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Cytogenetic and Molecular Remission in Chronic Myeloid Leukemia in Togo

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Abstract

The availability of tyrosine kinase inhibitors (TKIs) in Togo through the GIPAP program has revolutionized the management of chronic myeloid leukemia and increased patient life expectancy. However, diagnosis and molecular monitoring of therapeutic efficacy remain a real challenge due to the inaccessibility of cytogenetic and molecular biology tools. We've conducted, a cross-sectional, descriptive study that ran from December 21, 2022, to January 20, 2023, with the aim to evaluate the cytogenetic and molecular remission in CML patients followed at the CHU Campus de Lomé in Togo. Patients diagnosed with chronic-phase CML who had been treated for at least three months with imatinib or dasatinib and had achieved complete hematological remission were included. Dosage of BCR-ABL transcript levels was performed by RQ-PCR in Seattle, USA, using Dried Blood Spot. The transcript detection limit was 0.003% i.e., MR^4. A total of 38 patients were included, 68.4% of them were treated with imatinib and 31.6% with dasatinib. In terms of remission, 28.9% had not achieve a partial cytogenetic remission while 15.8% of patients had achieved a MR^4 remission and 7.9% a major molecular remission. Major molecular remission was achieved at a mean follow-up time of 95 months for patients taking imatinib and 22 months for those taking dasatinib. Patients in MR^4 were on imatinib after a mean of 68 months. All in one, our study showed a high rate of treatment failure. Better access to cytogenetic and molecular biology tools is needed to improve management.

Key words: CML; TKIs; remission; cytogenetic; molecular biology; Togo

Abbreviations: TKI; GIPAP; CML; RQ-PCR; CHR; MR; MMR; PCyR; CCyR, NR; DBS; ELN; CHR

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative syndrom resulting from the translocation t(9;22)(q34;q11) which gives rise to the BCR-ABL1 fusion gene encoding a protein with exacerbated tyrosine kinase function [1]. Previously always fatal, CML has become a chronic disease with a life expectancy close to that of the general population, thanks to the discovery of tyrosine kinase inhibitors (TKIs) [2]. International guidelines based on the quantification of BCR-ABL1 mRNA by real-time RT-PCR enable clinicians to regularly assess therapeutic efficacy [3]. In Togo in 2006, according to a study by Kueviakoe et al, CML accounted for 20% of hematological malignancies, with an annual hospital incidence rate of 2.91 cases [4]. This figure is constantly rising. Since the advent of imatinib in 2005, courtesy of The Max Foundation's GIPAP (Glivec International Patient Assistance Program), patient outcomes have improved considerably [5]. The range of TKIs offered by the GIPAP program was subsequently extended with the introduction of dasatinib in 2019 and bosutinib in 2023. However, molecular monitoring of patients is a real challenge because of the difficulty of accessing cytogenetic and molecular tests. The aim of this study, conducted with the support of The Max Foundation, was therefore to investigate the molecular remission to TKIs in patients treated for chronic myeloid leukemia at the CHU Campus in Lomé, Togo.

Materials and Methods

This was a cross-sectional, descriptive study, which took place from 21 December 2022 to 20 January 2023. It concerned patients followed up in the clinical hematology department of the CHU Campus and who were seen in consultation during the study period. Patients diagnosed with chronic-phase CML who had been treated for at least three months with imatinib or dasatinib and had achieved complete hematological remission were included, within the limits of available DBS (Dried Blood Spot) samples. Patients diagnosed during the study pe-

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riod and those with other hematological malignancies were not included. The variables studied were age, sex, length of follow-up, type of TKI received and BCR-ABL molecular transcript level. Cytogenetic and molecular response was assessed according to the International Scale as the ratio of BCR-ABL1 transcripts to ABL1 transcripts and was expressed and reported as BCR-ABL1 % on a log scale. BCR_ABL ≤10% is equivalent to partial cytogenetic remission (PCyR). BCR-ABL1 transcript level ≤1% is defined as complete cytogenetic remission (CCyR). BCR-ABL1 transcript level ≤0.1% is defined as major molecular response (MMR) or MR[3]. A BCR-ABL1 transcript level ≤0.01% or undetectable disease in cDNA with >10,000 ABL1 transcripts is defined as MR[4] [6]. The BCR-ABL transcript level was measured in Seattle, USA, by RQ-PCR using Dried Blood Spot (DBS). The transcript detection limit was 0.003% i.e MR[4].

Results

Thirty-eight patients were included in our study, with a mean age of 42 ± 16 years (8-75) and a sex ratio of 1.4:1. Twenty-six (68.4%) patients were treated with imatinib and 12 (31.6%) with dasatinib. The mean duration of follow-up was 51±55 months (7-211). It was 62 months for patients taking imatinib and 27±15 months for patients taking dasatinib. Overall, 28.9% of patients had no molecular remission, compared with 15.8% who had achieved a MR[4] (Figure 1). Depending on the treatment, a MMR was observed in 8.3% of patients taking dasatinib, compared with 7.7% of patients taking imatinib. Table I shows the different types of molecular remission according to TKI. On imatinib, patients on MMR had a mean follow-up of 95 months, compared with 22 months for patients on dasatinib. Tables II and III show the different types of remission obtained according to treatment and duration of follow-up.

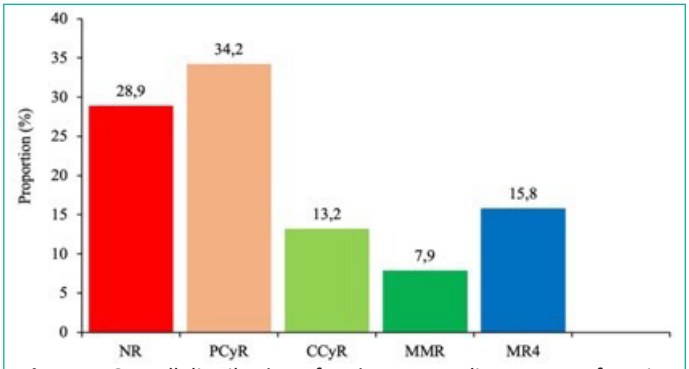

Figure 1: Overall distribution of patients according to type of remission.

Table 1: Molecular remission by TKI.

Molecular remission, n(%)	Dasatinib (n=12)	Imatinib (n=26)	Total (N=38)
NR	6(50,0)	5(19,2)	11(28,9)
PCyR	4(33,3)	9(34,6)	13(34,2)
CCyR	1(8,3)	4(15,4)	5(13,2)
MMR	1(8,3)	2(7,7)	3(7,9)
MR4	0(0,0)	6(23,1)	6(15,8)

Table 2: Length of follow-up for patients on imatinib by type of molecular remission.

Follow-up time (months)	NR (n=5)	PCyR (n=9)	CCyR (n=4)	MMR (n=2)	MR4 (n=6)	Total (n=26)
Median [IIQ]	69(23-69)	22(9-55)	27(21-75)	95(60-131)	49(22-110)	29(21-72)
Mean (±SD)	51(26)	53(68)	70(95)	95(100)	68(59)	62(62)
Mini-Maxi	22-73	7-205	14-211	24-166	14-154	7-211

Table 3: Length of follow-up for patients on dasatinib by type of molecular remission.

Follow-up time (months)	NR (n=6)	PCyR (n=4)	CCyR (n=1)	MMR (n=1)	MR4 (n=0)	Total (N=12)
Median [IIQ]	25 (16-29)	28 (19-44)	29(29-29)	22(22-22)	-	25(19-29)
Mean(±SD)	22(8)	35(24)	29(NA)	22(NA)	-	27(15)
Mini-Maxi	11-29	14-69	29-29	22-22	-	11-69

Discussion

CML is a frequent malignant disease in our practice [4] and its prevalence is constantly increasing due to the spectacular increase in patients' life expectancy, as a result of the systematic use of TKIs. Although the efficacy of TKIs no longer needs to be demonstrated, access to them in developing countries such as Togo is difficult, and has only been possible for the majority of patients thanks to the support of the GIPAP program [7].

Diagnosis and monitoring of CML are based on cytogenetics, combining conventional cytogenetics with molecular analysis using RQ-PCR to quantify BCR-ABL transcripts [7]. These molecular techniques are now essential for the diagnosis and prognosis of CML. However, because of the difficulty of accessing these tests in our practice, the diagnosis of CML is still based on cytological criteria (hemogram and myelogram), and follow-up is based solely on monitoring the achievement and maintenance of a complete hematological remission (CHR). Our study therefore enabled us to evaluate the molecular remission in patients followed for CML and in CHR. Its main limitations are its cross-sectional nature, which does not allow us to establish the actual mean time taken to obtain the various molecular remissions, and the small sample size due to the number of cards available for DBS sampling.

CML is a disease of the young, as demonstrated by the results of our study, which are consistent with those in the literature [8,9]. We found a slight male predominance, as did Koffi et al. in Côte d'Ivoire [9].

Overall, almost 30% of patients in our study had no partial cytogenetic remission after three months of follow-up. In addition, the mean time taken to obtain the different types of molecular remission, whether with imatinib or dasatinib, was well above the standards required according to the ELN recommendations, suggesting a high percentage of patients in therapeutic failure. The ELN defines treatment failure as the absence of partial cytogenetic remission (BCR-ABL1 >10%) between 1 and 3 months, complete cytogenetic remission (BCR-ABL1 >10%) after 6 months, major molecular remission (BCR-ABL1 >1%) after 12 months and loss of MMR or the occurrence of resistance or additional high-risk cytogenetic abnormalities [6]. This high percentage of failure in our study could be explained by late diagnosis of the disease, poor prognosis with a high Sokal score at diagnosis, poor therapeutic compliance, but also by bad indication of TKIs. In our practice, all newly diagnosed CML patients are started on imatinib as first-line therapy, while other treatment lines (dasatinib and bosutinib) are started in the event of resistance or intolerance. This indication, which does not correspond to international recommendations, is linked to the fact that imatinib was for a long time the only TKI available. The arrival of other TKIs could have improved prescribing, but the difficulty of performing caryotyping and molecular biology continues to hamper good practice. Indeed, when choosing a first-line TKI in the chronic phase of CML, it is necessary to take

into account the prognosis, as well as additional cytogenetic abnormalities [10]. It is important to note that resistance to imatinib has rapidly emerged [3]. Apart from poor compliance, this resistance will depend either on the molecule itself (pharmacokinetics, influx and efflux pumps), on the leukemic cell due to genetic instability or activation of other oncogenic signalling pathways, or on the target of the TKI (gene amplification, kinase domain mutation) [3]. Over 100 mutations affecting more than 70 amino acids have been identified [11,12]. They are associated with reduction in sensitivity to imatinib [13]. Four other TKIs are currently approved for first-line treatment in CML: dasatinib, nilotinib, bosutinib and radotinib [14-16]. Although there are no comparative studies, the choice of TKI should be guided by the sensitivity profile of specific BCR-ABL mutations if possible. Indeed, in cases of T315I mutation, only ponatinib, a 3rd generation TKI, is effective [17-20]. F317L/V/I/C and T315A mutations warrant treatment with nilotinib, bosutinib or ponatinib, whereas the V299L mutation indicates treatment with nilotinib or ponatinib [6]. The therapeutic indications are therefore not optimal in our daily practice and explain this high rate of therapeutic failure.

Even so, our study found 15.8% of patients in MR^4, all of them on imatinib. This is explained by the length of follow-up and the use of imatinib as first-line treatment. However, the possibility of discontinuing treatment, as envisaged in the STIM protocol [21], should not be considered in these patients.

Conclusion

Despite considerable progress in the management of CML, and the availability of TKIs through the GIPAP program, diagnosis and optimal follow-up remain a real challenge in resource-limited countries such as Togo. Our study revealed a high rate of therapeutic failure in patients in complete hematological remission. This highlights the urgent need to make cytogenetic and molecular diagnostic techniques more accessible, with the aim of improving the indication of first line TKIs, as well as ensuring appropriate therapeutic change in the event of resistance or intolerance.

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