Scientific Research Publishing

Open Journal of Blood Diseases, 2020, 10, 110-123
https://www.scirp.org/journal/ojbd
ISSN Online: 2164-3199
ISSN Print: 2164-3180

Hematobiological Profile of Patients with Chronic Myeloid Leukemia at the Diagnosis in Yaoundé: A Cross-Sectional Study

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How to cite this paper: Bisso Ngono, A.P., Angandji Tipane, P., Simeni Njonnou, S.R., Tiodoung Timnou, A., Flora Sango, A.J., Ndom, P., Tayou Tagny, C. and Mbanya, D. (2020) Hematobiological Profile of Patients with Chronic Myeloid Leukemia at the Diagnosis in Yaoundé: A Cross-Sectional Study. *Open Journal of Blood Diseases*, **10**, 110-123.
https://doi.org/10.4236/ojbd.2020.104013

Received: October 18, 2020
Accepted: December 20, 2020
Published: December 23, 2020

Abstract

Background: Chronic Myeloid Leukemia (CML) is a myeloproliferative blood neoplasia, characterized by the presence of a translocation between chromosomes 9 and 22 leading to the formation of the Philadelphia chromosome. Data on the biological profile of patients with CML at diagnosis are still lacking in sub-Saharan Africa, particularly in Cameroon. **Methods**: A cross-sectional study was carried out from January 2001 to July 2016 among patients recently diagnosed with CML at the Yaounde University Teaching Hospital, the Yaoundé Central Hospital and the Yaoundé General Hospital. Analyzed variables included socio-demographic, clinical presentation, the diagnosis means, biological parameters (hematological and biochemical). Sampling was consecutive. **Results**: We included 132 (76 males) patients with CML with a median age of 39.2 years at diagnosis. The 31 - 45 years age group was the most represented, with 40.9% of the study population. A risk

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factor was found in only 5 (3.8%) of patients. Clinical manifestations were recorded in only 27 (20.45%) patients, with fatigue being the commonest (10.6%). Almost all patients (128, 96.9%) have performed the karyotype while 22 (16.7%) have performed fluorescence *in situ* hybridization (FISH) and 4 (3.0%) the PCR. At diagnosis, 66% of the patients were in the chronic phase (CP), 11.3% in accelerated phase (AP), and 22.7% in blast crisis (BC). All patients presented hyperleukocytosis, with a white blood cell mean of 128,362/mm^3. Anemia was common (77.3%), usually moderate (61.4%). Thrombocytopenia was rare (8.3%), as far as basophilia (1.2%). Among those patients, mean values of creatinine, Glutamic pyruvate transaminase (GPT) and glycemia were normal while activated partial thromboplastin time (APTT), prothrombin time (PT), plasma uric acid level, gamma glutamic transferase (GGT), lactate dehydrogenase (LDH), and inflammatory parameters (ESR and CRP) were increased. **Conclusion**: Patients with CML presented at their diagnosis hyperleukocytosis and anemia as hematological clues. Other biological anomalies include increased signs of cellular destruction (plasma uric acid level, LDH), coagulation perturbation and inflammatory syndrome. The chronic phase of the disease was common.

Keywords

Chronic Myeloid Leukemia, Biological Clues at Diagnosis, Sub-Saharan Africa

1. Background

Chronic myeloid leukemia (CML) is a myeloproliferative disorder, as are essential thrombocythaemia (ET), Vasquez's disease (VD), and idiopathic chronic or primary myelofibrosis (PMF). It is characterized by the presence of a balanced translocation between chromosomes 9 and 22 (Philadelphia chromosome) resulting in the formation of the BCR-ABL1 fusion protein, with highly dysregulated tyrosine kinase activity [1] [2].

CML represents 15% - 20% of adult leukemia [3]. It is a malignant hematological malignancy for which epidemiological data are still poorly defined [4]. In France, CML has an annual incidence of almost 1 to 2 new cases per 100,000 population, with a discreet male predominance [5]. This incidence is comparable to the average of the countries of central and northern Europe [4] [6]. In the United States, the incidence of CML was 1.75/100,000 people per year and increased with age [7]. The American Cancer Society (ACS) estimates that 1090 deaths from CML will occur in 2018, 620 in men, and 470 in women [8]. CML occurs at any age, but more commonly in adult males 30 to 60 years old. There is no proven geographic or ethnic specificity even though Caucasians seem more affected than black individuals. Epidemiological data on patients with CML are rare in Sub-Saharan Africa (SSA). Most of the studies conducted on this topic focused on survival in patients treated with Imatinib [9]-[13]. Boma *et al.*, in the early 2000s, identified splenomegaly and hepatomegaly as poor survival risk fac-

tors [13]. In Ivory Coast, Silué *et al.* on the other side, identified additional chromosomal abnormalities, hepatomegaly, fever, bone pain, lymphadenopathies, poor general condition, high Sokal index, eosinophilia > 5% and circulating blasts as poor survival risk factors [14].

Only few studies have been performed on CML in Cameroon. They focused on epidemiological data (sociodemographic characteristics, comorbidities) and prognosis factors of treated patients [15] [16] [17] [18] [19]. To the best of our knowledge, there is no data on the biological presentation of patients with CML at diagnosis. It was therefore important for us to describe the biological profile of this population.

2. Methods

2.1. Study Design and Setting

We conducted a cross-sectional study in the Hematology and blood transfusion department of the Yaounde University Teaching Hospital, the Hematology department of the Yaounde Central Hospital and the Oncology department of the Yaoundé General Hospital from January 2001 to July 2016. Yaoundé General Hospital and Yaoundé University Teaching Hospital are tertiary hospitals in Yaoundé, the capital city of Cameroon (SSA), while Yaoundé Central Hospital is a secondary health facility. They have a catchment population of about 2 million inhabitants. Health insurance coverage is almost inexistent and the minimum wage is 64.3 USD per month [20].

Patients were retrospectively recruited from January 2001 to December 2015, while the prospective phase of the study took place from January to July 2016.

2.2. Variables and Measurements

- Inclusion criteria: Were included files of all subjects, with CML (diagnosis made by cytogenetic and/or molecular biology) and presenting at least at the initial biological workup a full blood count.
- Exclusion criteria: Were excluded patients with an incomplete file (particularly diagnosis means and biological workup).

The cytogenetic and molecular studies were performed by Cerba laboratories in Paris. Cytogenetic and molecular responses were evaluated according to the criteria of European Leukemia Net (ELN) 2013.

- Sample size: the sampling was exhaustive and consecutive.
- Variable and measurements:

Using a standardized questionnaire, we collected data on socio-demography (age, gender, and profession), clinical presentation (risk factors, signs and symptoms) in patients' records, or through an interview (for the patients recruited in the prospective phase). Biological parameters included: diagnosis means (Karyotype and molecular studies). Hematological workup included at least full blood count, looking for anemia, leukocytosis, basophilia or thrombocytopenia. Blood film and bone marrow aspiration results were also recorded.

Other biological exams were biochemical (transaminase, serum creatinine, fasting blood sugar, uricemia, GGT, LDH, CRP and ESR).

2.3. Statistical Analysis

Data have been analyzed using Statistical Package for Social Sciences (SSPS Inc, Chicago, Illinois, USA) V.20.0 and EPI-INFO V.3.5 software. Quantitative data are presented as means and qualitative data are presented as frequencies and percentages.

3. Results

Participants: We included 132 (76 males) patients with CML with a mean age of 39.2 years at diagnosis. The most frequent age group was 31 to 45 years with 54 (40.9%) patients (Figure 1). The patients were mainly (74; 56.1%) from the West region, followed by North-West with 24 (18.2%). Unemployed were the most numerous (26.5%), followed by private-sector workers (25%) and students (15.2%). The occupation was not mentioned in 21.2%.

Risk factors for CML were found in 5 (3.8%) patients, with chronic pesticides use, insecticide use, chronic exposition to paintings and hydrocarbons exposition been the main risk factors.

Diagnosis: The diagnosis was performed on standard karyotype for 108 (81.8%) patients. Molecular testings (FISH and Rt-PCR) were respectively performed in 22 (22.7%) and 6 (4.5%) patients. Two patients had positive karyotype and FISH at the same time, while two others had positive karyotype and Rt-PCR. Of the 97 patients whom disease classification was possible, 64 (66%), 11 (11.3%) and 22 (22.7%) patients were in chronic, accelerated, or blast phase at diagnosis, respectively. Symptoms were recorded in only 27 patients with fatigue found in 14 (51.5%), abdominal discomfort in 5 (18.5%) as well as night sweats. Splenomegaly was mentioned in 60 (45.5%) without any other information (Table 1).

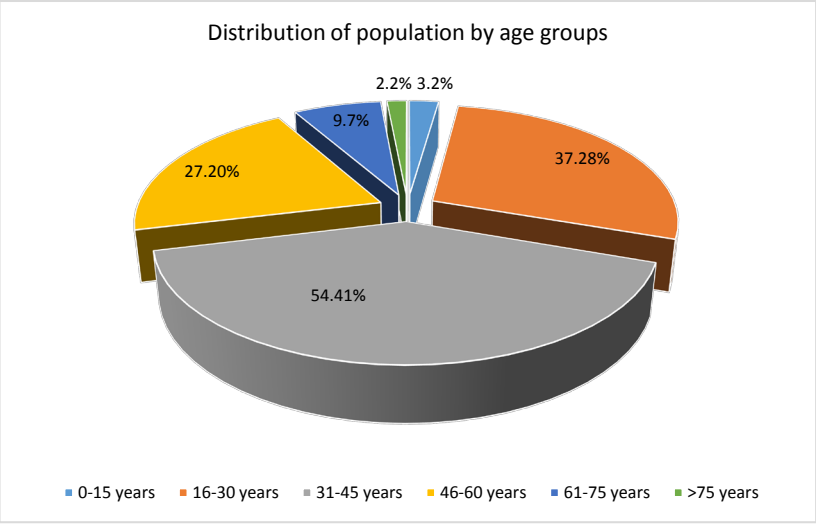

Figure 1. Distribution of the population by age groups.

Table 1. Study population sociodemographic and clinical characteristics.

Variables	Number (n)	Percentage (%)
Gender		
Male	76	57.6
Female	56	42.4
Region		
Adamaoua	2	1.5
Centre	9	6.8
East	0	0
Far-North	0	0
Littoral	8	6.1
North	10	7.6
North West	24	18.2
South	3	2.3
South West	2	1.5
West	74	56.1
Occupation		
Unemployed	35	26.5
Farmer	1	0.8
Trader	5	3.8
Civil servant	10	7.6
Private sector worker	33	25.0
Student	20	15.2
Missing data	28	21.2
Clinical characteristics		
Abdominal mass	3/27	11.1
Night sweats	5/27	18.5
Fatigue	14/27	51.8
Abdominal discomfort	5/27	18.5
Splenomegaly	60/132	45,4
Diagnosis exams performed		
Full blood count	132	100
Blood film	100	75.8
Bone marrow aspiration	10	7.6
Standard karyotype	128	97
FISH	22	16.7
RT-PCR	06	4.5

Hematological data: All patients presented the marked leukocytosis involving the granulocytic lineage, associated with early myeloid cells. The t (9; 22) and/or bcr-abl transcript was found in all patients. Leukocytosis ranged from 27,988 to 588,700/mm^3 with a mean value of 128,367 ± 23,000/mm^3. Most of the patients (60.6%) had their leukocyte count between 100,000 and 200,000/mm^3. Only 5 (3.8%) patients had leukocytosis values of more than 500,000/mm^3 (Figure 2).

Almost all (86.4%) of patients were anemic. Hemoglobin value ranged from 05 to 15 with a mean value of 9.9 ± 2 g/dL (Figure 3). Most of the patients (42.4%) had a hemoglobin level between 9 and 10 g/dL. The anemia was moderate for 61.4% and severe for 5.3% of the study group.

Platelet count ranged from 42,000 to 2,252,000/mm^3 with a mean value of 336,769 ± 280,000/mm^3. Most of patients (42.4%) had platelets count between 200,000 and 400,000/mm^3. Normal platelet count was found in 80 (60.6%), while 11 (8.3%) had thrombocytopenia and 41 (31.1%) patients had thrombocytosis (Figure 4). Only 10 (7.6%) patients had a platelet count greater than 1,000,000/mm^3.

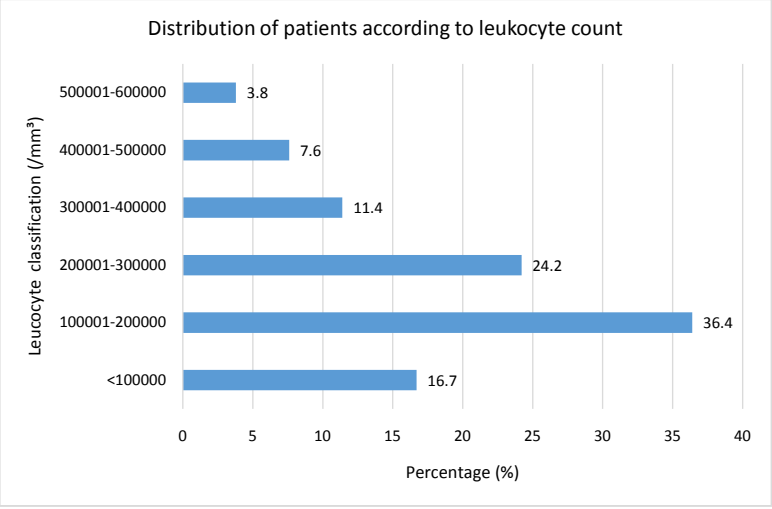

Figure 2. Distribution of patients according to leukocyte count.

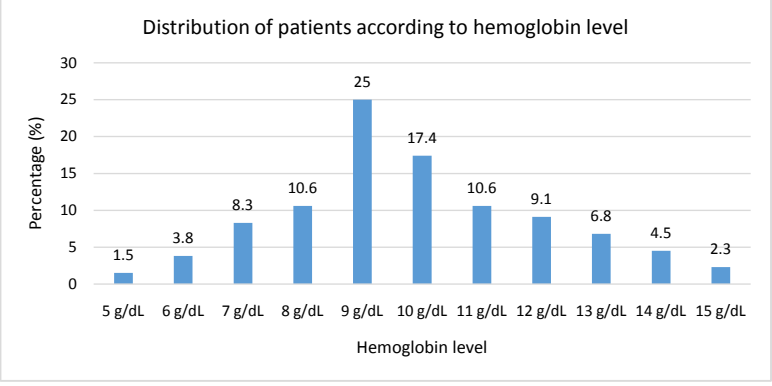

Figure 3. Distribution of patients according to hemoglobin level.

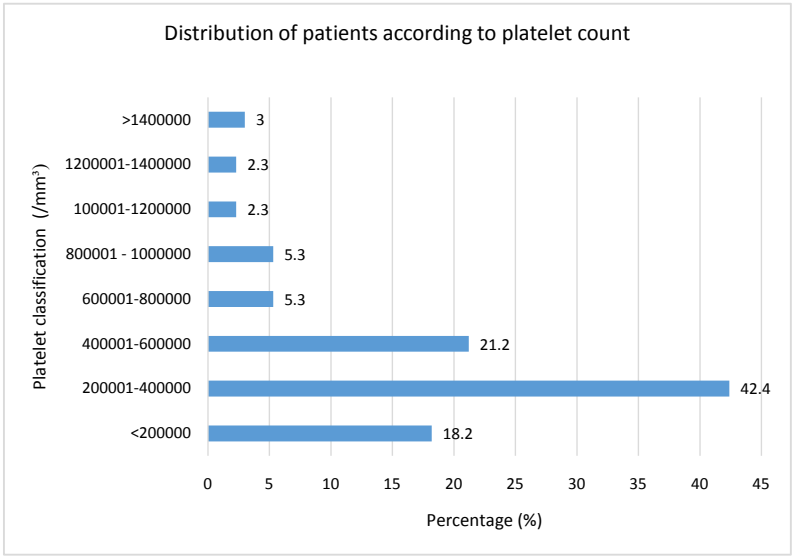

Figure 4. Distribution of patients according to platelet count.

A blood thin-film result was available for only 100 (75.8%) patients. Only 81 of them had information on basophile percentage. Among this population, 48 (59.3%) patients had normal values (<1%) while 32 (39.5%) and 1 (1.2) had respectively a basophile percentage between 2 and 20% and higher than 20%. The basophile mean count was 2800 ± 4100/mm^3. Myeloblast percentage was performed on blood and bone marrow for 88 patients. Thus 56 (63.6%) patients had <10% myeloblast, whereas 10 (11.4%) had between 10% - 20% myeloblast and 22 (25%) more than 20% myeloblasts. The myeloblast mean count was 13,600 ± 17,100/mm^3. Among patients who performed standard karyotype, apart from the classical Philadelphia chromosome, some genetic anomalies have been identified in 15 of them. Among them, Philadelphia chromosome duplication (3/132) and Philadelphia chromosome variants (6/132) were the main additional anomalies.

Other biological exams: Other exams have been performed at the diagnosis in our patients. Most of them were biochemical exams. Transaminase, urea, serum creatinine, and fasting blood sugar means were normal. However, APTT (39.7 s, normal value 20.6 - 28.6), PT (15.3 s, normal value 9.8 - 12.5), plasma uric acid (77.1 mg/L, normal value 40 - 60), GGT (107.2 U/L, normal value 10 - 71), LDH (2809.5 U/L, normal value 15 - 225), ESR (59.4, normal value 1 - 19 mm/H), and CRP (232.8 mg/L, normal value < 5 mg/L) means were increased. Table 2 summarizes the biological exams.

4. Discussion

This cross-sectional study aimed to assess the hematobiological profile at diagnosis in a group of patients with CML in a sub-Saharan African setting. This study represents one of the largest databases of patients with CML in SSA. Epidemiology and prognosis factors for CML are already determined in western and

some sub-Saharan African countries. If epidemiology and prognosis factors are determined for CML in western countries, data is still lacking for the patient's hematobiological profile at diagnosis in the sub-Saharan setting, and particularly in Cameroon [9] [11] [12] [14] [15] [21] [22] [23].

The mean age was 39.2 years (ranging from 11 to 76). It was similar to Chetcha *et al.* (39 years) in Cameroon, Segbena *et al.* (40 years) in Togo, Oyekunle *et al.* (38 years) in Nigeria, Silué *et al.* (39 years) in Ivory Coast and Mupepe in Democratic Republic of Congo [15] [21] [22] [24] [25]. The lower age at diagnosis of CML in SSA reflects epidemiological data, confirming thus, a lower age in low-and middle-income countries in contrary to high-income countries [26] [27] [28] [29]. We found a male predominance in our study, similarly to Chetcha *et al.*, Koffi *et al.*, Oyekunle *et al.*, Mukiibi *et al.* [10] [21] [22] [30]. A risk factor for CML was found in 5 (3.8%) of patients, with the recurrent use of pesticides and insecticides, and work in the field of hydrocarbons being the main risk factors. Risk factors are not usually found in SSA, only Djouadi-Lahlou identified 9 patients (over 1927) with risk factors for CML in Algeria [31].

Table 2. Results of the biological exams.

Variables	Mean	Range
Hematological exam		
Leukocyte count	128,418	27,988 - 588,700
Hemoglobin	9.9	5 - 15
Platelet	336,769	42,000 - 2,252,000
Basophile percentage	2.8	0 - 22
Coagulation tests		
APTT (s)	39.7	33 - 48
PT (s)	15.3	14 - 18
Biochemical exams		
GPT (U/L)	36	12 - 139
Urea (mg/dL)	30	10 - 100
Serum creatinine (mg/dL)	1.2	0.6 - 3.6
Fasting blood sugar (mg/dL)	80	50 - 110
Plasma Uric acid (mg/L)	77.1	13 - 147
GGT (U/L)	107.2	20 - 628
LDH (U/L)	2809	320 - 7741
ESR (mm/H)	59.4	9 - 123
CRP (mg/L)	232.8	24 - 831

As our study is mostly retrospective, there is a lack of clinical signs. Thereby, symptoms were recorded for only 27 patients and splenomegaly was mentioned in 60 (45.5%) patients. The splenomegaly prevalence is lower than that found by Chetcha *et al.* (75%) and Faye *et al.* (80%) [9] [16]. The patients in CP of CML were lower (66%) in our study population comparing to Chetcha *et al.* (79%), Faye *et al.* (85.5%), and Gaudong *et al.* (88%) findings [9] [12] [21]. We did not find any explanation for these proportions.

Full blood count (FBC), blood film and bone marrow aspiration were respectively performed in 100%, 75.8% and 7.6% of our patients. If the FBC rate is similar to other studies, the blood film rate is lower than that performed in Algeria [31]. By the same, the bone marrow aspiration rate was very low compared to that performed by Mupepe *et al.* [25]. Standard karyotype was performed in only 97% of patients (similarly to most of the studies), while FISH was done in 16.7% at diagnosis [9] [25] [31]. PCR was performed in 4.5% of patients. This was higher than Mupepe *et al.* (0%) but lower than Djouadi-Lahlou *et al.* (11%) and Kueviakoe and *al.* (100%) [25] [31] [32].

The leukocyte count ranged from 27,988 to 588,700/mm^3, with a mean of 128,367/mm^3. Most of the patients (60.6%) had their leukocyte count between 100,000 and 200,000/mm^3. This result was similar to Mupepe *et al.* findings, where the 100,000 to 300,000/mm^3 group accounted for 55.2% of the population [25]. Mukiibi *et al.* found almost similar results [30].

Hemoglobin levels ranged from 5 to 15 g/dL, with a mean of 9.9. Among our population, 86.4% had anemia. Most of the patients were between 9 and 10 g/dL. The anemia was moderate for 61.4% and severe for 5.3% of the study group. Our data are similar to that of Kueviakoe *et al.*, in Togo, who found an anemia prevalence of 88.9%. Their patients were also mostly in moderate anemia [32]. However, our hemoglobin level was similar to that of Algeria [31].

Concerning platelet count, it ranged from 42,000 to 2,252,000/mm^3, with a mean of 336,769. Most of our patients (42.4%) had it between 200,000 and 400,000/mm^3. It was normal for 60.6% while 32.1% had thrombocytosis. Our findings were similar to that of Mukiibi *et al.* and Mupepe *et al.* who found that most of their patients had a normal platelet count [25] [30].

Most of our patients (59.3%) had normal basophile count. This was similar to that of Edjeme Gnaneli *et al.*, who found normal basophile count in 77% of his study population [33].

Standard karyotype was performed in 128 (97%) patients, with Philadelphia chromosome (Ph Chr) identified in 108 (81.8%) patients. This was lower than Edjeme Gnaneli *et al.* findings (100%) but higher than Mukiibi *et al.* (13.3%) and Djouadi-Lahlou (10%) [30] [31] [33]. The RT-PCR has been performed in 11% of the study population in Algeria while all patients in Togo have done it [31] [32].

Other biological exams showed normal fasting blood sugar, serum creatinine, urea and GPT levels. However, biological signs of cellular necrosis, coagulation

perturbation and an inflammatory syndrome were found. This reflects the tumoral metabolism and processes. Mupepe *et al.* performed in Kinshasa, uricemia (ranging from 60 to 108 mg/L), fasting blood sugar (ranging from 50 to 172 g/dL) and serum creatinine (ranging from 1.2 to 4.7 mg/dL) [25].

This study should be interpreted in light of some limitations. Most of our patients were recruited in the retrospective phase. As a result, records were not found and data was missing from some of our patients, particularly for clinical signs. On the other hand, bone marrow aspiration, abdominal ultrasound and blood film were not performed routinely in patients with CML, which are necessary to establish the prognostic score at the time of diagnosis. This is due to their expensive cost for the Cameroonian population where the minimum wage is 60.6 USD. Another pitfall of this work was the impossibility to perform a correlation between the disease phase and the biological anomalies.

5. Conclusion

This study described the hematobiological profile at the diagnosis of patients with CML in Cameroon. These patients presented at their diagnosis marked hyperleukocytosis and anemia as hematological clues. Other biological anomalies include increased signs of cellular destruction (uricemia, LDH,) coagulation perturbation and inflammatory syndrome. The chronic phase of the disease was common. Further prospective studies with more laboratory exams are needed as well as an improvement of the technical platform of Cameroonian laboratories in order to locally perform diagnosis tests (standard karyotype, FISH and PCR).

6. Declarations

Ethics Approval and Consent to Participate

This work was approved by the board of the National Committee for Human Health Research (registration number 2016/06/778/CE/CNERSH/SP), the directors of the Yaoundé University Teaching Hospital, the Yaoundé Central Hospital and the Yaoundé General hospital. This work was carried out in accordance with the declaration of Helsinki [34]. All ethical rules involving research on disadvantaged groups such as prisoners have been respected [35]. Patients were free to attend the study without any outside constraint. We obtained informed and signed consent forms from each participant recruited in the prospective phase.

Acknowledgements

None.

Authors' Contributions

Conception and Design: APBN, PN, CTT, DM. Drafting of the manuscript: SRSN, PAT, APBN, PN, CTT, DM. Reviewing Manuscript: PN, CTT, DM. All the authors read and approved the final draft for publication.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

ACS: American Cancer Society
AP: Accelerate Phase
BC: Blast Crisis
CML: Chronic myeloid leukemia
CP: Chronic phase
ELN: European leukemia Net
ET: Essential thrombocythemia
LMIC: Low- and middle-income countries
PMF: Primary myelofibrosis
SOCHIMIO: Solidarité Chimiothérapie
SSA: Sub-Saharan Africa
USA: United States of America
TKI: Tyrosine kinase inhibitor
VD: Vasquez's disease
WHO: World Health Organization
YGH: Yaoundé General Hospital