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Cytogenetic Profile of Chronic Myeloid Leukaemia (CML) in Patients Received at the Medical Biology Laboratory of the Pasteur Institute in Dakar

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: The objective of this study was to determinate cytogenetic profiles of patients received at the medical biology laboratory of the Pasteur Institute of Dakar over a 2-year period.
Methods: Twenty-nine samples on heparinized tube from patients suspected of having myeloproliferative syndromes with clinical information sheets were sent to the Biomnis laboratory for cytogenetic study. Karyotyping and molecular cytogenetic analysis: fluorescence in situ hybridization (FISH) was performed on all patients.
Results: The mean age of the patients was 39 years [CI=95%] with extremes of 15 and 68 years. There was a male predominance with a gender ratio M/W of 1.41 and the most represented age group was 35-49 years. The molecular study showed the BCR-ABL transcript present in 86% (n=25) of patients and absent in 14% (n=4). In conclusion 82.76% (n=24) of the patients had chronic myeloid leukaemia with the transcript present in 100% including one patient with translocation t(9;22;16) (q34;q11;p13) as an associated chromosomal abnormality, one case of Phi+ acute leukaemia was also noted.
Conclusion: The FISH analysis is a significant technological advance in the diagnosis and monitoring of CML treatment in Senegal because it can detect several variants resulting from the t(9;22) translocation, which would allow the prediction of primary or secondary resistance in patients.

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Keywords: CML; BCR-ABL transcript; chromosomes; cytogenetic.

1. INTRODUCTION

Chronic myeloid leukaemia (CML) is a myeloproliferative syndrome that results from an acquired genetic mutation: the reciprocal translocation between chromosomes 9 and 22. The Philadelphia chromosome (Ph1) derived from this translocation generates a BCR-ABL protein responsible for the tyrosine kinase activity that causes CML [1]. The disease progresses in three phases. The chronic phase, with an average survival of 5 years, is generally followed by an accelerated phase, which precedes the almost inevitable acute transformation, which is fatal in 3 to 6 months. The management of CML has made considerable progress over the last decade. Until 2000, the treatments offered to CML patients were interferon alpha and bone marrow transplants, which were reserved for a minority of people and at the cost of significant toxicity [1]. The discovery of BCR-ABL opened a new chapter in the treatment of CML. Recent therapeutic advances have led to the application of highly effective so-called targeted therapies with anti-tyrosine kinase activity [2]. Imatinib (GLIVEC®) is a first-line treatment for patients with CML. Diagnosis and monitoring of this disease is mainly done by cytogenetic and cytogenomic approaches (karyotype and fluorescence in situ hybridization (FISH)), which identifies the t(9;22). RT-PCR is then used to identify the type of BCR-ABL transcript present, depending on the location of the breakpoints, which may vary on ABL [3].

With this in mind, we looked at the cytogenetic profile of patients with chronic myeloid leukaemia by karyotyping and FISH/BCR-ABL at the medical biology laboratory of the Institute Pasteur in Dakar.

2. METHODOLOGY

2.1 Type and Population of Study

This is a retrospective study of patients seen in the medical biology laboratory of the Pasteur Institute of Dakar for a cytogenetic study over a period of 2 years, which enabled us to identify 29 patients.

It concerned patients seen in consultation by a haematologist and/or oncologist and presenting clinical and/or biological signs of CML, who were referred to us for diagnosis or follow-up.

In all cases, a blood sample on a heparinized tube was taken and sent to the laboratory under optimal storage conditions, accompanied by an information sheet to be filled in by the attending physician with the following data:

- clinical and therapeutic information
- results of the CBC-platelets
- myelogram report

The sample is sent to the Biomnis laboratory for culture and chromosomal analysis by FISH.

2.2 Data Processing and Analysis

The regularly checked and corrected data were recorded and processed using Excel 2016 software. Anonymity was ensured by using the patient's registration number. The analysis focused first on the description of the socio-demographic profile of the patients and the results of karyotyping and FISH/BCR-ABL.

3. RESULTS

3.1 Socio-demographic Characteristics

The characteristics of our study population are summarised in Table 1. Among the 29 patients included, there were 12 women (41.38%) and 17 men (58.62%). Subjects aged between 35 and 49 years represented 37.93% of the sample. The median age was 39 years [CI=95%] with extremes of 15 and 68 years.

3.2 Genetics Results

3.2.1 According to karyotyping

After cell culture, metaphases were obtained in 16 patients or 55% of the sample (Fig. 1). However, one case with the translocation (9;22;16) (q34;q11;p13) has been described.

3.2.2 Molecular cytogenetic results (FISH) and associated chromosomal abnormalities

According to molecular cytogenetics, the BCR-ABL fusion gene was found in 25 patients or 86% of patients (Fig. 2).

Table 1. Socio-demographic characteristics

Number of patients	Number	Percentage
	29	100
Gender		
Men	17	58.62
Women	12	41.38
Medium Age	39 years	*
[Extremes]	[15 – 68 years]	
Age group		
<20	1	3.45
21-34	10	37.46
35-49	11	37.93
>50	7	24.14

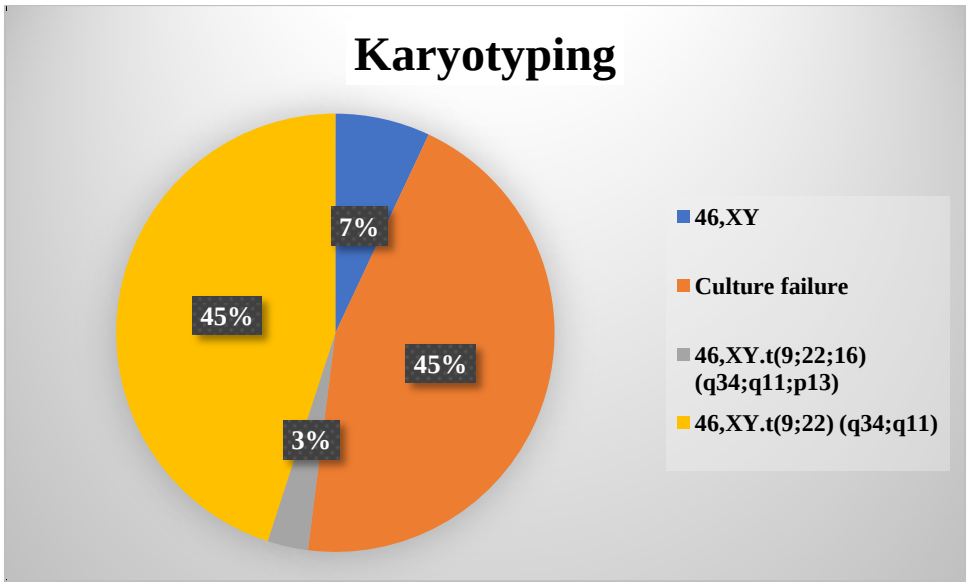

Fig. 1. Distribution of patients according to cell culture success

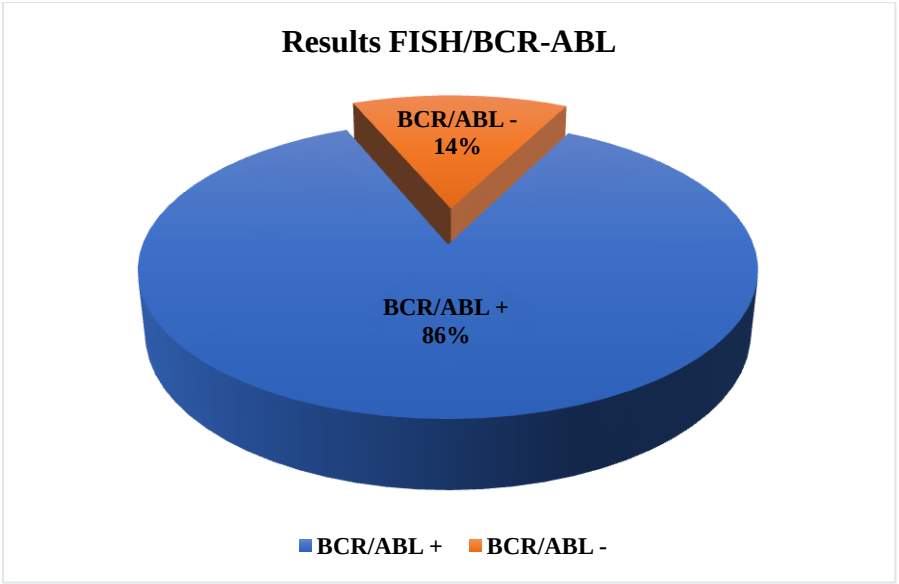

Fig. 2. Molecular cytogenetic results (FISH)

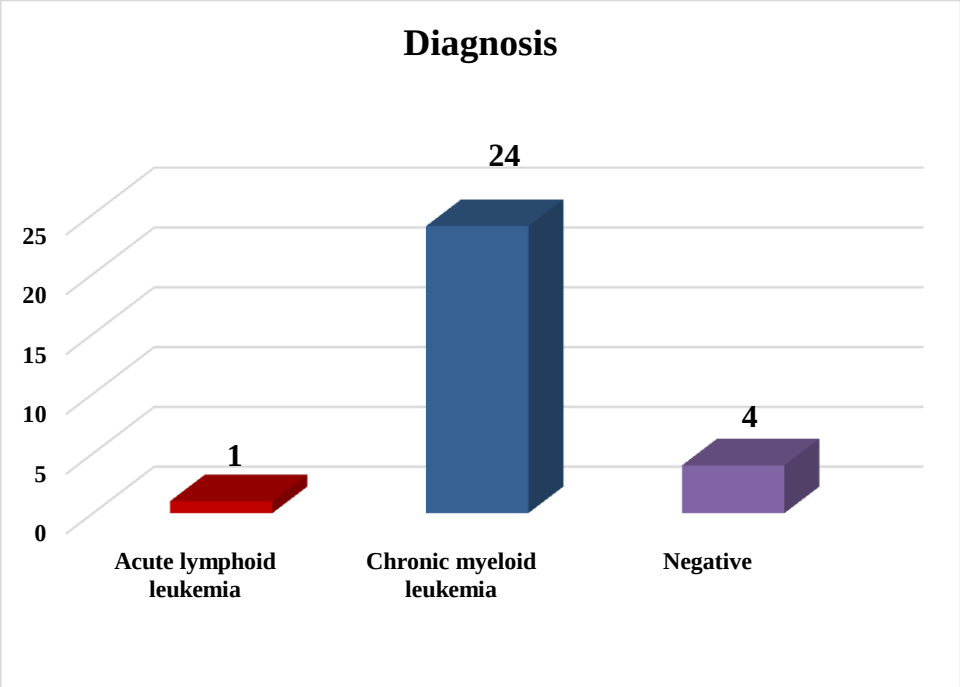

Fig. 3. Results according to diagnosis

According to the chromosomal abnormalities associated with the Philadelphia chromosome, these were noted in 4 patients, 2 patients had a duplication of the Philadelphia Chromosome, a variant translocation (9,22) associating chromosome 16 t(9;22;16) (q34;q11;p13), and a translocation at chromosome 11 and 18 t(11;18) (p11;p11) were also noted.

3.3 Diagnosis Retained

At the conclusion (Fig. 3), the diagnosis of chronic myeloid leukaemia (CML) was retained in 24 patients or 82.76%, one case of acute leukaemia with the BCR-ABL transcript and 4 patients without myeloproliferative syndromes or 13.79%.

4. DISCUSSION

This study looked at the cytogenetic profile of patients received in the laboratory of the Pasteur Institute in Dakar for diagnosis or molecular monitoring of myeloproliferative syndromes. This small number can be explained by the fact that the Pasteur Institute in Dakar probably does not receive all CML cases diagnosed in Senegal. In general, there is a problem of patient adherence to long-term medical monitoring in sub-Saharan Africa [4]. In our study cohort, we found a slight male predominance with a M/F sex ratio of 1.41. This result is similar to that found in the literature, both in Africa and in Togo, with a sex ratio of 1.61 [5] than in Europe or the U.S.A. However, in previous studies in Mali, women were found to be more affected than men in both children and adults [6,7]. The most represented age group in our study was slightly the 25-49 years olds with 37.93% followed by the 21-34 year olds with 37.46%. This result is also different from that reported in the literature. In Europe the median age at diagnosis is 60 years, and 65 years in the U.S.A [8].

The mean age of 39 (extremes of 15 and 68 years) was close to that of Mukiibi et al. [9]. in Central Africa, Dokekias et al. [10] in Congo Brazzaville, and de Souza et al. [11] in Brazil, who had reported a mean age of 38.9, 35 and 32 years respectively. On the other hand, Tardieu et al. [12] in France and Sureda et al. [13] in the USA found a mean age of 50 years. These results show that CML is a frequent disease in young adults.

After cell culture, we obtained metaphases in 16 patients or 55% of the sample. According to the associated chromosomal abnormalities 2 patients had a duplication of the Philadelphia chromosome, a translocation at chromosome 11 and 18 t(11;18) (p11;p11) and a translocation (9;22) associating chromosome 16 t(9;22;16)

(q34;q11;p13) were also noted. Dewald et al. reported a similar case of atypical signal in the nuclei [14] and concluded by karyotype to a complex translocation 46,XY, t(9;22;19)(q34;q11.2;q13.3) involving chromosome 19.

According to the results of molecular cytogenetics, the BCR-ABL transcript was found in 25 patients or 86% of whom 24 had chronic myeloid leukaemia and only one had acute myeloid leukaemia (Fig. 3). The BCR-ABL fusion gene is present in all CMLs, 3-5% of childhood acute lymphoid leukemia (ALL), and 15-30% of adult acute lymphoid leukemia (ALL) [15] in line with our results. Consequently, the BCR-ABL fusion gene is routinely screened for the diagnosis of CML and Ph+ acute lymphoid leukemia (ALL). Furthermore, since the introduction of tyrosine kinase inhibitors as a treatment for CML and Ph+ acute lymphoid leukemia (ALL), BCR-ABL fusion gene quantification is also performed as part of the therapeutic follow-up.

5. CONCLUSION

CML has long been a model in onco-haematology : the first chromosomal abnormality described in a malignant disease, numerous studies clarifying the mechanisms of leukaemogenesis, the introduction of standardised molecular techniques in the monitoring of the disease, the first disease in which targeted molecular therapy has been used successfully. Clinico-biologically, CML has become a "molecular disease" since in cases of cytogenetic remission (the most numerous), the only marker of the disease is molecular (BCR-ABL mRNA).

CONSENT AND ETHICAL APROVAL

As per international standard or university standard, patients' written consent and ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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