East African Medical Journal Vol. 93 No. 10 October 2016
IMATINIB MESYLATE IN CHRONIC MYELOGENOUS LEUKEMIA: A CONGOLESE EXPERIENCE
L. O. Ngolet, MD, Senior Lecturer, I. Kocko, F. O. Galiba Atipo Tsiba, MD, Lecturer, J. D. Guelongo Okouango Ova, A. Elira Dokekias, Clinical Haematology Unit, Teaching Hospital of Brazzaville, BP 32, Republic of Congo

Request for reprints to: L. O. Ngolet, Clinical Haematology Unit, Teaching Hospital of Brazzaville, BP 32, Republic of Congo

IMATINIB MESYLATE IN CHRONIC MYELOGENOUS LEUKEMIA: A CONGOLESE EXPERIENCE

L. O. NGOLET, I. KOCKO, F. O. GALIBA ATIPO TSIBA, J. D. GUELONGO OKOUANGO OVA and A. ELIRA DOKEKIAS

ABSTRACT

***Background*: Chronic myeloid leukemia is a clonal myeloproliférative disorder caused by reciprocal translocation t(9;22) that induces tyrosin kinase protein. Imatinib is a selective inhibitor of this protein.**
***Objectives*: To assess responses to imatinib and outcome of Congolese patients with chronic phase chronic myeloid leukemia.**
***Design*: retrospective study.**
***Settings*: Clinical Haematology unit of Teaching Hospital in Brazzaville, Congo**
***Subjects*: Newly diagnosed patients with chronic phase chronic myeloid leukemia treated with imatinib.**
***Results*: A total of 25 males and 14 females with a mean age of 36 years at time of the diagnosis were enrolled in the study. The mean duration of the illness was 11.4 months. Imatinib induced complete hematologic response at 3 months in 100%. Major cytogenetic response was noticed in 87.18%. After a median follow up of 12 months, chronic myeloid leukemia had not progressed to the accelerated or blastic phase in an estimated 91.8% of patients and 86.6% were alive.**
***Conclusion*: Imatinib is effective in newly chronic phase chronic myeloid leukemia patient even though cytogenetic response rate are lower in Africa than western countries populations**

INTRODUCTION

Chronic myelogenous leukemia (CML) is a malignant clonal alteration of the pluripotent hematopoietic stem cell. It is a triphasic disease with a chronic phase (CP) that lasts three to six years, followed by transformation to an accelerated and then a blastic phase, of short durations (1).Biologic basis has been elucidated. The characteristic abnormality of the CML is the Philadelphia chromosome (Ph+) that results from a reciprocal chromosomal translocation between chromosome 9 and chromosome 22.The genetic consequence of this translocation is a genetic sequence fusion to form the BCR-ABL oncogene, which encodes for a constitutively active Bcr-ABL kinase that mediates cellular transformation (2). These significant discoveries have led to major advances in CML treatment. Imatinib Mesylate, formerly STI571, is one of the major advances observed (3). Imatinib causes arrest of growth or apoptosis in hematopoietic cells that express BCR-ABL, but does not affect normal cells. Imatinib Mesylate (IM) has demonstrated unprecedented hematological and cytogenetic results, with complete cytogenetic results found in more than 80% of newly diagnosed patients (3, 4, 5) therefore; the goal of CML therapy has moved to the achievement of a major molecular response. In Sub-Saharan countries, the goal is different. Between 2005 and 2006 Imatinib has been provided free of charge to eligible Sub-Saharan African countries through the Gleevec*International Patient Assistance Program (GIPAP).Therefore, Imatinib is used as the first–line therapy for CP-CML. Because of this history of Imatinib use, data is available on patients with CML and the response to IM in the African region. In the Congo Imatinib is available since 2005. Therefore, we are complementing data by reporting response on imatinib of CP-CML Congolese patients and their outcome.

MATERIALS AND METHODS

The descriptive retrospective study took place in the Hematology Unit in the teaching hospital, the largest

hospital in the country, from January 2008 to December 2015 (8 years). The diagnosis of CML was established by using cytogenetic studies. Cytogenetic studies were performed in the Cytogenetic Laboratory in Kremlin Bicêtre Teaching Hospital (France). The technique performed was chromosome banding analysis of at least 20 bone marrow cell metaphases, after short-term and long-term culture with standard G or G banding techniques. Patients being treated with IM that agreed to participate in the study signed consents and were enrolled in the study. The approval for the study was obtained from the ethical committee and conducted in accordance with the declaration of Helsinki.

Inclusion criteria:
- Newly diagnosed Phi + CML in chronic phase
- Complete medical record
- Patient with adequate follow up

Non inclusion criteria:
- CML not confirmed by cytogenetic analysis
- Incomplete medical record

Cytogenetic and hematologic responses: Patients were enrolled in the GIPAP and were granted oral IM 400 mg daily. The hematological response induced by IM was assessed monthly. The cytogenetic response was evaluated at 6 months from the start of IM and

Response assessment: The hematologic and cytogenetic responses to IM were analyzed with regard to the European Leukemia Net Guidelines and U.S National Comprehensive Cancer Network (NCCN) Guidelines.

Hematological response (HR) indicates improvement in peripheral blood cell counts. It may be complete [CHR (White blood cell count below 10X109 / L, platelets below 450X109/L, immature cells absent or normalized differential, no signs or symptoms of disease)] or partial (persistence of immature cells , platelets below 50% of pre-treatment levels but above (450X109/L).

A Cytogenetic Response (CYR) defines the proportion of Ph+ cells identified in bone marrow or peripheral blood. CYR may be complete (CCYR): complete absence of Ph+ cells, partial (PCYR) 1-35% Ph cells, minor (36 – 65 % Ph+ cells), or minimal 66-95% Ph cells. A Major CYR (MCYR) is defined as CCRYR or PCYR. Loss of CYR is considered when an increase in Ph+ metaphases is observed.

Statistical analysis: Descriptive statistic was used to analyze the mean, median, incidence and percentage .Kaplan-Meyer survival analysis was applied to determine the Progression-Free Survival (PFS) and Overall Survival (OS). PFS was calculated as the time elapsed between IM initiation and progression of the CML.OS was calculated the initiation of IM to death due to any cause.

RESULTS

From January 2008 to December 2015, forty two patients with CML were admitted in the unit. Thirty nine of these patients were enrolled in the GIPAP and participated in the study. The median age was 36 years (range 16-69 years). A total of 25 people were male (64.10 %) and 14 were female (35.90%).The median duration of symptoms (time between beginning of the symptoms and admission at the department of hematology) was 11.4 months. The health performance status of the patient was determinate by the ECOG status (Eastern Cooperative Oncology Group). It was a grade 1 for 20 patients (51.3%) at the time of presentation. Cells blood counts of patients with CP CML showed at the admission: leukocytosis (median: 168.5giga/L) and anemia (median: 8.4g/dL). The prognostic score for survival of CML patients (Sokal score) was high for 18 patients (46.2%). The median for follow-up time was 28 months. The mean time between the diagnoses being made to initiating IM was 4 weeks (Table 1).

Hematological response: All patients achieved CHR in 3 months. 5.13% (n=2) lost their CHR at 6 months while receiving Imatinib .At 1 year 89.87% had a CHR (Table 2).

Cytogenetic response: At 6 months after the initiation of IM, 21 patients (88.18%) achieved a Major Cytogenetic Response (MCYR). The response was complete (CCYR) in 20.51% and partial (PCYR) in 66.67% (Table 3).

Outcomes: After a median follow up of 28 months (range: 5 and 68 months), 6 patients (15.4%) deceased, 1 was lost of follow (2.6%) and 32 (82.1%) were alive. The projected 26 month Overall Survival rate (OS) was 86.6% (95% CI: 34-71%).The rate was 43% at 53 months (Figure 1). 8 of the 39 patients had progressed to the accelerated or blastic phase. The estimated rate of Progression-Free Survival (PFS) was 91.8% (95%CI: 14-57%) at 12 months and 43.6% at 36 months(Figure 2).

Table1
Patient characteristics

Variable	N
Sex	
Male n(%)	25 (64.10)
Female n(%)	14 (35.90)
Total	39
Median age in year (range)	36 (16-69)
Time since diagnosis in month	
Median (range)	11.4 (0.5-50)
Median spleen size in cm (range)	16.4 (0-28)
Median hepatomegaly size in cm (range)	6.1 (0-19)
SOKAL score	
Low n (%)	7 (17.9)
Intermediate n (%)	14 (35.9)
High n (%)	18 (46.2)
Median Hb rate in g/dL (range)	8.4 (3.1-12.8)
Median white cell count in giga/L (range)	168.5 (14.6-381)
Median platelet count in giga/L (range)	415.4 (14.6-998)
Median Follow up in month (range)	28 (5-68)

Table 2
Hematologic response

Hematologic remission	3 months	6 months	12 months	24 months
Total patient	39	39	39	33
Complete	39 (100%)	37 (94. 87%)	35(89.74,%)	27(81.82%)
Partial	0	2 (5.13%)	4(10.26%)	6(18.18%)

Table 3
Cytogenetic response

Variable	N(%)
Complete n (%)	8(20.51)
Partial n (%)	26 (66.67)
Minor n (%)	4(10.26)
No response n (%)	1(2.56)
Total 39(100)	

Figure 1
Landmark analysis of overall survival

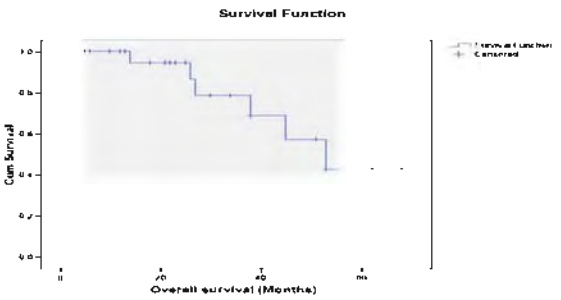
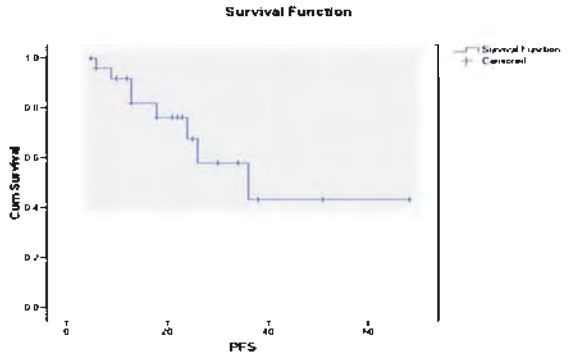


Figure 2
Landmark analysis of the Progression Free Survival Discussion



This study aims to complement previous studies by reporting Congolese experience with newly diagnosed CML patients under Imatinib treatment.

The CML found in Africa is described as being more aggressive due to multiple biological and clinical factors. The first factor is the patient's age. Developing countries have a younger population of CML than developed countries [7]. At the time of the diagnosis, the median age in Africa is around 40 years of age or less [8,9, 10]. Patterns of age at diagnosis and are not well understood [7]. For Fleming and Menendez, this epidemiological distribution is a picture of the African demographics and is not relative to any inherent biological characteristic [11]. The second factor is the delay in diagnosis of the disease. The delay for the diagnosis of CML in the region is long.

Three months in Nigeria, 18 in Ivory Coast and 11.4 months in our study[8,9]. This delay could influence the prognosis of the disease [8]Indeed, long delay for the diagnosis of CML is a known parameter that worsens the prognosis of the disease and response to therapy [9,11]. The third factor is the Sokal score at the time of CML diagnosis. African patients present to hospitals with an advanced stage of the disease [6] with CML high risk per the Sokal score for the majority of them. The Sokal score evaluates the risk of death by including age, spleen size, platelet count and percentage of blasts circulating. The estimated survival is lower for high Sokal scores [14].However, the small sample size in our study did not allow us to find any correlation between the Sokal score and the survival curve.

Consequently cytogenetic response induced by IM is lower in the African region. Cytogenetic response was complete in 20.51% our study, Ivorian and Togolese studies displayed cytogenetic responses of 17 and 20% respectively [8, 10]. These results findings are dramatically inferior to two published western studies that reported cytogenetic responses of 76% and 86%, respectively [4, 15]. Longer follow up of our enrolled patients and prospective studies should confirm our results and allow identification of factors associated to low rate cytogenetic response.

With a median follow up of 28 months, the mortality rate of CP CML patients that failed to respond to imatinib is 23%. Studies in Africa showed a range of mortality rates going from 15- 24 % within two years [8, 10]. The higher rate in the region is related as previously stated by the more aggressive clinical form of the disease in Africa. However, adherence of patients to imatinib is also questionable and request further studies.

Nonetheless with the poor prognosis of CML in Africa, we found a comparable impressive projected OS rate of 94.4% and PFS at 91.8% at 12 months versus 96% and 91% in Nigeria (6) for the same duration of time. But, our values changed drastically at 53 months with an OS of 43% and a PFS of 43.6% at 36 months.

In conlusion, without regard to low rate of complete cytogenetic response, survival analysis in our study at 12 months show very promising outcome that are similar to Western populations' reports. Further studies are necessary to understand differences noticed after tong follow up on imatinib between both populations.

ACKNOWLEDGEMENTS

The authors are grateful GIPAP for providing and facilitating the delivery of Imatinib in the Congo. We are also indebted to the Hematologic Laboratory in the Kremlin Bicêtre teaching hospital in Paris-France for the cytogenetic blood work and to Mr.Philip Nelson, PA-C who kindly reviewed the manuscript.

REFERENCES

1. Bhutani, V. M., Kumar, L. and Kochupillai, V. Lymphohematopoietic malignancies in *Indi.Med. Oncol.* 2002; 19: 141-50.
2. O'Dwyer, M. E., Mauro, M. J., and Druker, A. B. Recent advancements in the treatment of chronic myelogenous leukemia. *Annual Review of Medicine* 2002; 53: 369-81.
3. Druker, B. J., Talpaz, M., Resta, D. J., *et al.* Efficacity and safety of a specific inhibitor of the BCR- ABL tyrosine kinase in chronic myeloid leukemia. *New England Journal of Medicine* 2001; **344** (14):1031-7.
4. Druker, B., Guilhot, F., O'Brien, S. *et al.* Five-year follow-up of imatinib therapy for newly diagnosed chronic myelogenous leukemia in chronic-phase shows sustained responses and high overall survival. *N. Engl. J. Med.* 2006; 355: 2408-17.
5. Krause, S. W. and Holler, E. Imatinib in chronic myeloid leukemia. *Journal of Clinical Oncology* 2007; 26(20): 3358-63.
6. Muheez, A. D., Faluyi, J. O., Oyekunle, A. A. *et al.* The use of imatinib mesylate in Nigerians with chronic myeloid leukemia. *Cellular Therapy and Transpantation* 2008; 1(2):58-62.
7. Mendizabal, A. M., Naji, Y. and Levine, P. H. Geographic and income variation in age at diagnosis and incidence of chronic myeloid leukemia. *International*

of Haematology 2016; **103**(1): 70-8.

8. Koffi, K. G., Nanho, D. C., N'dathz, E. *et al.* The effect of imatinib mesylate for newly diagnosed Philadelphia chromosome-positive, chronic-myeloid leukemia in Sub-Saharan African patients: the experience of Côte d'Ivoire. Advances in hematology 2010; **10** (268921): 1-6.
9. Muheez, A. D., Julius, O. F., Oykekunle, A. *et al.* Characteristics of accelerated disease in chronic myelogenousleukemia. *Cellular Therapy and transplantation* 2008; **1** (2):15-9
10. Segbena, A. Y., Kueviakoe, I. M. D., Agbetiafa, K., Padaro, E., Ayibo, Y., Dorkenoo, A. and Agbo ,Y. M. Leucémie myéloïde chronique et imatinib, experience du CHU Campus de Lomé au Togo. *Médecine Santé et Tropicales* 2012 ; **22**(3) : 307-11.
11. Fleming, A. F. and Menendez, C. "blood", in principles of Medicine in Africa, Parry E, Godfrey R, Mabey D, and G. Gill, Eds., vol. 78,Cambridge University Press, Cambridge UK, 2004.
12. De Lavallade, H., Khorashad, J. F. A., Milokovic, D. *et al.* Imatinib and newly diagnosed patients with chronic myeloid leukemia: incidence on sustained responses in an intention-to-treat analysis. *Journal of Clinical Oncology* 2008; **26** (20): 3358-63.
13. Kantarjian, H. M., Smith, T. L., McCredie, K. B. *et al.* Chronic Myelogenous Leukemia: Mutlivariate Analysis of the Association of Patients Characteristics and Therapy with survival. Blood 1985; **66** (6): 1326-35.
14. Sokal, J. E. Evaluation of survival data from chronic myelocytic leukemia. *Am. J. Haematol.* 1976; **1**(4): 493-500.
15. Kantarjian, H. M., Cortes, J. E., O'Brien, S. *et.al.* Imatinib mesylat therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia: high incidence of early complete and major cytogenetic responses". *Blood* 2003;**1**: 97-100.