Short Report

Prevalence and aetiology of anaemia in lymphoid malignancies

J. GHOSH, R.K. BIKRAMJIT SINGH, R. SAXENA, R. GUPTA, S. VIVEKANANDAN, V. SREENIVAS, V. RAINA, A. SHARMA, L. KUMAR

ABSTRACT

Background. We prospectively studied the prevalence, type and causes of anaemia in newly diagnosed patients with lymphoid malignancies.

Methods. Between January 2007 and June 2008, a total of 316 newly diagnosed, consecutive patients (aged 15 years or above) of Hodgkin lymphoma, non-Hodgkin lymphoma and chronic lymphocytic leukaemia with anaemia (haemoglobin < 11 g/dl), were analysed to determine the prevalence and a subgroup of 46 patients was analysed for the cause of anaemia.

Results. Hodgkin lymphoma, non-Hodgkin lymphoma and chronic lymphocytic leukaemia were the diagnoses in 81 (25.8%), 203 (64.7%) and 30 (9.6%) patients, respectively. Anaemia was present in 134 patients (42.4%). Anaemia of chronic disease was present in 33/46 (71.7%) and iron deficiency in 18/46 (39.1%) patients. Vitamin B12 and/or folate deficiency was detected in 10/46 (21.7%) patients (B12 deficiency alone in 7, folate deficiency alone in 1 and combined B12 and folate deficiency in 2). Autoimmune haemolytic anaemia was detected in 5/46 (10.9%) although direct Coombs test was positive in 17/46 (37%) patients. Among patients with Hodgkin lymphoma and non-Hodgkin lymphoma, anaemia due to bone marrow involvement was present in 16/40 (40%). In most patients with bone marrow involvement, anaemia was due to other causes. In only 3 patients, anaemia was attributable to bone marrow involvement alone. Anaemia was multifactorial in 18/46 (39.1%) patients. Nutritional deficiency alone or in combination was present in 22/46 (47.8%) patients.

Conclusion. Anaemia is common in lymphoid malignancies at initial presentation. Besides managing anaemia of chronic disease and bone marrow involvement, nutritional and autoimmune causes should be ruled out.

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Tata Memorial Hospital, Parel, Mumbai 400012, Maharashtra, India
J. GHOSH Department of Medical Oncology
Dr B.R. Ambedkar Institute–Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India
R.K. BIKRAMJIT SINGH, V. RAINA, A. SHARMA, L. KUMAR Department of Medical Oncology
R. SAXENA Department of Haematology
R. GUPTA Department of Laboratory Oncology
S. VIVEKANANDAN Department of Neurobiochemistry
V. SREENIVAS Department of Biostatistics
Correspondence to LALIT KUMAR; *lalitaiims@yahoo.com*

INTRODUCTION

Anaemia is a serious and common problem in patients with lymphoid malignancies. The prevalence of anaemia at the time of diagnosis in patients with chronic lymphocytic leukaemia (CLL), non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) has been reported to be as high as 26%, 49% and 37.4%, respectively in different studies.[1,2] Multiple mechanisms contribute to the development of anaemia in these patients. These include anaemia of chronic disease (ACD), autoimmune haemolytic anaemia (AIHA), bone marrow infiltration, nutritional deficiencies and blood loss either alone or in combination. Cytokines such as IL-6 have been shown to increase hepcidin levels which result in iron restriction and signs of anaemia of chronic disease.[3] It is now recognized that anaemia may lead to symptoms that adversely affect physical status and diminish functional capacity and quality of life (QOL).[4,5] The presence of anaemia is also associated with poorer prognosis and increased mortality.[6,7] However, this factor is poorly recognized and under-treated. The European Cancer Anaemia Survey (ECAS) found that only 47.3% of anaemic patients at any time during ECAS received treatment for anaemia.[2] It is also important to identify functional iron deficiency as this hinders response to erythropoiesis-stimulating agents.[8] Data on the prevalence of anaemia in lymphoid malignancies from India is scarce. We prospectively studied the prevalence and type of anaemia in newly diagnosed patients of lymphoid malignancies and made an effort to determine its cause for optimal management.

METHODS

Newly diagnosed patients (age ≥15 years), with lymphoid malignancies (HL, NHL and CLL; *n*=336) between January 2007 and June 2008 were included in the study. Data regarding diagnosis, stage of disease and haemoglobin level was taken from the patient record. Patients with a haemoglobin level <11 g/dl, who had not received any treatment, were defined to have anaemia. Patients who had received blood transfusion, iron, folic acid or vitamin B complex in the previous 2 weeks, those with underlying renal dysfunction (serum creatinine >2 mg/dl), relapsed disease and previously treated patients were excluded. The study was approved by our Institute's Ethics Committee. Written informed consent was taken from all 46 patients whose blood sample was collected for analysis of the cause of anaemia. The evaluations included a complete haemogram, peripheral blood smear examination, red blood cell indices including mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red blood cell distribution width (RDW); haematocrit, reticulocyte count, direct Coombs test (DCT), bone marrow aspiration/biopsy; biochemistry including renal function tests, liver function tests, serum lactate dehydrogenase (LDH); serum iron, %saturation, total iron-binding capacity (TIBC), serum ferritin, serum vitamin B12, serum folic acid and serum erythropoetin levels. All tests were done using appropriate and recommended techniques.

Definitions

Anaemia: Haemoglobin level <11 g/dl as in the Rai classification for CLL the cut-off used is 11 g/dl; *vitamin B12 deficiency*: serum B12 levels <200 pg/ml; *folate deficiency:* folate level ≤4 ng/dl; *autoimmune haemolytic anaemia*: if DCT was positive with

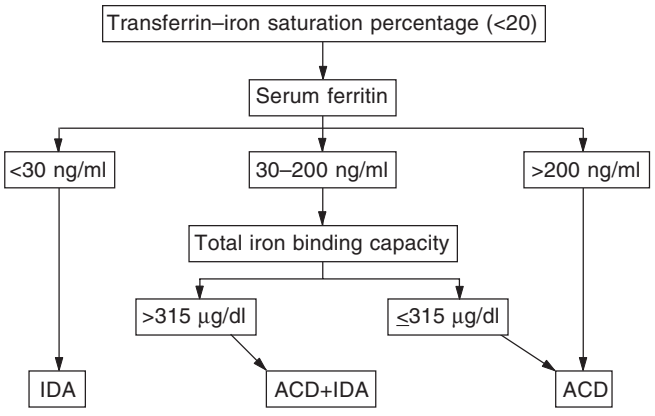

FIG 1. Definitions of iron deficiency anaemia (IDA), anaemia of chronic disease (ACD) and ACD with IDA

evidence of haemolysis on peripheral smear (spherocytosis, agglutination, polychromasia).[9–11] Iron deficiency anaemia (IDA) and ACD were defined as shown in Fig. 1.

Statistical analysis

Pearson Chi-square test was used to analyse the difference in prevalence of anaemia in different groups. Kruskal–Wallis test was used to determine the difference in mean serum erythropoietin levels between patients with IDA, ACD, and IDA with ACD.

RESULTS

Three hundred and thirty-six patients with lymphoid malignancies (HL, NHL and CLL) were registered during the study period. As some patients who had registered but did not come for any follow-up visit, the haemoglobin level was available for 316 patients. Anaemia was present in 42.4% of patients (134 of 316, 95% CI 36.96%–47.85%). It was more common among women (52/87, 59.8%) compared with men (82/229, 35.8%, p<0.001). Although there was no difference in the prevalence of anaemia in different age groups in men (p=0.15), women in the 31–45 years age group had a significantly higher prevalence of anaemia (22/24, 91.7%, p<0.001, Table I). Of 316 patients, in 2 patients the subtype of lymphoma was not known; 81 (25.8%) had HL, 203 (64.7%) had NHL and 30 (9.6%) had CLL. The prevalence of anaemia was not different in patients with different diagnoses: HL 48.1% (39/81); NHL 39.9% (81/203); CLL 43.4% (13/30; p=0.44).

Among the 46 patients for whom a detailed analysis was done for the cause of anaemia, 14 (30.4%) had HL, 26 (56.5%) had NHL and 6 (13%) had CLL (Table II); 38/46 (82.6%) patients were in advanced stages (stages III and IV). The median age of the men in this subgroup was 55 years (range 16–90) and among women was 51 years (range 15–76). ACD was present in 33/46 (71.7%, 95% CI 57.45%–82.68%) patients and IDA was present in 18/46 (39.1%, 95% CI 26.39%–53.54%) patients. Vitamin B12 and/or folate deficiency was detected in 10/46 (21.7%, 95% CI 12.26%–35.57%). Vitamin B12 deficiency alone was seen in 7, folate deficiency alone in 1 and combined B12 and folate deficiency was seen in 2 patients. AIHA was present in 5/46 (10.9%, 95% CI 4.73%–23.04%) patients, although DCT was positive in 17 (37%) patients. Among patients with HL and NHL, anaemia due to bone marrow involvement was present in 16/40 (40%). In most patients with bone marrow involvement, it was associated with other causes of anaemia. In only 3 patients, anaemia was attributable to

TABLE I. Prevalence of anaemia in different age groups in men and women

Age group (years)	Men (%)	Women (%)	Total (%)
15–30	20/51 (39.2)	8/13 (61.5)	28/64 (43.8)
31–45	12/53 (22.6)	22/24 (91.7)	34/77 (44.2)
46–60	27/65 (41.5)	6/23 (26.1)	33/88 (37.5)
≥61	23/60 (38.3)	16/27 (59.3)	39/87 (44.8)
Total	229	87	316

Men p=0.148 Women p<0.001

TABLE II. Characteristics of patients (*n*=46) who underwent detailed investigations for anaemia

Characteristic	HL (*n*=14)	NHL (*n*=26)	CLL (*n*=6)	Total (%)
Gender				
Men	10	16	6	32 (69.6)
Women	4	10	0	14 (30.4)
Stage				
I	1	1	1	3 (6.5)
II	3	1	1	5 (10.9)
III	2	6	3	11 (23.9)
IV	8	18	1	27 (58.7)
Type of anaemia				
Anaemia of chronic disease (ACD)	5	11	2	18 (29.1)
Iron deficiency anaemia (IDA)	1	2	0	3 (6.5)
Autoimmune haemolytic anaemia (AIHA)	1	0	0	1 (2.2)
Myelophthisic anaemia	0	3	0	3 (6.5)
Vitamin B12/folate deficiency (B/F def)	1	1	1	3 (6.5)
ACD+IDA	4	3	0	7 (15.2)
ACD+B/F def	1	0	0	1 (2.2)
ACD+AIHA	1	1	0	2 (4.3)
ACD+IDA+B/F def	0	2	1	3 (6.5)
ACD+IDA+AIHA	0	1	1	2 (4.3)
IDA+B/F def	0	2	1	3 (6.5)
Direct Coombs test positive	7	8	2	17 (37)
Bone marrow involvement	3 (21.4%)	13 (50%)		

HL Hodgkin lymphoma NHL non-Hodgkin lymphoma CLL chronic lymphocytic leukaemia

bone marrow involvement alone (myelophthisic anaemia). The cause of anaemia was multifactorial in 18/46 (39.1%, 95% CI 26.39%–53.54%) patients. Nutritional deficiency (vitamin B12, folate or iron alone or in combination was present in 22/46 (47.8%, 95% CI 34.12%–61.86%) patients.

The mean (SD) corrected reticulocyte count in patients with DCT-positive anaemia was 1.92 (1.77), range 0.24–5.88. The mean (SD) serum bilirubin in these patients was 0.94 (0.52) mg/dl (range 0.50–2.10 mg/dl). There was a negative correlation between serum erythropoietin levels and haemoglobin (–0.5688, p<0.001). However, there was no difference in serum erythropoietin levels between patients with ACD, IDA and ACD with IDA (Kruskal–Wallis test, p=0.25).

DISCUSSION

The prevalence of anaemia in patients with lymphoid malignancies was high in our study (42.4%). We used a haemoglobin level of <11 g/dl to define anaemia based on the value used in the Rai staging system for CLL. Anaemia was more common among women than men (59.8% *v.* 35.8%, p<0.001). This could be a reflection of the higher prevalence of anaemia in women (55%) in the general population than among men (24%).[12] The prevalence of anaemia in different age groups was not different among men; but, a significantly higher proportion of women in the 31–45 years age group were anaemic (p<0.001). This could also be a reflection of the higher prevalence of anaemia in women in the reproductive age group. The prevalence of anaemia in patients with HL, NHL and CLL was 48.2%, 39.9% and 43.3%, respectively and it was not significantly different. Earlier studies reported from our centre had a similar prevalence of anaemia in patients with HL and NHL.[13,14] Others have reported a prevalence of 37.4% in HL[2] and 32%–49% in NHL.[2,6,15,16] The prevalence of anaemia in CLL in our patients was higher (43.3%) compared with that in other studies (26%).[1] This difference could probably be because of the small number of patients with CLL in our study.

Deficiency of iron, vitamin B12 and/or folate were the cause of or contributed to anaemia in 47.8% of patients. However, since haemoglobin levels after replacement of iron/vitamin B12/folate were not available, it remains uncertain as to what extent anaemia may have improved after correction of these deficiencies.

Other studies have not looked into the cause of anaemia. However, in the ECAS, 11.6% of patients received iron alone or in combination.[2] DCT was positive in 17/46 (37%) patients with evidence of overt haemolysis in only 5/46 (10.9%) patients. Other studies have also found that although DCT was positive in 14% of NHL and CLL, AIHA was seen only in 2% of patients with NHL and 10% of patients with CLL.[17–19] The possible explanation could be that although the disease causes formation of antibodies, it does not lead to destruction of antibody-coated cells or there may be a low titre of the antibody and thus does not cause destruction of red blood cells.[18]

Although a negative correlation existed between levels of erythropoietin and haemoglobin, there was no significant difference in the serum erythropoietin levels among patients with IDA, ACD, and ACD with IDA. This is in contradiction to the expected lower level of serum erythropoietin in ACD compared with that in IDA.[19]

The cause of anaemia being multifactorial in 39.1% of patients in our study would suggest that the cause of anaemia in patients with lymphoid malignancies must be investigated. This would help in better management of lymphoma in general and anaemic patients in particular.

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