(RESEARCH ARTICLE)

Epidemiological, therapeutic, cytogenetic, and molecular profile of chronic myeloid leukemia at the national reference university hospital of N'Djamena from 2010-2020, Chad

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Abstract

The aim is to determine the epidemiological and cytogenetic profile (Philadelphia chromosome: Ph1) and the bcr-abl gene in patients with chronic myeloid leukemia (CML) and to assess the therapeutic response of patients to hydroxy-urea and Imatinib treatment. From January 1, 2010 to December 30, 2020, an observational study for diagnostic and analytical purposes was carried out in 54 cases of CML at the National Reference University Hospital (CHU-RN) of N'Djamena. All selected patients presented with splenomegaly on physical examination.

Significant differences were observed between the proportion of housewives (31.48%) and civil servants (3.70%), emaciated patients (27.84%) and those with fever (3.70%) with the probabilities of 0.001 and 0.001 respectively. Hyperleukocytosis ranged from 100,000-149,000 GB / mm^3 (42.30%) and the platelet count ranged from 20,000 / mm^3 to 611,000 / mm^3. Polymorphic and massive myeloma was 30-80% of cases, a medullary karyotype with 33.33% Ph1 + chromosome and 66.66% Ph1-, 33.33% bcr-abl transcript and 33.33% transcribed b3 a2 respectively.

The treatment regimens were: Hydroxy-Urea (HU) + prednisolone (60%), and Imatinib + prednisolone (40%). Partial hematological remission was obtained in 40% of cases. CML is a condition that occurs at all ages and especially in men in our region. The continuation of this study at the national level will allow the public authorities to achieve national prevalence and to organize effective prevention and early management.

Keywords: Chronic myeloid leukemia; Epidemiology; Clinic; cytogenetic; Molecular; Chad

1. Introduction

Chronic myeloid leukemia is a malignant hemopathy belonging to the group of myeloproliferative syndromes characterized by monoclonal bone marrow proliferation predominantly on the granular line [1]. In 95% of cases, it is associated with a specific acquired cytogenetic abnormality: the Philadelphia Ph1 chromosome [2-3]. CML accounts for 2-5% of leukemia in children and 15% of leukemia in adults. [4-5]. this cytogenetic anomaly is a reciprocal translocation between the long arms of chromosomes 9 and 22 [t (9; 22)] whose break points are located respectively in q11 and in q34. The consequence of this translocation is the formation of a hybrid gene called bcr-abl: This gene will encode a protein with tyrosine kinase activity responsible for the leukemia V transformation [6].

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The natural history of CML includes three evolutionary phases:

- Chronic phase: This first phase is gradual onset; it lasts on average 3 to 4 years [7];
- An accelerated phase where the disease progresses more quickly. It usually lasts 6 to 12 months [8-9];
- A blast phase, in which there are 30% or more blasts in the blood and / or in the bone marrow. It lasts from 3 to 6 months. [7].

The incidence of MCL worldwide is 1-2 patients / 100,000 inhabitant / year, with a sex ratio close to 2 between 1.4 and 2.2 affected men per woman [5, 10].

In France, an annual incidence of 600 new cases with a prevalence of 1 in 17,000 French people. The median age at diagnosis is 50 years. The lowest incidence is 0.7 found in Switzerland and the United States, equal to 1.7 [5, 10]. This incidence is lower in Algeria according to the Algerian review in 2004. It can vary depending on the country, it represents 7-15% of adult leukemia according to the published series.

In Mali, two studies have been devoted exclusively to CML. The first in 1981 revealed that CML was hemopathy at that time. Malignancy most frequently encountered at the National Hospital of Point G in Bamako [11].

From the second study carried out in 1996 on this pathology, we could retain, among others that the incidence of CML was 7 new cases per year in the medical hematooncology (HOM) and G-spot internal medicine departments and represented 0.35% of hospitalizations [12]. For 30 years, the only recognized curative treatment for CML has been allogeneic hematopoietic stem cell transplantation, but this treatment is only possible for a small number of patients. Since the 1980s, the vast majority of patients have been receiving interferon alfa, which causes significant side effects and often only moderately effective.

The updated results of the IRIS study, after five years, confirmed the place of imatinib as a first-line treatment in the treatment of chronic myeloid leukemia in the chronic phase, with overall survival close to 90%. Responses improve over the course of time with complete cytogenetic and major molecular response rates reaching 87% and 70%, respectively, at five years [13].

In Chad, there are a few cases of chronic myeloid leukemia that have been observed in the hematology unit but no previous study has been done.

The aim of this etiological diagnostic study is to describe the biological, clinical and epidemiological aspects of CML and to contribute to better therapeutic management of chronic myeloid leukemia in Chad.

2. Material and methods

1.1. Framework, Type and duration of study

This is a prospective observational study that took place in N'Djamena (Chad) for the recruitment of CML patients. Blood samples collected from subjects showing signs of hematologic disease for CML testing:

- Laboratory Hematology Unit of the National Reference University Hospital (CHU-RN) of N'Djamena (Chad).
- Center for the Study and Research in Applied Biology (CERBA) of Paris / France, within the framework of the agreements for the execution of examinations impossible to carry out on site or all stages of molecular biology and research.
- Institute Pasteur of Tunis and the Laboratory of medical analyzes specialized in genetics of Tunis where all the stages of molecular biology were also carried out.

This is an etiological, analytical and observational diagnostic study for cases diagnosed between January-2010 to December-2020 (a period of 10 years).

1.2. Study population

This is any patient coming with clinical and laboratory signs of CML.

1.3. Inclusion criteria

Patients with CML who met the following criteria were included in this study:

- Have CML documented by a blood count and / or a myelogram and / or by cytogenetics;
- Have been followed in the service.

1.4. Non-inclusion criteria

Patients without CML documented by blood count and / or myelogram and / or cytogenetics.

1.5. Epidemiological investigation

We look for epidemiological data in each of our patients (age, sex, profession, medico-surgical and gyneco-obstetrical history, lifestyle and date of onset of the disease, the first signs of reason for consultation and the waiting time. diagnostic).

1.6. Clinical investigation

The collection of clinical data was carried out from questionnaires co-signed on the survey form.

The ordered somatic examination of each patient made it possible to look for a tumor syndrome with:
- Lymphadenopathy (≥ 1cm) ;
- Splenomegaly (type according to HaCkett).
- Hepatomegaly ;
- We appreciated the general condition.
- Weight loss or not, fever.

1.7. Data processing

The chi-square test (χ^2) was used for the comparison of qualitative variables with a significance level set at 0.05.

3. Microbiological analysis

The biologics we looked at were whole blood, serum, or plasma. These products have been tested in the various laboratories with the various screening kits.

1.8. Thin smear technique

- The drop of blood should be half smaller than that used for the thick drop.
- Apply the edge of another glass slide to the drop of blood at an angle of 45 °, allow the blood to spread by capillary action all along the edge of the blade.
- Push the blade forward while keeping it at the same angle.
- It is essential to push the blade all at once and without stopping or restarting; blood should follow the blade and should not be pushed by it.
- A well-done smear should consist of a thin, even layer of blood, without the tip of the smear touching the edge of the slide. Dry the smear immediately by shaking the slide or placing it in front of a ventilator.

1.8.1. May Grunewald Giemsa coloring (MGG)

- For better staining of the smears, the pH of the solution should be adjusted to 7.2.
- Staining can be fast or slow depending on whether you are using ready-to-use May-Grunwald solutions or Giemsa stock solution or diluted 1/10 (1-part Giemsa to 9 parts distilled water).

1.8.2. The stages of MGG staining

- Cover the smear with May-Grunewald's solution, leave to act for 2 to 3 min.
- Discard the dye by washing with water.
- Cover the smear with Giemsa solution and leave to act for 5 min.

- Discard the stain by washing with water, draining and drying the stained slide between two sheets of blotting paper or at laboratory temperature.

Microscopic observation of MGG staining is done at the x100 objective with immersion oil.

1.9. Assessment method

1.9.1. Diagnostic assessment

- Blood count ;
- Cytogenetic ;
- Myelogram ;
- Molecular biology.

1.10. Search and quantification of the V617F JAK2 mutation by RQ-PCR and of the bcr-abl transcript by RT-PCR

As part of the North-South collaboration, six cases of suspected CML were collected and sent to the CERBA laboratory in Paris, France for the search for medullary karyotype and bcr-abl genes. The RQ-PCT and RT-PCR tests were performed according to the techniques developed by laboratory biologists CERBA, of the Pasteur Institute of Tunis and the Laboratory of medical analyzes specializing in genetics of Tunis, the results of which were sent to us for the care of our patients.

1.11. Another patient assessment

The purpose of this assessment will be to look for possible complications that could compromise the vital prognosis, these are:

- Assessment of hemostasis (TP, TCK);
- L I-D-R with Tuberculin.
- ABO and rhesus blood group.
- ECG ;
- Hemoglobin electrophoresis ;
- Blood sugar ;
- Uricemia ;
- Blood ionogram with calcemia, creatinemia.

1.12. Infectious assessment

- GE ;
- HIV retroviral serology.

    Blood culture if there is a call sign.

1.13. Therapeutic protocols

- Hydroxyurea 100 mg / kg / day per os + Prednisolone 20mg / kg / day per os;
- Imatinib 400 mg / day per os + Prednisolone 20mg / kg / day per os.

1.14. General Full Remission (RCG)

The absence of a Philadelphia chromosome on cytogenetic examination may be complete or partial, even incomplete.

1.15. Complete Hematologic Remission (CRR)

This is the normalization of the blood count and the disappearance of the clinical signs of the disease.

1.16. Incomplete Hematologic Remission (IHR)

At least 50% decrease in white blood cells or normalization of white blood cell count but with persistent splenomegaly or myeloma.

1.17. Failure

This is a lack of improvement of the initial picture.

4. Results

1.18. Epidemiological aspects

During the survey (2010 to 2020), 1027 patients with signs of all hematological diseases were recruited, including 54 cases of CML (5.25%). The average age of the selected patients was 33 years with the extreme ranging from 7 to 60 years of the 54 cases of CML identified, 30 (57.69%) patients were lost to follow-up, 19 (36.53%) died and 5 (9.25%) patients were alive and being followed.

1.19. Distribution of patients according to the therapeutic protocol

Of the five (5) living patients, 3 (60%) were on hydroxyurea (HU) + prednisolone, and 2 (40%) on Imatinib + prednisolone. Two of the patients followed were HBsAg positive and one case of HIV1 +. Partial hematological remission was observed in 40% (2 cases) versus 60% (3 cases) of failure.

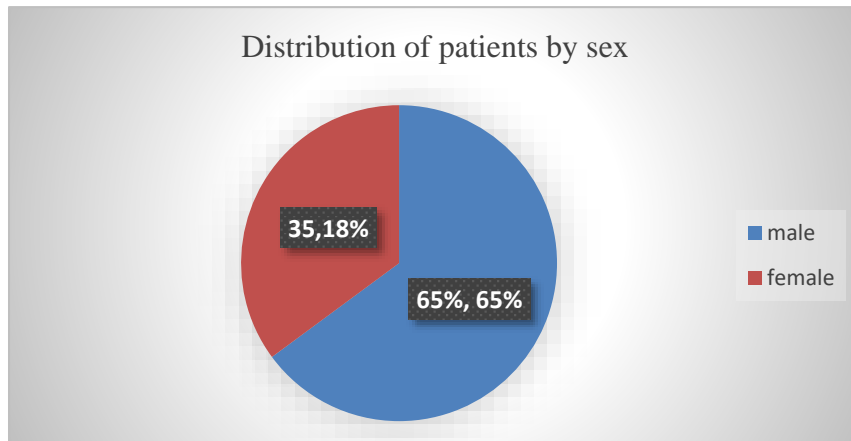### 1.20. Distribution of patients according to age group

Table 1 shows the distribution of patients according to age group. The average age was 33 with the extreme ranging from 7 to 60. The most affected age group was 46-55 years old (31%).

Table 1 Distribution of patients according to age group

Age (year)	Number	%
0-15	2	4
16-25	9	17
26-35	13	25
36-45	7	13
46-55	16	31
56-65	6	11.1
>65	1	1.8
Total	54	100

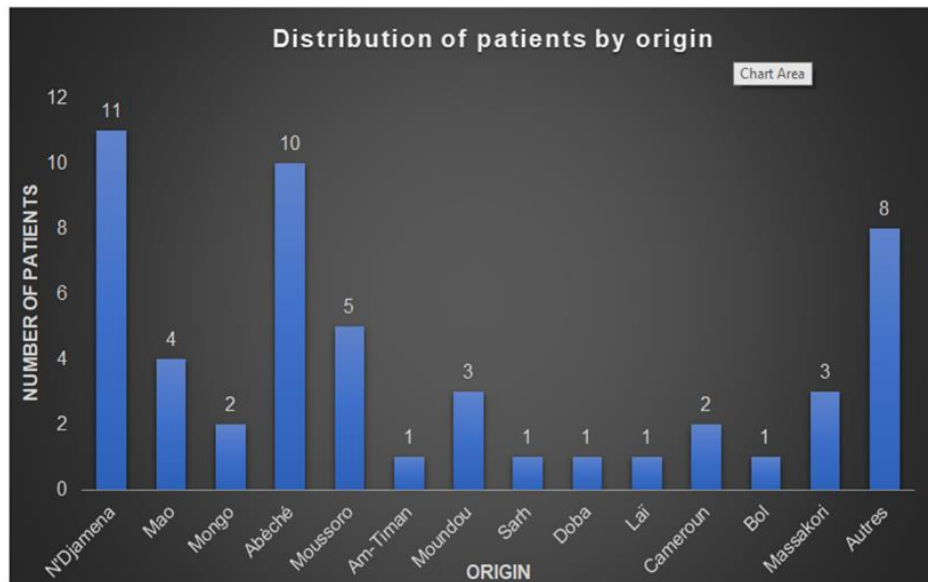### 1.21. Distribution of patients by sex

Figure 1 illustrates the distribution of patients by sex. Men were the most affected 35 (64.81%) compared to women 19 (35.18%) or a sex ratio of 1.8 (M / F).

Figure 1 Distribution of patients by sex

1.22. Distribution of patients by origin

Figure 2 illustrates the distribution according to the origin of the patients. Origin is one of the socio-demographic characteristics of patients with CML, including 11 (20.37%) residing in N'Djamena the capital of Chad, 10 (18.51%) in Abéché, 5 (9.25%) from Mossoro, 1 (1.85%) from (Amtiman, Sarh, Doba, Laï, Bol), 3 (55.55%) from (Moundou, Massakory) and 2 (3.70%) (Kousseri/Cameroon border from the capital and Mongo respectively and 4 (7.40%) from Mao. The other eight (8) (14.81%) did not specify the place of origin. The origin of the patients was more important in N 'Djamena (20.37%) followed by Abéché (18.57%).

Figure 2 The distribution of patients according to origin
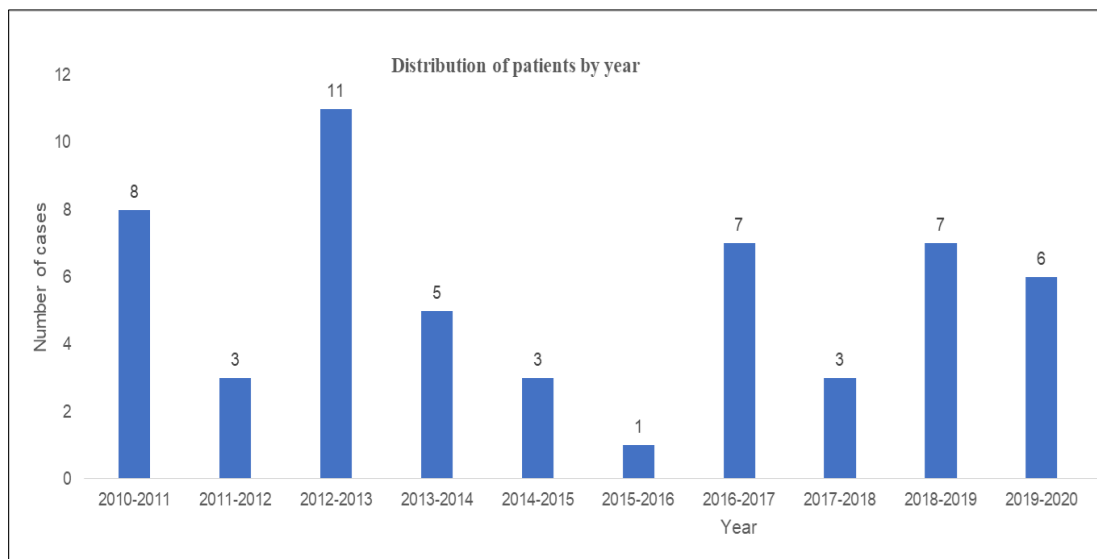
1.23. Distribution of patients by profession

Table 2 shows the distribution of patients by profession. The prevalence of patients by profession is 17 (31.48%) for housewives, 10 (18.51%) farmers, 15 (27.77%) breeders, 3 (5.55%) pupils / students, 5 (9.25%) painters / carpenters, 2 (3.70%) civil servants, 2 (3.70%) others of which no details of any profession were notified. Housewives (31.48%) were in the lead followed by breeders (27.77%), a non-significant difference (x^2 = 0.023; dof = 1; p = 0.90). A significant difference was observed between the proportion of housewives (31.48%) and (3.70%) civil servants (x^2 = 51.94; dof = 1; p = 0.001).

Table 2 Distribution of patients by profession

Profession	Number	%
Housewives	17	31.4
Farmers	10	18.5
Breeders	15	27.7
Pupils / Students	3	5.5
Painters / Carpenters	5	9.2
Functionary	2	3.7
Other	2	3.7
Total	54	100%

1.24. Distribution of patients by year

The distribution of CML cases by year over the period from 2010 to 2020 was: 8 cases (15%) from 2010 to 2011, 3 cases (5.55%) from 2011-2012, 11 cases (20.37%) from 2012 to 2013, 5 cases (9.25%) from 2013 to 2014, 3 cases (5.55%) from 2014 to 2015, 1 case (2%) from 2015 to 2016, 7 cases (13%) from 2016 in 2017, 3 cases (5.55%) from 2017 to 2018, 7 cases (13%) from 2018 to 2019 and 6 cases (11.11%) from 2019 to 2020 respectively. The predominance of patients was observed in the year 2012-2013 followed by 2010-2011 and the years 2016-2017, 2018-2019 respectively (Figure 3).

Figure 3 Distribution of patients by year

1.25. Distribution of patients according to recorded clinical signs

Figure 4 illustrates the various clinical signs recorded during the investigation. All the patients presented conjunctival pallor and splenomegaly. Among them, 8 (14.81%) cases of hepatomegaly, 15 (27.77%) of weight loss (non-significant difference: $x^2 = 2.279$; dof = 1; $p = 0.10$), two (2) cases fever (3.70%); thirteen (13) cases (24.07%) of diffuse pain and one (1) case (1.85%) of dyspnea. We found one (1) case of hemorrhagic syndrome.

A significant difference ($x^2 = 34.08$; dof = 1; $p = 0.001$) was observed between the proportion of emaciated patients (27.84%) and those with fever (3.70%).

The photos (a, b, c) in Table 5 illustrate the cases of splenomegaly at stages IV and V of the patients surveyed. We found in all the patients surveyed, the different stages of splenomegaly according to Hackett stage 0: 2 (3.70%), stage 1: 4 (7.40%), stage 2: 10 (18.51%), stage 3:25 (46.29%), stage 4:12 (22.22%), stage 5: 1 (1.85%) respectively.
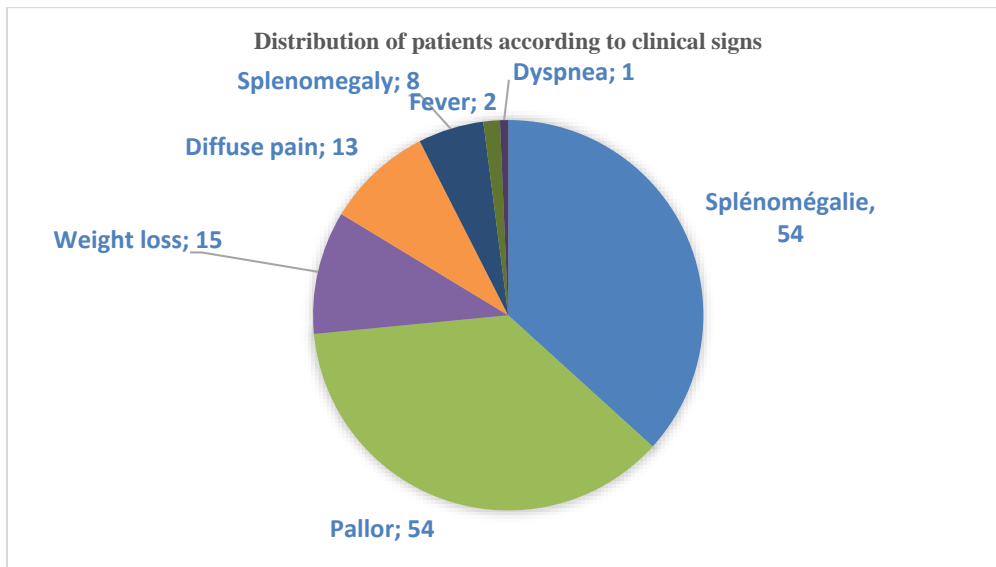
Figure 4 Distribution of patients according to clinical signs

1.26. Distribution of patients based on Blood Formula Numeration (BFN) data

Table 3 Distribution of patients according to BFN data

Blood Formula Numeration (BFN)	limit value	Number	%
Hemoglobin level (g/ dl)	<5.9	7	12.96
	6-9.9	30	57.69
	10-11.9	15	28.84
	>12	2	3.70
	Total	54	100
White Blood Cell Count /mm^3	<100 000	15	28.84
	100 000-149 000	22	42.30
	150 0000-300 000	12	23.07
	300 000-500 000	2	3.70
	>500 000	3	5.55
	Total	54	100
Platelet count / mm^3	<150 000	14	25.92
	150 000-450 000	19	36.53
	>450 000	21	40.38
	Total	54	100
Neutrophils	<20	11	21.15
	20-40	15	27.77
	>40	28	51.85
	Total	54	100
Basophils	<1	3	5.55
	1-5	42	80.76
	>5	9	16.66
	Total	54	100
Eosinophils	<2	10	19.23
	2-5	14	26.92
	>5	30	55.55
	Total	54	100

All patients presented with hyperleukocytosis with a minimum of 144,000 / mm³ and a maximum of 515,000 / mm³ with a mean of 329.5,000 / mm³.Anemia was present in 95% of cases with a hemoglobin minimum of 5.6 g / dl and a maximum of 12.1 g / dl with an average hemoglobin level of 8.85 g / dl.

The platelet count varied between 20,000 and 611,000 / mm³ with an average of 315.5,000 / mm³ and a median of 300,000 / mm³.
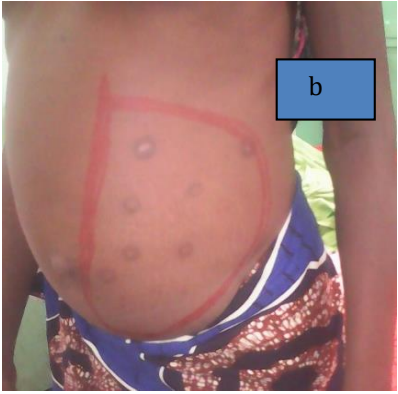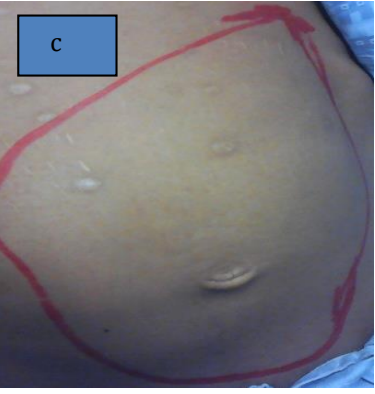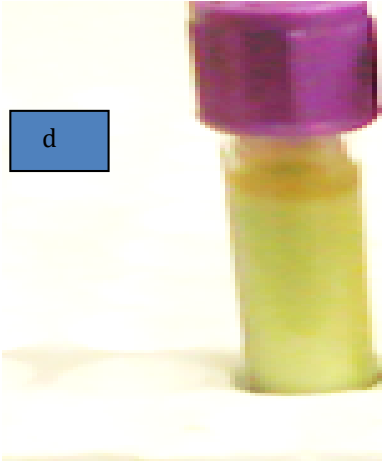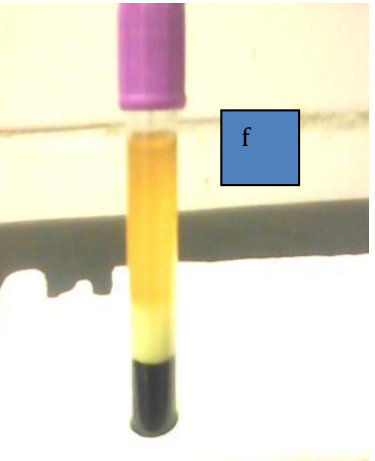
The polymorphous and massive myeloma was in 30 to 80% of cases and composed essentially of metamyelocytes, myelocytes with few promyelocytes and blasts (from Table 4, figure: g, h, i, j, k, l).
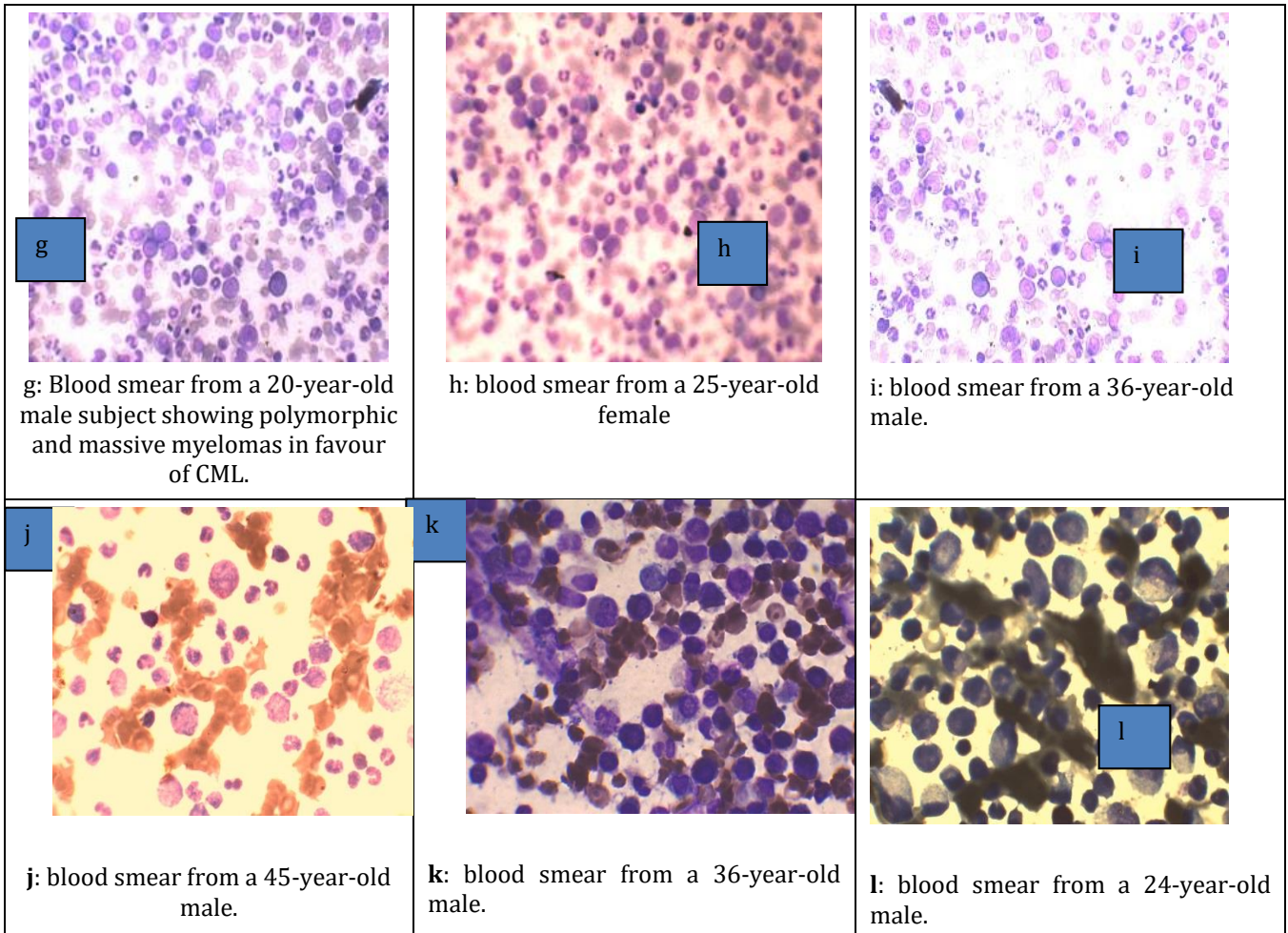
1.27. Cytogenetic examination (Search and quantification of the V617F JAK2 mutation by RQ-PCR)

As part of the North-South collaboration, six (6) cases of suspected CML were collected and sent to the CERBA laboratory in France for the medullary karyotype. Of the 6 samples, 2 (33.33%) were Philadelphia chromosome positive (Ph1 +) and four (66.66%) Philadelphia chromosomes negative (Ph1-).

1.28. Molecular biology (bcr-abl transcript search by RT-PCR)

Table 4 Macroscopic and microscopic characteristics of chronic myeloid leukemia

a: splenomegaly stages IV, 23-year-old patient.

b: splenomegaly stage IV, 25-year-old patient

c: splenomegaly stage V, 36-year-old patient.

d : milky appearance of the blood of a 20-year-old patient with CML.

e: blood sample from a normal subject.

f: blood sample from a 46-year-old subject with HIV / AIDS and CML. The blood is separated into 3 phases: 1 (upper part of the tube: plasma); 2 (middle of the tube: milky appearance); 3 (blood pellet).

g: Blood smear from a 20-year-old male subject showing polymorphic and massive myelomas in favour of CML.

h: blood smear from a 25-year-old female

i: blood smear from a 36-year-old male.

j: blood smear from a 45-year-old male.

k: blood smear from a 36-year-old male.

l: blood smear from a 24-year-old male.

(Photos : Mbairané and al, 2017- 2018)

Two Ph1 + patients who had traveled to France themselves were detected as bcr-abl transcribed by RT-PCR. Two others, one of whom was at the Pasteur Institute in Tunis and the other at the Laboratory of Medical Analysis Specialized in Genetics in Tunis, were detected the same type of b3a2 transcript.

5. Discussion

The average age of the population in our study was 33 years with the extremes of 7 and 60 years. The most affected age group was 46 to 55 (31%). In addition, there is a difference in most of the average ages found in Abidjan: 41 years in 2008, 44 years in Morocco in 2014, 47.03 ± 17.15 years for studies conducted at the University Hospital Center (CHU) of Kinshasa in 2010. The European statistical series also found the average of 41 years in 1986, 1990, 1995, 2004 and 2009 respectively [1, 14, 16, 33, 38, 40].

We found a male predominance with a sex ratio of 1.8 which was classically found in the literature in 2009 [17-18]. Kueviakoe et al in Lomé found a sex ratio of 1.4 in 2006 [19]. Nacoulma, Segbena et al found sex ratios of 1.5, 1.75 and 2.12 in 2007 and 1997 respectively [20, 21]. On the other hand, SANOGO et al reported a sex ratio of 0.9 in 2010 [22].

The majority of patients were from the province of N'Djamena (20.37%) followed by the Province of Abéché and 8 (14.81%) subjects did not have any details regarding the place of origin. The results of this study corroborate those obtained by other authors elsewhere [23].

In this study, 52 (96.29%) details were provided on the patient's profession and 2 (3.70%) had no information available. Housewives were in the lead, followed by breeders and farmers (Table 2). Moreover, a study carried out in Algeria specifically in Tlemsen by Benouda et al in 2010 simply stated that the majority of patients were retirees and that they had done several jobs during their life [23]. The exposure of these socio-professional categories to CML is probably linked to the use of unapproved chemicals (herbicides, insecticides, pesticides, etc.) in agriculture, breeding and for intra-home spraying to control harmful insects.

Regarding the level of education, 23 (42.59%) of the patients were out of school, 15 (27.77%) at the primary level; 11 (20.37%) of secondary level and finally 5 (9.25%) higher level respectively. We could explain this by the socioeconomic and political situation of developing countries in general and Chad in particular. In addition, the authors simply reported that 46.2% of patients were of average socio-economic status in 2008 [1].

Splenomegaly was found in 100% of the cases in our study. Our results were similar to those observed elsewhere [20, 26]. On the other hand, lower proportions were observed: 95.6% (Morocco in 2005) 64.8% (in Algeria) and 96.2% in Bamako in Mali [1, 24]. Some European authors have also reported a proportion of 95% [14, 15, 25].

Hepatomegaly was reported in 15.38% of cases in our study, while the study by Nihal Zekkari found a high proportion of 48% of cases in 2014 [23, 27].

In our study, no patient presented with the sign of lymphadenopathy. This result was contrary to those obtained by Paye (40%) of cases in 1960 and Benabdeljelil (35%) of cases in 1980 in Morocco [28, 29].

We found one case (2%) of hemorrhagic syndrome in this study. In addition, at the Kinshasa University Hospital, 34.5% of patients had hemorrhagic syndrome in 1997 while at the Hassane II University Hospital of FES, 30% of cases of gingivorrhagia, ecchymosis type was found in 2010 [23, 28, 30]. The low proportion of hemorrhagic syndrome obtained in this study could be explained by the fact that in Chad, only one hematology unit was supposed to receive referrals and often late.

At the end of the biological data of this study, the parameters of the blood count were:

- Hemoglobin (Hb) averaging 8.85 g / dL with extremes of 5.6 g / dL and 12.1g / dL);
- Leukocytes on average 329.5000 / mm^3 with the extremes of 144 and 515000 / mm^3);
- Platelets averaging 315.5,000 / mm^3 with the extremes between 20,000 and 611,000 / mm^3;
- All the patients had hyperleukocytosis with the mean 329.5000 / mm^3.

The results obtained from this study were different from those obtained by certain African authors: Konam at the CHU of Yopougon in Côte d'Ivoire in 1997, Nacoulma in Burkina Faso found an average rate of leukocytosis at 243,000 / mm^3 and 214,000 / mm^3 respectively [20, 31]. The results of this study were also different from those reported by studies in Europe between 1955-1975 [32].

The low prevalence rate of 5 living patients (9.25%) in this study compared to 30 (57.69%) patients lost to follow-up and 19 (36.53%) deceased could be explained by a delay in diagnosis. but also, the late referrals and the lack of therapeutic means for the adequate and correct management of CML patients.

Regarding anemia, the average hemoglobin (Hb) was 8.85g / dL (range 5.6 to 12.1g / dL), 98% of our patients had moderate anemia. This result was similar to that obtained by a study carried out in Bamako in 2007-2008 which had reported a proportion of 98% of cases of moderate anemia in patients with the hemoglobin level which oscillated between 5 to 12.7g / dL with the average of 8.77g / dL in 69% of cases [1]. In addition, several African authors have reported a proportion of anemia of 90% of cases in CML patients [20-26-33-34-35-36-37].

The anemia could be explained by a combination of comorbid factors such as malaria, multiple transfusion with ineffective transfusion yield, traditional treatment with harmful scarification practice as well as other bacterial (salmonellosis) and viral (HIV) infections. -AIDS, HBsAg).

The platelet count found in this study averaged 315.5,000 / mm^3 with the extremes of 20,000 and 2,611,000 / mm^3. Thrombocytopenia and hyperplaquetosis were also noted in this study. Therefore, our work was comparative with the study done elsewhere which found platelet counts between 109,000 and 2,092,000 / mm^3 with the mean of 444,186.84 / mm^3 and a median of 334,500 / mm^3 [1, 36].

The hyperplaquetosis and thrombocytosis determined in this study population were in agreement with the data in the literature [39-40].

6. Conclusion

CML should be considered a priority public health problem, and its management should be reviewed nationally.

In the light of this work spread over a period of ten years, having concerned 54 patients, it appears that the epidemiological, clinical, biological and therapeutic aspects of recruited CML have made it possible to update knowledge on malignant hemopathies in hospitals, and formulate research questions for a better understanding of this condition.

Research studies on factors favoring the onset of CML and strategies for earlier diagnosis in Chad should be continued. Access for patients to free chemotherapy, to bring together the scientific and technical conditions allowing the monitoring of evolution by molecular biology, and the karyotype is desirable.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Statement of informed consent

Verbal consent of each patient or their beneficiary to whom / to whom we have explained the procedure and the importance of the study and their participation.

Ethical and administrative considerations

Our study previously received:

- Authorization from the Dean of the Faculty of Human Health Sciences.
- Authorization from the Director General of the General National Reference Hospital of N'Djamena.

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