Hyperleucocytosis in patients with chronic leukaemia (Myeloid & Lymphoid type)

Abdulrahman Hefdhallah Amer[1,*], Abdulrahman AL-Haifi [1]

[1]Department of Medical Laboratories, Faculty of Medical Sciences, Al-Saeeda University & Department of Laboratory Medicine, Faculty of Medical Sciences, Thamar University, Dhamar-Yemen.

Article Info :

Article type:
Research Article
Received:
08April 2022
Revised:
18April 2022
Accepted:
16May 2022

***Corresponding Author:**

Abdulrahman H. Amer

Email: hefdhallaha@tu.edu.ye

Telephone: +967777750189

Conflict of interest: Nil

Al-Saeeda Journal of Medical Sciences (SJMS)

ISSN: 2710-4877 (Print); ISSN: 27104885 (Online)

Available Online at: journal.su-edu.net/index.php/su-journal

A peer reviewed medical journal published by Faculty of Medical Sciences - Al-Saeeda University, Dhamar, Yemen

SJMS; Volume 4, Issue 1; May : 2022; Page No. 20-33

Hyperleucocytosis in patients with chronic leukaemia (Myeloid & Lymphoid type)

Abdulrahman H. Amer[1]*, Abdulrahman AL-Haifi[1]

[1]Department of Medical Laboratories, Faculty of Medical Sciences, Al-Saeeda University & Department of Laboratory Medicine, Faculty of Medical Sciences, Thamar University, Dhamar- Yemen

Article Info:

Article Type

Research article

Received

08 April 2022

Revised

18 April 2022

Accepted

16 May 2022

Corresponding Author:

Abdulrahman H. Amer

Email: hefdhallaha@yahoo.com

Telephone: 00967777750189

Conflict of interest: Nil

To cite this article:

Abdulrahman H. Amer, Hyperleucocytosis in patients with chronic leukaemia (Myeloid & Lymphoid type). *SJMS.* 2022; 4(1): P; 20-33.

Abstract

Chronic myeloid leukemia (CML) is a clonal disorder of hematopoietic stem cells. The disease arises as a consequence of a rare gene abnormality. Chronic lymphocytic leukemia is a neoplastic disease characterized by the accumulation of small mature-appearing lymphocytes in the blood, marrow, and lymphoid tissues. This study aimed to determine alteration in some of the basic haematological parameters in patients with chronic leukemia and to evaluate the hematological parameters in patients with chronic leukaemia who have laboratory evidence of hyperleucocytosis and those without. In this study, 134 patients were enrolled with newly diagnosed chronic Leukemia patient (Myeloid and Lymphoid) at Al-Gumhouri Teaching Hospital Sana'a and National oncology center Sana'a in the period of the study (From 18 August to 30 November 2009) and studied, (CBC) were done using automated blood cell analyzer, Blood film examination and Bone marrow examination.

Out of the total 134 patients studied, 108/134 (81%) were chronic myeloid leukaemia and 26/134 (19%) were chronic lymphocytic leukaemia.109/134 (81.3%) were more than 30 years old and 25/134 (18.7%) were less than 30 years old. In CML: 64 (59.3%) were males and 44 (40.7%) were females, with male: female (M:F ratio) of 1.5:1. In CLL: 18 (69.2%) were males and 8 (30.7%) were females, with male: female (M: F ratio) of 2.3:1.100/108 (92.6%) CML patients were anemic at diagnosis with a haemoglobin level ranging between 5.3 and 12.9 g/dl, Mild to Moderate anaemia found in the majority of the CML patients studied 95/108 (87.9%). 11/134 (8.2%) patient had normal haemoglobin level (12-14.6 g/dl). leucocytosis was present in all (100%) patients, of which 4/134 (3%) patients had WBC count ranging from 12 – 50 x 109/L. 24(18%) out of 134 patients had leucocytosis (more than 50□109/L). hyperleucocytosis with WBC count more than 100 x109/L found in 91/134 patient (68%) & those with hyperleucocytosis (WBC count more than 300 x109/L) found in 15/134 (11%). Anaemia present in 123/134(91.8%) patients with 100/108 (92.6%) CML type & 23/26 (88.5&) CLL type. 11/134

(8.2%) patient shows normal hemoglobin concentration. Thrombocytopenia found in 24/134 (17.9%) patient with 12/108 (11.1 %) CML type & 12/26 (46%) CLL type. Thrombocytosis with platelet count more than 1000 found in 4/108 (3.7) CML patient only. A statistically significant difference in the total white blood cell count & platelet count (P = 0.02&0.01 respectively) follows the severity of anaemia (for hemoglobin concentration) noticed in CML patients. A statistically significance (P = 0.04) lower hemoglobin concentration in patients with hyperleucocytosis than those without. No statistically significant difference in the hematological parameters follows the severity of anaemia (for hemoglobin concentration) noticed in CLL patients. A statistically significant difference in the total white blood cell count follows the age of the chronic leukemia patients (P =0.02).

Conclusion: Hyperleukocytosis occur more in CML than in CLL type of chronic leukemia and the laboratory evidence of hyperleukocytosis in chronic leukemia requires particular attention with special care in the diagnosis and treatment.

Keywords: CML, CLL, (CBC), Blood film examination and Bone marrow examination.

Introduction:

Chronic myeloid leukaemia (CML) is a potentially fatal stem cell neoplasia that constitutes nearly 14 % of all leukaemia. CML is caused by translocation of chromosome 9 and 22 to create what is called Philadelphia chromosome. This translocation remove a critically regulatory domain from tyrosin kinase (ABL) such that its protein product is constitutively active, this lead to uncontrolled cell growth and proliferation. The modified protein is known as BCR-ABL oncoprotein (1).

Laboratory tests are of great importance for this disease. The tests used for CML include complete blood cell count with platelet, cytogenetic analysis, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR).

The hematological count are the least sensitive measure of the disease with a limit of detection of leukaemic burden of 1011 cells (cytogenetics can detect a burden of 109, PCR detect a burden as few as 105 leukaemic cells).

The chronic myelogenous leukemias include classical chronic myelogenous leukemia, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, and chronic neutrophilic leukemia.

Classical chronic myelogenous leukemia presents with anemia, exaggerated granulocytosis, a large proportion of mature neutrophils, absolute basophilia, normal or elevated platelet counts, and frequently, splenomegaly (2).

The marrow is very hypercellular, and cytogenetic analysis will show a Ph chromosome in 90 percent of cases, and molecular diagnostic analysis will reveal a rearrangement of the BCR gene on chromosome 22 in 99 percent of cases.

Chronic lymphocytic leukemia is a neoplastic disease characterized by the accumulation of

small mature-appearing lymphocytes in the blood, marrow, and lymphoid tissues.

It is the most common adult leukemia in Western societies. Generally, the neoplastic lymphocytes are of the B-cell lineage. In less than 2 percent of cases, however, the neoplastic cells are of T-cell origin and are considered under the heading T-cell prolymphocytic leukemia.

Hyperleukocytosis in CML & CLL

About 15 percent of patients present with symptoms or signs referable to leukostasis as a result of the intravascular flow-impeding effects of white cell counts over 300 × 109/liter (in the present study hyperleucocytosis in CML found in 14/108 (13%). The effects of total leukocyte counts from 300 to 800 × 109/liter include impairment of the circulation of the lung, central nervous system, special sensory organs resulting in some combination of tachypnea, dyspnea, cyanosis, dizziness, slurred speech, visual blurring, diplopia, retinal vein distention, retinal hemorrhages, papilledema or impaired hearing. Such symptoms or signs usually respond to the rapid decrease in white cell count by a combination of leukapheresis and hydroxyurea therapy (3).

In CLL: Leukemic leukocytosis in excess of 800 × 109/liter may produce blood hyperviscosity (in the present study hyperleucocytosis in CLL found in 1/26 (3.9%).

The aims of this study are:

1. To determine alteration in some of the basic haematological parameters in patients with chronic leukaemia.

2. To evaluate the hematological parameters in patients with chronic leukaemia who have laboratory evidence of hyperleucocytosis and those without.

Methods:

The study included all patients with Chronic Leukemia (Myeloid and Lymphoid) attended to Al- Gumhouri Teaching Hospital Sana'a and National oncology center Sana'a Yemen. In the period of the study (from 18 August to 30 November 2009).

Basic Hematological Parameters:

All the basic hematological tests (CBC) were done using automated blood cell analyzer with morphological study. Blood film examination (peripheral blood smear). Bone marrow examination.

Study design: Cross-Sectional Study.

Sample size: 134 participants.

Ethics issues:

The study was approved by the Human Research Ethics Committee (HREC) in Al-Gumhouri Teaching Hospital Sana'a and National oncology center Sana'a Yemen and from Faculty of Medicine and Health Sciences at Thamar University, Dhamar –Yemen.

Results:

In the present study, chronic leukaemia (CL) distribution shows CML type predominance compared to CLL, with CML to CLL ratio of 4.2:1, which agrees with the results of most workers. CML was the predominant type of CL in adults included in this study 108/134 (81%), this agrees with the universal observation about the predominance of CML in adults. the majority of our CML patients 83/108 (77%) were adults, which agree with the universal concept about the predominance of CML in adults.

All the CLL patients studied were old age group, which agree with the universal concept about the predominance of CLL in this age group. Sex distribution of our CL patient's shows male to female ratio of 1.6:1, also our CML patients shows male: female ratio of 1.4:1 & CLL male to female ratio was 2.3:1, these results agrees with that found in other studies.

Table 1: Distribution of Chronic Leukaemia Patients studied According to the Type, Age and Gender.

TYPE	No. (%)	Age (yrs.)	No. (%)	Sex	No. (%)	M:F ratio
CML	108 (81%)	< 30	25 (23%)	M	15 (60%)	1.5:1
				F	10 (40%)	
		≥ 30	83 (77%)	M	49 (59%)	1.4:1
				F	34 (41%)	
CLL	26 (19%)	< 30	0 (0%)	M	0 (0%)	0
				F	0 (0%)	
		≥ 30	26 (100%)	M	18 (69.2%)	2.3:1
				F	8 (30.8%)	
Total	134 (100%)	< 30	25 (18.7%)	M	15 (60%)	1.6:1
				F	10 (40%)	
		≥ 30	109 (81.3%)	M	67 (61.5%)	1.6:1
				F	42 (38.5%)	

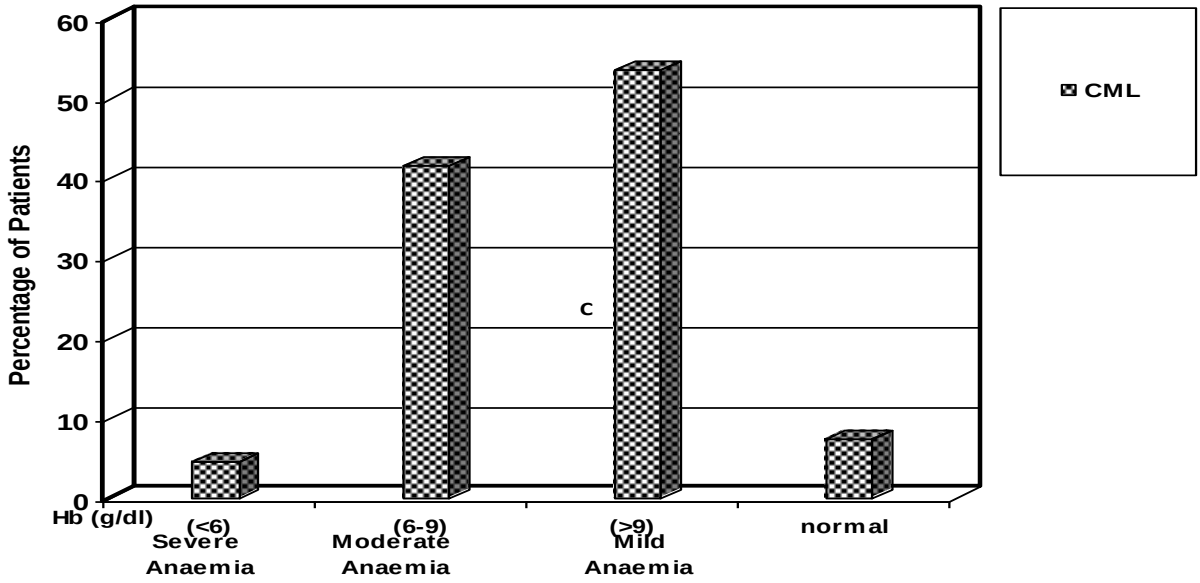

Figure 1: Distribution of Chronic Myeloid Leukaemia According to Severity of Anaemia.

Mild to Moderate anaemia found in the majority of the CML patients studied 95/108 (87.9%), severe anaemia found in 5/108(4.6%).

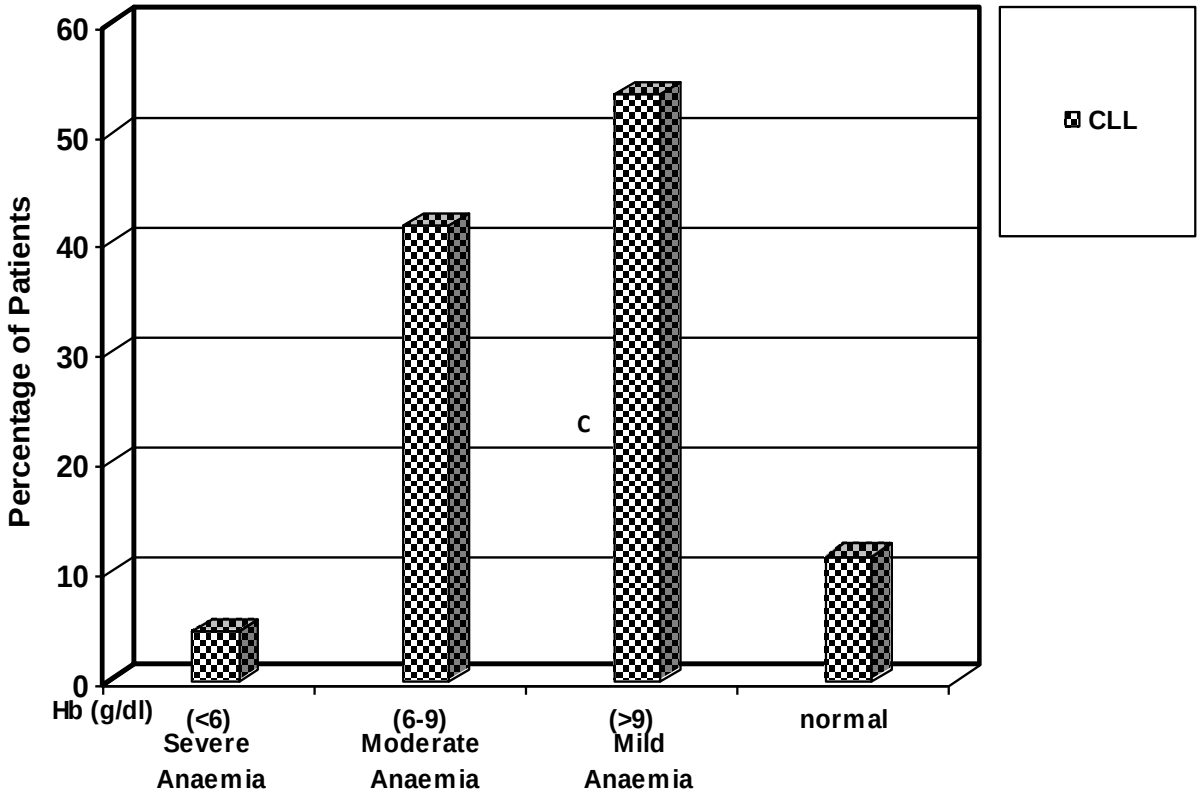

Figure2 Distribution of Chronic lymphoid Leukaemia According to Severity of Anaemia

Mild to Moderate anaemia found in the majority of the CLL patients studied 22/26 (85%), severe anaemia found in 1/26(3.9%).

Table 2: Blood Cells Parameters (Total WBC Count and Differential WBC Count) in Chronic Leukemia

PARAMETERS		CML	CLL	TOTAL
		NO. (%)	NO. (%)	NO. (%)
		108 (80.6%)	26 (19.4%)	134 (100 %)
Total WBC count ($\times 10^9$ /L)	4 – 11	0 (0%)	0 (0%)	0 (0%)
	12 – 50	3 (2.8%)	1 (3.8%)	4 (3%)
	51 – 100	17 (15.7%)	7 (26.9%)	24 (18%)
	> 100	74 (68.5%)	17 (65.4%)	91 (68%)
	> 300-653	14 (13%)	1 (3.9%)	15 (11%)
Differential WBC count ($\times 10^9$ /L)	Neutrophils	(87.8 ± 57.2) (44.8%)	(11 ± 17.7) (7.5%)	(72.9± 60.2) (39.2%)
	Band form	(12.1 ± 18.4) (6.2%)	(0.2 ± 0.5) (0.1 %)	(9.8± 17.1) (5.3%)
	Myelocytes	(37.5 ± 34.8) (19.2%)	(0.06 ± 0.3) (0.04%)	(30.2± 34.6) (16.2%)
	Blast cells	(6.8 ± 6.8) (3.4%)	(0.6 ± 1.1) (0.4%)	(5.6± 6.6) (3 %)
	lymphocytes	(20 ± 37.3)	(133 ± 81.8) (90.9%)	(41.9± 66.2) (22.5%)

The total leukocyte count in CML is always elevated at the time of diagnosis and is nearly always over 25 × 109/L; over two third of the CML patients have total white counts over 100 × 109/liter (88/108 (81.5%). Hyperleucocytosis (white counts over 300 × 109/liter) was detected in 14 /108 (13%) CML patients & in 1/26 (3.9%) CLL patient. This agrees with almost all standard works in this field of study. The total absolute lymphocyte count is increased (mean 20 × 109/liter) in patients with CML at the time of diagnosis as a result of the balanced increase in T-helper and T-suppressor cells.

The diagnosis of CLL requires a sustained monoclonal lymphocytosis greater than 5 × 109/liter, all the included cases in this study shows this fact and in the present study the mean absolute lymphocyte count generally is 90.9 × 109/liter.

Table 3: Blood Cells Parameters (Hemoglobin and Platelet count) in Chronic Leukemia

PARAMETERS		CML	CLL	TOTAL
		NO. (%)	NO. (%)	NO. (%)
		108 (80.6%)	26 (19.4%)	134 (100 %)
Hemoglobin (g/dL)	< 6	5 (4.6 %)	1 (3.9%)	6 (4.5 %)
	6-9	45 (41.6%)	10 (38.5%)	55 (41%)
	> 9	50 (46.3%)	12 (46.1%)	62 (46.3%)
	normal	8 (7.4%)	3 (11.5%)	11 (8.2%)
Platelet count ($\times 10^9$ /L)	<150	12 (11.1%)	12 (46%)	24 (17.9%)
	150 – 450	43 (39.8%)	14 (54%)	106 (79.1%)
	451 – 800	40 (37.1%)		
	801-1000	9 (8.3%)		
	> 1000	4 (3.7%)	0 (0%)	4 (3.0%)

The platelet count is elevated in about 53/108 (49.5%) percent of CML patients at the time of diagnosis and is normal in most of the rest 43/108 (39.8%). The platelet count may increase during the course of the chronic phase 49/108 (45.3%); platelet counts over 1000 × 109/liter are not unusual 4 (3.7%) (Table: 3). This might reflects the proliferative feature of the thrombopoietic lineage as part of the myeloproliferative process in the CML type of the chronic myeloproliferative disorder (CMPD).

Table 4: Relation between total WBC & platelet count and severity of anaemia in CML patients

PARAMETER	HAEMOGLOBIN LEVEL in CML (Severity of anaemia)			P- value
	severe (Hb: < 6 g/dl) NO. (%) 5 (4.6٪) (± SD.)	moderate (Hb: 6-9 g/dl) NO. (%) 45 (41.7٪) (± SD.)	mild (Hb: >9 g/dl) NO. (%) 58 (53.7٪) (± SD.)	
Hemoglobin (g/dl)	(5.64±.024)	(7.7±0.89)	(10.95±1.2)	0.1
Total WBC count ($\times 10^9$/L)	(156.5±70.3)	(249.6±118.5)	(179.5±103.4)	0.02
Platelet count ($\times 10^9$/L)	(460.8±377.03)	(487.7±289.7)	(448.1±255.9)	0.01

A statistically significant differences detected in the total WBC & platelet count in relation to the hemolglobin level in CML patients studied. No similar difference found in CLL patients studied.

Table 5 Relation between total WBC & platelet count and severity of anaemia in CLL patients

PARAMETER	HAEMOGLOBIN LEVEL in CLL			P- value
	(Hb: < 6 g/dl) NO. (%) 1 (3.8٪) (± SD.)	(Hb: 6-9 g/dl) NO. (%) 10 (38.5٪) (± SD.)	(Hb: >9 g/dl) NO. (%) 15 (57.7٪) (± SD.)	
Hemoglobin (g/dl)	(4.1±0)	(7.14±0.98)	(11.44±1.6)	0.2
Total WBC count ($\times 10^9$/L)	(237±0)	(162.04±120.4)	(144.9±73.5)	0.2
Platelet count ($\times 10^9$/L)	(86±0)	(134.5±110.2)	(245.3±175.7)	0.2

No statistically significant differences detected in the total WBC & platelet count in relation to the hemolglobin level CLL patients studied.

Table 6: Relationship between hyperleucocytosis and Hematological Parameters of Chronic Myeloid Leukaemia.

PARAMETER	HYPERLEUCOCYTOSIS in CML (total WBC count: more than 300 ($\times 10^9$/L))		P- value (t-test)
	Present	Absent	
	NO. (%)	NO. (%)	
	٪14 (13	٪94(87	
	± SD.	± SD.	
Hemoglobin (g/dl)	(8.45±1.8)	(9.5±2.08)	0.04
Total WBC count ($\times 10^9$/L)	(406.6±123.2)	(178.01±76.9)	0.1
Platelet count ($\times 10^9$/L)	(353.07±345.3)	(481.9±259.9)	0.08

A statistically lower hemoglobin level in CML patients with hyper-leucocytosis found in comparison with those without hyperleucocytosis. This agree with the finding of other worker**.**

Table 7: Relationship between WBC count and Age in Myeloid Leukaemia patients

WBC count According to Age		P- value (t-test)
(<40 years)	(≥40 years)	
NO. (%) 55 (41.05%)	NO. (%) 79 (58 .95%)	
± SD.	± SD.	
(192.2±105.9)	(201.06±115.9)	0.02

A statistically significant higher WBC count in chronic leukaemia patients studied (Both myeloid & lymphoid) found in older patients (More than 40 years) than younger patients. This finding disagree with those of other studies and it

might attributes to the few cases of childhood CML cases included in the present study.

Discussion

Chronic myeloid leukaemia (CML) is a potentially fatal stem cell neoplasia that constitutes nearly 14 % of all leukaemia. CML is caused by translocation of chromosome 9 and 22 to create what is called Philadelphia chromosome. This translocation remove a critically regulatory domain from tyrosin kinase (ABL) such that its protein product is constitutively active, this lead to uncontrolled cell growth and proliferation. The modified protein is known as BCR-ABL oncoprotein (1).

Laboratory tests are of great importance for this disease. The tests used for CML include complete blood cell count with platelet, cytogenetic analysis, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR).

The hematological count are the least sensitive measure of the disease with a limit of detection of leukaemic burden of 1011 cells (cytogenetics can detect a burden of 109, PCR detect a burden as few as 105 leukaemic cells) (1).

Hyperleukocytosis in CML & CLL

About 15 percent of patients present with symptoms or signs referable to leukostasis as a result of the intravascular flow-impeding effects of white cell counts over 300 × 109/liter (in the present study hyperleucocytosis in CML found in 7/104 (6.7%). The effects of total leukocyte counts from 300 to 800 × 109/liter include impairment of the circulation of the lung, central nervous system, special sensory organs, and penis, resulting in some combination of tachypnea, dyspnea, cyanosis, dizziness, slurred speech, delirium, stupor, visual blurring, diplopia, retinal vein distention, retinal hemorrhages, papilledema, tinnitus or impaired hearing. Such symptoms or signs usually respond to the rapid decrease in white cell count by a combination of leukapheresis and hydroxyurea therapy (1 and 18 -20).

In CLL: Leukemic leukocytosis in excess of 800 × 109/liter may produce blood hyperviscosity (in the present study hyperleucocytosis in CLL found in 1/24 (4.17%) (1, 22).

In the present study, chronic leukaemia (CL) distribution shows CML type predominance compared to CLL, with CML to CLL ratio of 3.3:1 (Table: 1), which agrees with the results of most workers(1 - 5).

CML was the predominant type of CL in adults included in this study (Table: 2) 80/104 (76.9%), this agrees with the universal observation about the predominance of CML in adults (1 - 5).

The majority of our CML patients 57/80 (71.25%) were adults (with>30 yrs.), (Table: 1) which agree with the universal concept about the predominance of CML in adults (1 - 5).

All the CLL patients studied were old age group, which agree with the universal concept about the predominance of CLL in this age group (1 - 5).

Sex distribution of our CL patients shows male to female ratio of 1.7:1, also our CML patients shows male:female ratio of 1.4:1 (Table: 1) these results agrees with that found in other studies (1 - 6). & CLL male to female ratio was 5:1, (Table: 1).

Mild to Moderate anaemia found in the majority of the CML patients studied 95/108 (87.9%) (Fig. 1), severe anaemia found in 5/108(4.6%).

Mild to Moderate anaemia found in the majority of the CLL patients studied 19/24 (79.2%) (Fig. 2), severe anaemia found in 2/24(8.3%).

CML by definition involves a total WBC count more than 25 × 109/liter .In the present study, the total leukocyte count in CML is always elevated at the time of diagnosis and is nearly always over 25 × 109/L; over two third of the CML patients have total white counts over 100 × 109/liter (55/80 (60.88%). Hyperleucocytosis (white counts over 300 × 109/liter) was detected in 5 /80 (6.25%) CML patients & in 2/24 (8.3%) CLL patient. This agrees with almost all standard works in this field of study.

The total WBC count in the majority of CL patients studied (73/80(91.25%) CML cases / 22/24 CLL (91.7%) cases) were more than 50 to 653□109/L, this rang agree with the finding of another worker (7).

There is a marked granulocytosis including all stages of granulocytic maturation, from blasts to segmented neutrophils. There is a predominance of more mature forms, from myelocytes to segmented neutrophils. in the present study, Myeloblasts are only 4.7% of WBCs (Figure 4) myelocytes are 18.3% and bands account for 4.7 percent; and segmented neutrophils account for 44.2 percent of total leukocytes (Figure 4).The distribution of the differential cell count in CML patients studied shows a bi-peak distribution of the white cells at the neutrophil and myelocytes stages, this findings agree with the globally accepted classical findings in the typical/classical type of CML (Figure: 4) (1).

The total absolute lymphocyte count is increased (mean about 20 × 109/liter) in patients with CML at the time of diagnosis as a result of the balanced increase in T-helper and T-suppressor cells (1).

The platelet count is elevated in about 53/108 (49.5%) percent of CML patients at the time of diagnosis and is normal in most of the rest 43/108 (39.8%). The platelet count may increase during the course of the chronic phase 49/108 (45.3%); platelet counts over 1000 × 109/liter are not unusual 4 (3.7%) (Table: 2).This might reflects the proliferative feature of the thrombopoietic lineage as part of the myeloproliferative process in the CML type of the chronic myeloproliferative disorder (CMPD) (11-16).

A statistically significant differences detected in the total WBC & platelet count in relation to the

hemolglobin level in CML patients studied (Table:3). No similar difference found in CLL patients studied (Table: 5).

A statistically lower hemoglobin level in CML patients with hyper-leucocytosis found in comparison with those without hyperleucocytosis (Table: 4).This agree with the finding of other worker (8).

A statistically significant higher WBC count in chronic leukaemia patients studied (Both myeloid & lymphoid) found in older patients (More than 40 years) than younger patients (Table:6). This finding disagree with those of other studies (9, 10) and it might attributes to the few cases of childhood CML cases included in the present study.

The diagnosis of CLL requires a sustained monoclonal lymphocytosis greater than 5 × 109/liter, all the included cases in this study shows this fact and in the present study the mean absolute lymphocyte count generally is 90.9 × 109/liter.

Mild anemia (12/26 (46.1%)) and/or thrombocytopenia (12/26 (46%) are common at diagnosis in this study, but significant decreases (hemoglobin <6 g/dL found in 1/26 (3.9%)) (figure: 2).

Thrombocytopenia detected in 12/26 (46%) CLL cases studied, this thrombocytopenia might attributes to marrow replacement/infiltration and / or hypersplenism.

Conclusions:

1. Hyperleucocytosis occur more in CML than in CLL type of chronic leukaemia.

2. Laboratory evidence of hyperleucocytosis in chronic leukaemia requires particular attention with special care in the diagnosis and treatment.

3. Hyperleucocytosis in chronic leukaemia is associated with lower hemoglobin concentration compared to patients without hyperleucocytosis.

Recommendations

1. The availability of well-equipped laboratory supplied with recent highly sensitive methods enable detection of hyperleucocytic leukaemia at an early stage. This is fundamental for the proper management of chronic leukaemia patients.

2. Monitoring of the blood viscosity in patients with hyperleucocytic chronic leukaemia are recommended with particular attention to blood transfusion during initiation of therapy to prevent leukostasis and the fatal sequences.

3. Establishment of medical documentation and registry unit for patient with leukaemia is fundamental with particular attention to the laboratory data reporting in an accomplished manner.

References:

1. Nicholson E, Holyoake T. The chronic myeloid leukemia stem cell. Clin Lymphoma Myeloma. 2009; 9 *Suppl* 4:S376-81. doi: 10.3816/CLM.2009.s.037. PMID: 20007106.

1. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration?. *Blood*. 2006 Mar 1;107(5):1747-50.

2. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration?. *Blood*. 2006 Mar 1;107(5):1747-50.

3. Machin SJ. Acquired coagulation, non-immune platelet disorders and vascular purpuras. A. Victot Hoffbrand, S. Mitchell Lewis, Edward GD, Tuddenham, editors Postgraduate Hematology. 4th ed. *Butterworth-Heinemann*. 1999:643-44.

4. Mosher DF: Disorder of blood coagulation. In: Bennett JC, Plum F. Cecil Textbook of Medicine, 20th ed. Philadelphia, W.*B. Saunders Company*, 1996: pp 987 – 1003.

5. Khan MQ, Shivarudrappa AS, el-Bialy S, Al-Khawagi MZ, Al-Mofarreh M. Leukaemia cases in Central Hospital, Riyadh (Saudi Arabia*). Journal of the Indian Medical Association*. 1991 Feb 1;89(2):38-42.

6. D'Antonio J. Chronic myelogenous leukemia. *Clin J Oncol Nurs*. 2005 Oct;9(5):535-8.

7. Corso A, Lazzarino M, Morra E, Merante S, Astori C, Bernasconi P, Boni M, Bernasconi C. Chronic myelogenous leukemia and exposure to ionizing radiation—a retrospective study of 443 patients. *Annals of hematology*. 1995 Feb;70(2):79-82.

8. Savage DG, Szydlo RM, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. *British journal of haematology*. 1997 Jan;96 (1):111-6.

9. Rowe JM, Lichtman MA: Hyperleukocytosis and leukostasis: *common features of childhood. Blood*. 1984 May;63(5):1230-4

10. Goldman JM, Melo JV. Chronic myeloid leukemia—advances in biology and new approaches to treatment. *New England Journal of Medicine*. 2003 Oct 9;349(15):1451-64.

11. Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. *New England Journal of Medicine*. 1999 Jul 15;341(3):164-72.

12. Clarkson B, Strife A, Wisniewski D, Lambek CL, Liu C. Chronic myelogenous leukemia as a paradigm of early cancer and possible curative strategies. *Leukemia*. 2003 Jul;17(7):1211-62.

13. Talpaz M, Shah NP, Kantarjian H, Donato N, Nicoll J, Paquette R, Cortes J, O'Brien S, Nicaise C, Bleickardt E, Blackwood-Chirchir MA. Dasatinib in imatinib-resistant Philadelphia chromosome–positive leukemias. *New England Journal of Medicine*. 2006 Jun 15;354 (24):2531-41.

14. Wang YL, Bagg A, Pear W, Nowell PC, Hess JL. Chronic myelogenous leukemia: laboratory diagnosis and monitoring. *Genes, Chromosomes and Cancer*. 2001 Oct;32(2):97-111.

15. Quintás-Cardama A, Cortes J. Molecular biology of bcr-abl1–positive chronic myeloid leukemia. Blood, *The Journal of the American Society of Hematology*. 2009 Feb 19;113(8):1619-30.

16. Hussein AG, Ali MS, Hassan MS, Mansoor SS, AL-Ameri AM, Muhsin RJ. Haematologic parameters in acute promyelocytic leukemia patients treated with ALL trans-retinoic acid. *Journal of the Faculty of Medicine Baghdad*. 2007 Apr 1;49(1):51-5.

17. RS C. Kumar V. Robbins SL. Robbins Pathologic Basis of Disease. *Philadelphia WB Saunders.* 1989;5:37.

18. Lichtman, Marshall A., and Jacob M. Rowe. "Hyperleukocytic leukemias: rheological,

clinical, and therapeutic considerations." (1982): 279-283.

19. Lichtman MA. Rheology of leukocytes, leukocyte suspensions, and blood in leukemia possible relationship to clinical manifestations. *The Journal of clinical investigation*. 1973 Feb 1;52(2):350-8.

20. Dabrow MB, Wilkins JC. Hematologic emergencies: management of hyperleukocytic syndrome, DIC, and thrombotic thrombocytopenic purpura. Postgraduate medicine. 1993 Apr 1;93 (5):193-202.

21. Dacie JV, Lewis SM. Practical haematology. *In Practical hæmatology* 1995 (pp. 609-609).

22. Armitage P, Berry G. Factorial designs. Statistical methods in medical research, 2nd edn, Oxford: *Blackwell Scientific Publications*. 1987:227-39.