ORIGINAL ARTICLE

FACTORS ASSOCIATED WITH INCREASED RED BLOOD CELLS TRANSFUSION REQUIREMENTS IN PATIENTS WITH HODGKIN AND NON-HODGKIN LYMPHOMA

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Background: Anaemia is a common feature of lympho-proliferative disorders and is an important cause of poor quality of life in these patients. When indicated, packed red blood cells (PRBC) units are transfused to treat anaemia. Objective of this study was to identify risk factors associated with PRBC transfusions in lymphoma patients. **Methods:** This was a retrospective study done on Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL) patients who had PRBC transfusions during chemotherapy. Information regarding gender, type of lymphoma, stage, baseline haemoglobin, marrow involvement and total number of PRBC units transfused was collected. **Results**: A total of 481 patients with diagnosis of HL and NHL were registered during one year period. Out of these, 108 (22.4%) had PRBC transfusions during treatment. HL and NHL patients were 30 (27.8%) and 78 (72.2%) respectively. NHL patients were older than HL (37 vs. 32 years), (p=0.03). HL patients had lower mean haemoglobin 9.3±2.56 g/dl as compared to NHL 11.33±2.42 g/dl, (p<0.05). There was significant difference in number of PRBC units transfused based on lymphoma type (NHL 6.74±5.69 vs. HL 3.97±3.0 units, p<0.05). Bone marrow involvement resulted in increased transfusion requirements (7.84±4.36 vs. 5.26±5.49 units, p<0.05) while stage of disease didn't affected significantly (I/II-4.88±4.85 and III/IV 6.30±5.33 units p=0.2). **Conclusion:** A significant number of lymphoma patients need PRBC transfusions during chemotherapy. NHL patients and bone marrow involvement makes patients at higher risk for transfusions. In places, where blood bank support is not adequate, patients should be informed right from beginning to arrange donors for possible transfusions during chemotherapy.

Keywords: Anaemia, Haemoglobin, Lymphoma, Red blood cells, Transfusion

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INTRODUCTION

Lymphomas belong to a group of neoplasms of the hematopoietic and lymphoid tissues that develop from lymphocytes.[1] They account for 3–4% of all cancers and are divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphomas are about 90% of cases and include a large number of sub-types.[2] Treatment involves chemotherapy and immunotherapy/radiotherapy.

Anaemia is a frequent and important cause of comorbidity in patients with cancer, occurring in a large number of patients at some point in their illness and increases the relative risk of death significantly.[3] Anaemia is a common feature in lympho-proliferative disorders and is present in approximately one third to one half of patients on their initial hospital admission.[3] Studies have shown that chemotherapy induced anaemia is a bad prognostic factor in lymphoma patients.[4,5] Moullet *et al* described the incidence of anaemia in 32% of NHL patients and was a significant prognostic factor for overall survival (OS) and progression free survival (PFS) in patients with bone marrow involvement.[5] In another study, the prevalence of anaemia was noted in 44.8% and 41.7% patients of HL and NHL, respectively. The percentage of patients who required transfusion at any time from cycle 1 onwards increased from 0 to 20.4% in Hodgkin Lymphoma and from 5.9 to 33.2% in non-Hodgkin lymphoma.[6]

The anaemia in cancer is multifactorial; including bone marrow involvement, gastrointestinal blood loss, nutritional deficiencies, renal impairment, abnormal iron reutilization, inappropriately low serum erythropoietin levels for the degree of anaemia and a decrease in bone marrow response to erythropoietin.[7] Cytokines of inflammation such as interleukin and tumour necrosis factor-alpha were also found contributing in the development of anemia.[8]

Regardless of the aetiology, anaemia can affect cardiopulmonary, reproductive, and vascular and central nervous system, resulting in a variety of symptoms including fatigue, exhaustion, dizziness, anorexia, nausea, headache, chest pain, dyspnea and depression. Treatment of anaemia not only prevents serious cardiovascular and pulmonary complications but also helps improve quality of life (QoL) in these patients.[9] The traditional method of increasing

haemoglobin (Hb) levels in patients with severe cancer associated anaemia has been blood transfusion. Despite the inconvenience, cost, and potential risk associated with this, blood transfusion remains common practice in symptomatic patients.[10] Packed red blood cells (PRBC) were usually transfused empirically when haemoglobin concentrations declined below 10 g/dl. Transfusion trigger of <8 g/dl leaves thousands of patients with potentially debilitating mild-to-moderate anaemia (Hb 8–12 g/dl) that can significantly impair QoL, even if it is not life threatening in itself.[11] PRBC transfusions are associated with complications including haemolytic reactions, febrile episodes, infections, iron overload and possible adverse effects on the immune system.

Hodgkin lymphoma and major types of aggressive NHL are treated with curative intention. Thus, preventing and alleviating any degree of cancer associated anaemia and its associated decrease in QoL becomes a significant goal. Apart from PRBC transfusions, other measures such as the use of erythropoietin stimulating agents (ESA) has also shown promising results in the management of anaemia in cancer patients.[12,13]

In areas where blood bank support is suboptimal, making arrangement for blood transfusion becomes responsibility of the families of patients. Sometimes, it becomes very difficult for family to arrange donors, particularly if they are told at eleventh hour. In high risk patients, blood bank and families should be warned about the need for transfusions in the coming days. Our study is an effort to detect risk factors which can contribute to increased transfusion requirements in lymphoma patients.

MATERIAL AND METHODS

This study was conducted at a tertiary level cancer Hospital in Pakistan. The study was approved by the ethical review committee of the Hospital. Data were collected through the computer based hospital information system. Hodgkin and Non-Hodgkin Lymphoma patients of more than 18 years of age, from January to December 2011, who had packed red cells (PRBC) transfusions, were included in the study. Information regarding gender, type of lymphoma, stage, base line haemoglobin, bone marrow involvement and total number of PRBC units transfused were noted. Type of chemotherapy given was also recorded. PRBC transfusions were given when Hb dropped <8.0 g/dl or <10g/dl in symptomatic patients. Data was analysed using SPSS-19.0. Independent samples t-test was used at 5% level of significance to know differences in continuous variables

RESULTS

Four hundred and eighty one patients with a diagnosis of lymphoma were registered during this period (1st January to 31st December 2011). Out of these 481 patients, 108 (22.4%) had packed red blood cell (PRBC) transfusions. Thus, 108 patients were included in final analysis (Table-1).

There were 73 (67.6%) males and 35 (32.4%) females. Hodgkin lymphoma (HL) and Non Hodgkin Lymphoma (NHL) patients were 30 (27.8%) and 78 (72.2%), respectively. Among the NHL, diffuse large B cell lymphoma (DLBCL) was the commonest subtype (Table-2).

Mean age for all the patients was 35.3 years±10.8 years (Range 19–71 years). NHL patients were older with mean age of 36.7 years±10.8 years (Range 19–71 years) than HL, 31.8 years±10.2 years (Range 19–52), p=0.03. Of all patients, 25 (23.1%) were in early stage (stage I-11) and 83 (76.9%) were in stage III and IV (Table-1). Mean Haemoglobin for entire group (at the base line) was 10.8±2.57 g/dl (Range 4–17). Hodgkin lymphoma patients had lower mean haemoglobin 9.3±2.56 g/dl (Range 4–14) as compared to Non-Hodgkin lymphoma 11.33±2.37 g/dl (Range 5–17) p<0.05. Mean packed red blood cells (PRBC) units transfused in HL patients were 3.97±3.0 as compared to 6.74±5.69 in NHL, p<0.05 (Table-3).

Mean PRBC units requirements were not influenced by the stage of disease, with mean PRBC units transfused in Stage I/II disease was 4.88±4.85 while it was 6.3±5.33 in Stage III/ IV, p=0.2. There were 31 patients with bone marrow involvement while there was no bone marrow disease in 76 patients and one patient didn't have bone marrow done. PRBC units transfused to patients with and without bone marrow involvement were 7.84±4.36 and 5.26±5.49, respectively, p<0.05. Major types of chemotherapy regimens used were CHOP (n=52), ABVD (n=27) and Hyper-CVAD (n=18) (Table-4).

Table-1: Patient's characteristics

Total Number of Patients=108	
Type of Lymphoma	N (%)
HL	30 (27.8%)
NHL	78 (72.2%)
Male	73 (67.6%)
Female	35 (32.4%)
Age (Mean±SD)	35.3 years±10.8 years (Range 19–71 years
HL	31.8 years±10.2 years (Range 19–52 years
NHL	36.7 years±10.8 years (Range 19–71years
Stage	
I/II	25 (23.1%)
III/IV	83 (76.9%)
Bone marrow status	
Involved	31 (28.7%)
Not involved	76 (70.4%)
BM not done	1 (0.9%)

Table-2: Different subtypes of Non-Hodgkin Lymphoma

Type of Lymphoma	Number	Percent (%)
Hodgkins Lymphoma	30	27.8
Diffuse Large B Cell Lymphoma	46	42.6
T Cell Lymphoma	8	7.4
Lymphoblastic Lymphoma	7	6.5
Anaplastic Large Cell Lymphoma	7	6.5
Burkitt's Lymphoma	6	5.6
Mantle Cell Lymphoma	2	1.9
Lymphoplasmacytic Lymphoma	1	0.9
Follicular Lymphoma	1	0.9

Table-3: Number of packed red blood cells units

Parameter	Value	*p*-value
Hemoglobin in all patients (Mean±SD)	10.8±2.57 g/dl (Range 4–17)	
Hemoglobin in HL (Mean±SD)	9.3±2.56 g/dl (Range 4–14)	<0.05
Hemoglobin in NHL (Mean±SD)	11.33±2.37 g/dl (Range 5–17)	
PRBC units transfused in HL (Mean±SD)	3.97±3.0 (Range 0–12)	<0.05
PRBC units transfused in NHL (Mean±SD)	6.74±5.69 (Range 0–23)	
PRBCs units transfused in Stage I/II disease (Mean±SD)	4.88±4.85	0.2
PRBCs units transfused in Stage III/ IV (Mean±SD)	6.30±5.33	
PRBCs units transfused with bone marrow involvement (Mean±SD)	7.84±4.36	<0.05
PRBCs units transfused without bone marrow involvement Mean±SD)	5.26±5.49	

Table-4: Different types of chemotherapy

Type of chemotherapy	Number of patients	Percentage (%)
CHOP	52	48.1
ABVD	27	25
HCVAD	18	16.7
SMILE	3	2.8
ICE	2	1.9
RTOG	2	1.9
EURO-LB	1	0.9
NO CHEMOTHERAPY	3	2.8

CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone); **ABVD** (Doxorubicin, Bleomycin, Vinblastine, Decarbazine), **HCVAD** (Course A: Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, Cytarabine and methotrexate-intrathecal. Course B: Methotrexate, Leucovorin, Cytarabine, Cytarabine and methotrexate-intrathecal); **SMILE** (Methotrexate, Leucovorin, Ifosfamide, Mesna, Dexamethasone, Etoposide, L-asparaginase, GCSF); **ICE** (Ifosphamide, Carboplatin, Etoposide); **EURO-LB** (Methotrexate, Asparaginase, Daunorubicin, Dexamethasone, Cyclophosphamide, Vincristine, Mercaptopurine, Cytarabine**) RTOG** (Methotrexate, Cytarabine, Vincristine, Procarbazine, Dexamethasone, Leucovorin)

DISCUSSION

Anaemia is present in significant proportion of patients diagnosed with lymphoma. In some studies, up to 30–40% of lymphoma patients were found to have anaemia.[3] Presence of anaemia not only leads to decreased quality of life but is also associated with poor outcomes in these patients.[4] Mild to moderate anaemia may be symptomatic or can contribute to poor quality of life, necessitating a need for packed red blood cells (PRBC) transfusions. In this study, we described the characteristics of HL and NHL patients who needed PRBC transfusions during treatment with chemotherapy and also highlighted factors responsible for increased transfusions requirements. This is an effort to identify high risk patients who may require PRBC transfusions and also amount of units needed. This is of particular importance for under resourced countries where blood bank support may not be sufficient to meet the need of patients. In this setting, patients and families have to make arrangements for donors. For high risk patients, families could be informed in the beginning so that appropriate arrangements can be made. HL and NHL patients were included in our study. In this study, a large number of patients (22.4%) required PRBC transfusions. Patients were younger in HL compared to NHL. This is consistent with established data that HL is common in younger age group and NHL is considered as disease of older people. There were more males than females which may be a reflection of the fact that lymphomas are relatively common in men.[1] The majority of our patients belonged to advanced stage disease (III/IV); although these patients had more transfusions than early stage (I/II) but difference was not statistically significant (p=0.2). Thus, the presence of an early stage disease does not rule out the need for transfusion during treatment. An association of anaemia with advanced stage disease has been mentioned in previous studies; however, relationship of transfusions is not well documented.[2] In addition, not all anaemic patients will require transfusions. Although base line Hb was higher in NHL than HL (p<0.05) but interestingly, NHL patients required more RBC units transfusion as significant difference in the numbers of RBC units as compared to the HL (p<0.05). One explanation for this could be the fact that NHL chemotherapy regimens are more intense than HL. This will lead to more myelo-suppression resulting in significant cytopenia and anaemia. A baseline low or high Hb does not necessarily make patient high risk or low risk for PRBC transfusions, respectively. A patient with normal or near normal Hb at the baseline may also need transfusions during chemotherapy. Anaemia is common in lymphoma patients with bone marrow involvement (BMI).[15] In this analysis, we found BMI with disease in 28.7% of patients. The difference in the number of PRBC units transfused was significant between bone marrow positive and negative patients. There were more transfusions in patients with BMI compared to without marrow disease (p<0.05). Haematopoiesis is reduced in diseased marrow and toxic chemotherapy further adds to myelo-suppression. The underlying type of lymphoma and BMI makes patient high risk for transfusions. Patients (also the families) belonging to this group (NHL patients and BM involvement) should be informed in the start of therapy about the need for transfusions during the course of treatment. This will help families to arrange blood donors. At least donors screening could be done before hand.

We did not look particularly at the impact of different types of chemotherapy regimens on transfusion requirements. However, different studies have highlighted a relationship between different chemotherapeutic agents and amount of blood transfusions.[16] PRBC transfusion alleviate symptoms of anaemia and improve quality of life in cancer patients; however, there may be potential complications of such approach such as transmission of infections and transfusion reactions. Some studies have shown significant role of erythropoietin stimulating agents (ESA) in the treatment of cancer related anemia.[17,18] In under resourced countries, where patient has to pay for the cost of treatment, this option may not be feasible in some cases due to cost. In addition, availability may be an issue as well in some areas. During the treatment of lymphoma patients, an effort should be made to rule out any correctable cause of anaemia such as haemolysis, hematinic deficiency and bleeding. The appropriate treatment of these causes (if found in a patient) could result in reduced PRBC transfusions. The retrospective nature of the study, small number of patients, not evaluating the effect of each chemotherapy regimen; and not studying the presence or absence of haemolysis, bleeding or any hematinic deficiency, were some of the limitations of our study that we are obliged to acknowledge.

CONCLUSION

A significant proportion of lymphoma patients require packed red blood cells transfusions during treatment. The type of lymphoma and presence of bone marrow involvement affect transfusion requirements. Normal haemoglobin at the baseline does not exclude a need for blood transfusion during chemotherapy. Bone marrow involvement and underlying NHL makes patients high risk for transfusions. In places, where blood bank support is not adequate, patients and their families should be informed from the very beginning of the treatment about the need for red blood cells transfusions, so that appropriate arrangements could be made in timely manner. If any correctable cause of low haemoglobin is found, it should be addressed appropriately. There is need for prospective studies to confirm our findings.

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