth and development of the country as the dependent ratio may be increased. This report was in contrast to median age of cancer patients evaluated in other studies in Europe where cancer cases were found mostly in the middle age and elderly patients. The median age of cancer patients was found to be above 55 years in a number of studies [16,23].

Regardless of the aetiology of anemia among cancer patients, uncorrected anemia has been found to be associated with poor functional ability [24], and with increased mortality [25]. Some researchers have demonstrated an association between anemia and performances statususing either the European Cooperative Oncology group performance scores (ECOG-PS), World Health Organization (WHO) performance status and Karnofsky Performance Scale (KPS) [26,27]. The correlation between patient's WHO performance status and Hb levels was elucidated by Natacha et al. in their study of 1,403 cancer patients [28]. These previous studies justified our selection of patients with WHO performances status of O and I in order toreduce confounding factors in this study.

There was a gradual decrease in hemoglobin level with increasing number of chemotherapy cycles in our study. This was observed as patient went from week 0 to week 6. At the end of therapy 72% of the patient were anemic. This observation was supported by studies carriedout by other researchers [2,28,29]. They all observed increased incidence of moderate to severe anemia with increasing cycles of chemotherapy among cancer patients with solid tumors.

In our study, breast cancer was found to be most common tumor site (68%) in cancer patients undergoing chemotherapy. This was supported by other studies in Nigeria and other parts of the world. In Nigeria, and Institute of Human Virology of Nigeria (IHNN) [30] analyzed data using population- based cancer registries in Nigeria. Breast was found to be the most common female cancer. This finding was supported by other researchers in various institutes that carried out epidemiological studies on cancer [17,19,31,32]. Majority of the cancer patients (72%) presented with stage III disease. In Nigeria as in most developing countries, late presentation with unfavourable prognosis is common [33].

Conclusion

Our finding was supported by studies done by other researchers which showed that most cancer patients in resource poor countries present with locally advanced disease. Chemotherapy has a significant role as neoadjuvant, adjuvant or palliative treatment modality in locally advanced diseases in a setting of poor resourced health facilities; additionally there is a lack of oncologists and related expertise to coordinate cancer research.

Limitations of the Study

We agree here that late presentation and patients' performance status alone

may not explain all about the prevalence of anemia in our sampled patients, consideration were given to other determinants such as co-morbidities, sociocultural factors in cancer, belief systems and health seeking behavior, patient age and genetic factors which are both limitations and also beyond the scope of this research. We recommend another in-depth research that will expand on these factors. This work might also be limited by the sample size which might not have been sufficient for making generalized conclusive statements. There are also few studies in this area which can be used as a point of reference.

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Conflict of interest

This research work is original and has not been published in any journal but has been presented in abstract form with the knowledge of the authors. It is our wish to publish this work taking cognisance of challenges of chemotherapy induced anemia in patients undergoing chemotherapy using serial hemoglobin measurement in National Hospital Abuja, Nigeria. Nigeria has high cancer prevalence with history of late presentation and advanced stage of the disease thereby necessitating the use of chemotherapy as part of neoadjuvant, adjuvant and palliative treatment. These chemotherapy which are used in various forms and cycles have the overall effect on the hemoglobin level of the patient. It is necessary to monitor patients on chemotherapy in resource constrained environments like Nigeria because of cost implication of managing anemia and its complications. Most patients with advanced stage of disease do benefit from intermittent blood transfusion as there are limited access to recombinant human erythropoietin. This paper is to measure the effect of chemotherapy on the hemoglobin over several cycles. This is to guide Clinicians on how to avert chemotherapy induced anemia. Low hemoglobin level or anemia has been found to be independent prognostic factor in disease free survival and over survival of cancer patient. This paper is to advance frontiers of knowledge and a reminder to Clinicians on importance of monitoring dose of chemotherapy as well as patient performance status.

There is no conflict of interest to declare.

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