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REVEIW ARTICLE

ANAEMIA IN CANCER PATIENTS UNDERGOING RADIOTHERAPY: OUR EXPERIENCE AT THE NATIONAL HOSPITAL ABUJA, NIGERIA

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ABSTRACT

Introduction: Anaemia is the commonest haematological complication in cancer patients with aetiology usually multifactorial. The cut-off value for anaemia vary from centre to centre but a haemoglobin (Hb) level of 12g/dl in male and 11g/dl for female is usually acceptable in most Radiation Oncology Centres in Nigeria for therapeutic purposes. Administration of radiotherapy without adequate haematological support may tilt the patient into clinical anaemia. The study aims to ascertain the effect of radiotherapy on the haemoglobin level of cancer patients undergoing therapy.

Materials and Methods: Patients with solid tumours with intent for radical treatment were recruited within a period of 8 months. Informed consent of participants was obtained. Demographic characteristics of the cancer patients and their various oncologic diseases were gathered. Baseline Hbandblood film pictures were measured on the first day of consultation then once every 2 weeks for 6 weeks. Data collected were summarized and presented in tables.

Results: Out of 63 cancer patients, 92.1% were female. Mean and median ages of patients were48.55and 50 years respectively. Breast 47.6% (30) was commonest tumour while 74.6%(47) presented with stage III disease. Prevalence of anaemia in the study was 42.9%. At the end of therapy 55.6% (63) cancer patients had their Hb level between 11.52 – 12.13g/dl.

Conclusion: Prevalence of anaemia in cancer patients undergoing radiotherapy was high. Female group dominated the study population. Patients had a downward trend in their Hb level as their treatment progressed thereby calling for need early identification and timely intervention.

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INTRODUCTION

Anaemia as seen in most clinical situation in cancer patients is haematologically similar to that of the chronic anaemia except that the onset is generally sudden. The aetiology is usually multifactorial especially in our environment where many cancer patients hardly present early or have access to Radiation Oncology centres (Miller, 1990). Anaemia usually occur as a consequence of direct inhibitory effect of inflammatory cytokines, erythropoietin deficiency, blunted erythropoietin response, blood loss, nutritional deficiencies, renal insufficiency, socio-cultural and religious factors. Also, treatment associated factors may aggravate the incidence of anaemia and these may compromise patient's tolerance of treatment (Demitri, 2001). Although anaemia is not well

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tolerated in cancer patients, aggressive treatment of anaemia can be just as detrimental as no treatment. According to National Cancer Comprehensive Network (NCCN) (National Comprehensive Cancer Network, 2009), anaemia is defined as inadequate circulating level of haemaglobin or red blood cells normal for an individual. Anaemia is further classified based on severity by NCCN[3] into mild (10g/dl), moderate (8 – 9g/dl), severe (6.5 – 7.9g/dl) and life threatening less than (< 6.5g/dl). However, the cut-off value of Hb level in anaemia vary from centre to centre. A common anaemia related problem is fatigue, which impairs the patient's ability to perform normal daily activities (Ludwig, 2001). However, a study done by Birgegard and his colleagues (Birgegard, 2005) revealed other common signs and symptoms of anaemia such as dizziness, depression, tachycardia, exertion dyspnea, palpitation, risk of cardiac failure, menstrual problem, loss of libido, anorexia, nausea, pallor of the skin, impaired cognitive function, impaired T cell and macrophage function.Generally, patients with low haemoglobin have a reduced loco-regional tumour control and survival probability. While several mechanisms can be proposed to explain this relationship, tumour hypoxia is clearly one of the major factors. Several studies have shown that tumours are more hypoxic than the surrounding normal tissue (Molls, 1998). Tumour cells can become resistant to cancer treatment because of hypoxia; this is due to decrease oxygen transport capacity as a result of tumour associated anaemia. Hypoxic regions have been identified by Nordsmark*et al* (Nordsmark, 1996) in locally and advanced breast and cervical cancers, head and neck cancers, rectal cancer, brain tumours, soft tissue sarcormas and malignant melanomas.

Anaemia is a frequent complication in cancer seen in up to 75% of patients with malignancies (Groopman, 1999). It can occur in up to 40 – 50% of cancer patients even before they start treatment. After initiation of radiotherapy, chemotherapy or chemoradiation, the incidence of anaeemia may climb up to 90%. This observation was supported by work done by Hendenus and his colleagues (Hendus, 2007) on cancer patients at presentation and also during treatment. This was found to be at the range of 10-39% at presentation and 87% during treatment with erythropoietin stimulating agents(ESA_S) .Another study done by European Cancer Anaemia Survey (Ludwig, 2004) indicated that prevalence of anaemia (Hb< 12g/dl) among 15,367 cancer patients was 39.3% at enrollment and 67% during survey. The Surveillance, Epidemiology and End Result (SEER) programme of the National Cancer Institute (NCI) estimated cancer incidence in the United States to be approximately 75% in persons greater than 60 years of age (National Cancer Institute, 2011). The Institute of Human Virology of Nigeria (IHVN)) analyzed data from 11 Hospital Based Cancer Registry programme in Nigeria from 2009 – 2010. They described the role of hospital cancer registry and how their data can be beneficial to improving healthcare system in low and middle income countries in general.

This study by IHVN revealed that the commonest five cancers in males and females reported by 11 Hospital Based Cancer Registry in Nigeria between 2009 – 2010 were as follows: Male – Prostate cancer (29.2%), colorectal (7%), lymphoma (6.8%), liver cancers (4%), skin cancers (3.8%) (Institute of Human Virology bf Nigeria, 2012). In female the commonest cancers were as follows: Breast cancer (40.4%), cervical cancer (17.3%), ovarian cancer (3.7%), lymphoma (3.1%) and skin cancers (2.1%). The conclusion of the study was that breast and cervical cancer account over 60% of all cancer cases affecting Nigerian women. While in the males, prostate and colorectal cancers are the most common cancers in males aged 45 years and above (Institute of Human Virology bf Nigeria, 2012). In another study done by Sa'adatu *et al*, on cervical cancer patients in Zaria, Northern Nigeria using 70 female patients with cancer of cervix revealed that anaemia occurred in 34.29% of them requiring blood transfusion (Sa' adatu, 2007). The impact of anaemia on radiotherapy has been well investigated. In a retrospective study of 889 patients of head and neck tumour treated with radiotherapy, long term outcome were evaluated (Frommhold, 1998). The estimated five-year survival rate for patients with Hb less than 13g/dl for males and less than 12g/dl for females was 58.2% compared with 28.4% for patients with Hb level below these respective values ($P < 0.0001$). Dische *et al*has shown that a group of 37 patients treated with 6 fractions of radiotherapy regimen for cancer of the lung and with aHb concentration level of less than 13g/dl had worse survival than 72 cases with Hb greater than 13g/dl. (Dishe, 1986). In another study by Warde *et al* using 735 patients with T_1/T_2glottic cancer treated with radiotherapy alone, the pretreatment Hb level was found to be independent prognostic factor for loco-regional control (Warde, 1998). This observation was in agreement with previous studies on effect of pre-treatment Hb level on response to cancer therapy. Another study from Kiel Germanyexamined 96 patients with cancer treated with radiotherapy with doses rangingfrom30-60 Gray. A shorter survival was seen in eight (8) patients or Hb less than 11g/dl irrespective of radiation dose delivered. This report was significant as it emphasized the importance of Hb concentration level in overall survival and quality of life of cancer patients undergoing radiotherapy irrespective of radiation dose. In different studies, Hong *et al* found that there was a trend of partial response to radiotherapy being associated with lower Hb level that did not reach statistical significance (Hong, 1991). This result was not surprising as many confounding factors may have influenced the outcome of this result.

Harrison *et al* found that 202 randomly selected patients who were referred for Radiation Oncology evaluation, and who ultimately received radiotherapy. The results showed that 48% of these patients presented with anaemia, defined as Hb< 12g/dl and a total of 57% ultimately became anaemia by the end of therapy (American Cancer Society, 2012). Their studysupported that anaemia was more common in female than male when stratified by sex, 32% of male and 57% of female presented with anaemia, which increased to 51% of men and 64% of women by the end of treatment (American Cancer Society, 2012). Many studies have documented the association between anaemia and poor outcome in cancer of head and neck, respiratory track, pelvic and genito urinary organs (Kumar, 2000). In another study, Overgaard *et al* were among the first investigators to observe a correlation between loco-regional tumour control and haemoglobin concentration.[21]In one report, men with prostate cancer experienced increase in anaemia during radiotherapy (Bush, 1986). Tarnawski *et al* analyzed 847 cases of supraglottic laryngeal cancer managed with radical radiotherapy revealed that haemoglobin concentration throughout treatment was a more significant prognostic factor than pre-treatment haemoglobin (Tarnawski, 1997). They were of the view that on-treatment haemoglobin level has more influence on treatment outcome than baseline or pre-treatment haemoglobinlevel. Although blood transfusion is the fastest means to alleviate anaemia-related symptoms, there are both short and long term risk associated with it (Bohlius, 2005). Treating anaemia with blood trasnfusion can be

associated with problems of allo-immunization, allergic reactions, circulation overload, immune suppression (Vaupel, 1989), short-lived elevation in Hb level (Barret-Lee, 2000) and lack of blood supply in many countries. The use of erythropoietin (rhEpo) overcomes many of these drawbacks and has been shown to reduce transfusion requirement (Casinu, 1994) and increased quality of life (Case, 1993). Evaluation of anaemia is very important in cancer patients undergoing radiotherapy and chemotherapy as hypoxic cells are known to be 2 – 6 times more radio-resistance and chemo-resistance than aerated cells (Teicher, 1990).

MATERIALS AND METHODS

This study was at National Hospital Abuja. The hospital provides both in-patient and out-patient services. It provides services in the various department; surgery, radiology, pediatrics, obstetrics gynecology, internal medicine, laboratory medicine, family medicine as well as special clinics. Hospital based prospective study was done. A total of 63 patients with solid malignances with intent for radical treatment were recruited within a period of 8 months (September 2012 – May 2013). Those excluded from the study includes; palliative intent, patients less than 18 years of age, haematological malignancies, patients on follow-up or irregular with treatment, Hb< 12g/dl for male, Hb< 11g/dl for female, WHO performance status less than 2. Approval was by the National Hospital Abuja, Nigeria Research and Ethics Committee. All the participants gave their written informed consent. Data on demographic characteristics and their oncologic diseases were gathered. Patient's baseline or pretreatment Haemoglobin (Hb) were measured on the first day of consultation. Patients were simulated and treated with Linear Accelerator at 2Gy per fraction. The Hblevels of the participants were measured once every 2 weeks in the course of radiotherapy. Also their blood film pictures were read and analyzed. The whole process was terminated after 3 consecutive haemoglobin reading or after week 6. Anaemia was classified for this study into:severeanaemia (<10g/dl), moderate anaemia (10 – 10.9g/dl), mild anaemia (11 – 12g/dl) and normal(> 12g/dl).

Data was collected and analyzed using Standard Statistical Package for Social Science (SPSS) version 10. They were summarized in proportion and percentages for categorized groups while uncategorized quantitative variables were summarized using mean and standard deviation. They were presented in tables.

RESULTS

Table 1. Demographic of the patients

Variables	Frequency (n=63)	Percent(%)
Age in categories((Yrs)		
25 – 34	11	17.5
35 – 44	19	30.2
45 – 54	10	15.9
55 – 64	11	17.5
≥ 65	12	19.0
Mean (Std Dev)	48.55(6.32)	
Sex		
Male	5	7.9
Female	58	92.1

Table 1 shows that majority of patients were aged 35-44 years 19(30.2%). Age range of the patients was between 25 – 75 years, with a median age of 50 years, meanage of 48.55 and standard deviation of 6.32 years. They were mainly females 58(92.1%).

Table 2. Distribution of Tumour Site, stage of tumor and WHO Performance Status by Sex

Variables	Frequency (n=63)	Percent(%)
Tumour Site		
Breast	30	47.6
Gastrointestinal	-	-
Head and Neck	5	7.9
Urogenital	10	15.9
Gynaecological	14	22.2
Musculo skeletal (sarcomas)	2	3.2
Lung	2	3.2
Stage of Tumor		
I	1	1.6
II	15	23.8
III	47	74.6
IV	-	-
	Status	
WHO Performance Status by Sex	0	1
Male	3	2
Female	35	23

Table 3. Distribution of Hb and blood picture by duration of treatment for patients

	Treatment Duration			
Variables	n=63			
	Week 0	Week 2	Week 4	Week 6
Hbg/dl	n(%)	n(%)	n(%)	n(%)
<10	-	-	1(1.6)	3(4.8)
10 – 10.9	13(20.6)	15(23.8)	21(33.4)	20(31.7)
11 – 12	38(60.3)	42(66.7)	35(55.5)	35(55.6)
12+	12(19.1)	6(9.5)	6(9.5)	5(7.9)
Mean (Std Dev)	12.60(0.98)	11.92(1.40)	11.29(1.05)	10.89(1.18)
Blood picture	n(%)	n(%)	n(%)	n(%)
Normocytic Normochromic	48(76.2)	42(66.7)	36(57.1)	36(57.1)
Hypochromic	6(9.5)	11(17.5)	16(25.4)	17(27.0)
Macrocytosis	2(3.2)	-	2(3.2)	-
Microcytosis	2(3.2)	-	-	-
Poikliocytosis	1(1.6)	2(3.2)	-	-
Anisocytosis	1(1.6)	2(3.2)	5(7.9)	2(3.2)
Elliptocytosis	1(1.6)	1(1.6)	1(1.6)	4(6.3)
Dimorphic Picture	2(3.2)	5(7.9)	3(4.8)	4(6.4)
Target Cells	-	-	-	-
Blast cells	-	-	-	-

Table 2 showed that out of 63 cancer patients, Breast constituted commonest site 47.6% followed by Gynaecological tumors 22.2% with no Gastrointestinal tumor. Majority of the tumors were at stage III of the disease 74.6%. Of 5 tumors in

males 3 were at stage 0 while out of 58 in females 35 were at stage 0. Table 3 showed percentage distribution of Hb level by duration of treatment for patients. There was gradual fall in the Hb level from week 0 to week 6, while week 0 is defined as the time from initial administration of dose of radiation to the first 2 weeks. The mean and standard deviation of Hb level from week 0, week 2, week 4 and week 6 were given as 12.6g/dl (0.98), 11.92g/dl (1.40), l1.29g/dl (1.05) and 10.89g!dl (1.18). From the Blood film picture. it was noticed that there were variation in the blood film pattern. At week 0 of radiotherapy, 76.2% of 63 cancer patients on radiotherapy had normocytic normochromic and 23.8% had anaemic blood picture while at end of week 6, about 57.1% of 63 cancer patients on radiotherapy had normocytic normochromic and 42.9% had anaemic blood picture.

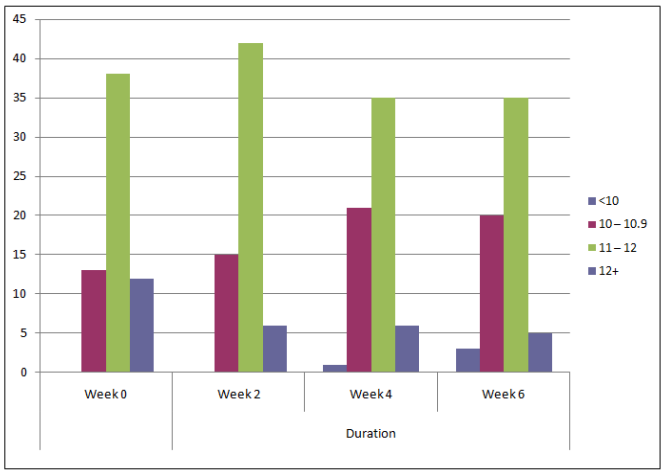

Fig. 1. Bar chart on categories of Hb level based on weeks of treatment

DISCUSSION

In the study, majority of the cancer patients were female. This finding was in agreement with studies done by other researchers (Ludwig, 2004 and Daniel Santini, 2005). The sex distribution above was found to be in contrast to many other studies which showed that male cancer patients generally were in higher proportion than female cancer patients (Natacha Verbeke, 2008; Laurie, 2007; Pilar, 2001; Laura, 2011 and Johan Vansteenkiste, 2002). This higher percentage of female cancer patients may be explained on the account of willingness of female participants in cancer study, and readiness to report to hospital for medical evaluation when sick or routine check than their male counterpart in our environment.Majority of the patients were in age range 35 – 44 years. This report was in contrast to median age of cancer patients evaluated in different studies where cancer cases were found mostly in the middle aged and elderly patients. The median age of cancer patients were found to be above 55 years in a number of studies (Ludwig, 2004; NatachaVerbeke, 2012; Guardiola, 2007; Seshadri, 2005). However, a number of cancers have been identified with risk factors such as low socio-economic, gender, race and geographical area. This view was supported by work done by Cassidy *et al* (Jim Cassidy, 2008). The commonest tumor site from this study was breast and the least was lung. This result was in agreement with other studies which showed that many breast cancer patients undergoing radical mastectomy or breast conservative surgery usually benefit from adjuvant dose of radiotherapy (Chem, 2004; Overgaard, 2007; Recht, 2001). As the female gender dominated this study population and that breast is commonest site in female tumour supported our findings in this work. The percentage distribution by stage of tumour showed that most patients (74.6%) in this study were at stage III disease. This report was in agreement with study done by Kaiser *et al* which showed that 60 – 75% of cancer patients that invariably developed anaemia were at advanced stages. This higher stage in this study may be related to late presentation in the Radiation Oncology Clinic, delay in tumor diagnosis, paucity of Radiation Oncology centres, lack of experience and delay in initiating treatment due to logistics. The implication of this is that most outcome and prognosis is always poor. This is evidenced by the mortality rate related to tumour in our environment.

The percentage distribution of Hb by duration of treatmenet for cancer patients showed that from week 0 to week 2, the effect of radiation on haemoglobin level was not noticed. This observation has radio biological implication as most acute phase reaction is usually noticed after first two weeks of radiotherapy. As haematopoietic, mucosa and crypt of intestinal epithelium are included in these groups of early responding tissues, most reactions from these cells are usually noticed at this time. However, as patients proceeded into week 4 to week 6, the effect of radiation on the haemoglobin level started to be noticed. This is depicted by drop in mean Hb level. There was gradual decline in Hb level as the radiotherapy treatment proceeded from week 0 to week 6. The result of this study was in agreement with work done by Harrison *et al* which evaluated pre-treatment anaemia in cancer patients in radiotherapy clinic and found that 41% of the patients had Hb level below 12g/dl. This result was further strengthened by the report from Amit *et al.* which evaluated pre-treatment anaemia in 300 cancer patients in radiotherapy clinic and found that 54.7% of the patients had Hb level below 12g/dl. Other researchers have confirmed from their findings that radiotherapy has effect on baseline Hb level and also that in patients undergoing radiotherapy that average weekly nadir Hb greater than 12g/dl significantly correlated with improved local control, disease-free survival, predicted cause-specific survival and overall survival (Grogan, 1999; Daly, 2003). This study was further supported by the work done by Dunst *et al* from Martin Luther King University which evaluated initial (0 GY) and mid-therapy (19.8GY) haemoglobin level and tumour oxygenation measurement. Mid-therapy Hb level was found to be the most important determinant of local control and survival. This assertion was supported by another finding that single baseline measurement of Hb level is not the most important but the follow-up Hb level measurement during treatment.[47]Further studies to strengthen our findings were found in the work done by other researchers on pre-treatment Hb value and effect of haemoglobin level on radiotherapy outcome in cervical cancer patients (Lee, 1998; Lee, 2003 and Thomas, 2001). Also, Langendijk *et al* in their study of importance of pre-treatment haemoglobin level in inoperable non-small cell lung carcinoma treated with radical radiotherapy found that higher pre-treatment Hb was associated with better loco-regional control and overall survival (Langendijk, 2003). Kapp *et al* evaluated effect of packed cell red blood cell transfusion in anaemia cervix cancer patients treated with radical radiotherapy with pre-treatment Hb< 11g/dl and treatment Hb> 11g/dl. Their conclusion was that treatment Hb remained predictive for disease-specific survival, pelvic control and metastases-free survival.[52]While our study did not involve overall survival, disease-specific

survival and disease-free survival, the result of various findings point to the importance of pre-treatment and on treatment haemaglobin level in cancer patients undergoing radiotherapy. This study was in agreement with work done by Lee *et al* and Natasha *et al*, who found that prevalence of anaemia in cancer patients to be 55.7% and 64% respectively (Sa' adatu, 2007 and AmitBahl, 2008). Marylou *et al* found a high prevalence and incidence of anaemia in patients with cancer who were admitted into Intensive Care Unit. The prevalence of anaemia was 68% and incidence was 46.6%. The difference between this and our study may be explained by the fact that patients in intensive care unit already had poor performance in status. This study was also in agreement with result from Ludwig *et al* which found that anaemia occurred in 39.7% of patients who did not receive cancer treatment at any time during the survey (Ludwig, 2004).

This study was in agreement with report by Ludwig *et al* which found that cancer patient treated and evaluated after, that anaemia occurred in 28.7% of patients who received radiotherapy.[10]Our study was strengthened by the report of the blood film pictures of cancer patients treated with radiotherapy. It showed that 42.9% (63) of the cancer patients undergoing radiotherapy were anaemic. To reduce a lot of confounding factors which will likely influence the results of this study, all the patients who participated had World Health Organization (WHO) performance status of 0 and I. out of the 63 patients studied, 60.3% (63) had WHO performance status of I.The correlation between patients performance status and haemoglobin level was elucidated by Natasha *et al* in their study of 1,403 cancer patients. They found that there was clear correlation between the severity of anaemia and WHO performance status (Amit Bahl, 2008). In their study there were patients at enrollment with poor performance status at lower Hb level than at higher Hb level. WHO score of 2 – 4 were recorded for 65% of patients with Hb less than 8 and 9.9g/dl, 22% of those with Hb between 10 and 11.9g/dl and 1% of those with Hb> 12g/dl. With this brilliant analysis by Natasha *et al*, it was wise to select patients with good WHO performance status hence the justification for the criteria of recruiting cancer patients with WHO performance status of 0 and I in this study (Amit Bahl, 2008). Also, Kosmidis *et al* observed that at low level of Hb some cancer patients may experience severe anaemia-related symptoms that have a profound effect on their quality of life (QOL), physical and mental functioning and subjective sense of well-being (Kosmidis, 2005).

Conclusion

The prevalence of anaemiaamong patients who had radiotherapy in this study was found to be highas reflected in the blood film. Female group dominated the study population because the commonest tumour site was breast. It was noticed that patients who had initial adequate haemoglobin level for their gender had a downward trend in their Hb level as the treatment commenced. Therefore, it would be reasonable to take a proactive approach in identifying this population of cancer patients who need treatment for radiotherapy induced anaemia and to provide timely intervention. While pre-treatment Hb level measurement is very important, it is the on-treatment Hb level that is very critical as patients with initial adequate Hb value may easily be tilted into clinical anaemia as their treatment progress. We recommend a minimum Hb 11g/dl for any cancer patient selected for Radiotherapy in any Hospital in Nigeria.

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Limitation of the study

Financial implication of the research work limited the number of patients that could have been recruited for the study.

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