Chronic Myeloid Leukemia in Nigerian Patients: Anemia is an Independent Predictor of Overall Survival

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ABSTRACT

OBJECTIVES: The advent of the tyrosine kinase inhibitors has markedly changed the prognostic outlook for patients with Ph^+ and/or *BCR-ABL1*$^+$ chronic myeloid leukemia (CML). This study was designed to assess the overall survival (OS) of Nigerian patients with CML receiving imatinib therapy and to identify the significant predictors of OS.

METHODS: All patients with CML receiving imatinib from July 2003 to June 2013 were studied. The clinical and hematological parameters were studied. The Kaplan–Meier technique was used to estimate the OS and median survival. *P*-value of <0.05 was considered as statistically significant.

RESULTS: The median age of all 527 patients (male/female = 320/207) was 37 (range 10–87) years. There were 472, 47, and 7 in chronic phase (CP), accelerated phase, and blastic phase, respectively. As at June 2013, 442 patients are alive. The median survival was 105.7 months (95% confidence interval [CI], 91.5–119.9); while OS at one, two, and five years were 95%, 90%, and 75%, respectively. Multivariate Cox regression analysis revealed that OS was significantly better in patients diagnosed with CP ($P = 0.001$, odds ratio = 1.576, 95% CI = 1.205–2.061) or not in patients with anemia ($P = 0.031$, odds ratio = 1.666, 95% CI = 1.047–2.649). Combining these variables yielded three prognostic groups: CP without anemia, CP with anemia, and non-CP, with significantly different median OS of 123.3, 92.0, and 74.7 months, respectively ($\chi^2 = 22.042$, $P = 0.000016$).

CONCLUSION: This study has clearly shown that for Nigerian patients with CML, the clinical phase of the disease at diagnosis and the hematocrit can be used to stratify patients into low, intermediate, and high risk groups.

KEYWORDS: chronic myeloid leukemia, imatinib, survival, Nigeria, anemia

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Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder characterized by the presence of all the stages of myeloid development in the peripheral blood and is believed to be driven by the aberrant protein tyrosine kinase, a product of the mutant *BCR-ABL1* gene.[1,2] The chimeric gene results from a reciprocal translocation [t(9;22)(q34;q11)] that places the *ABL* gene from chromosome 9 next to the *BCR* gene on chromosome 22, demonstrable as the Philadelphia chromosome (Ph).[3,4] CML is believed to be a rare disease, with an estimated incidence of one to two new cases per 100,000 people per year.[5]

As a result of our experience in managing Nigerian patients with CML receiving tyrosine kinase inhibitors (TKIs), we have observed several notable differences in the epidemiology of the disease, raising questions as to the possibility of fundamental differences in the natural history of the disease and its impact on the patients' socioeconomic life situation. CML may affect any age group; the peak incidence is between 40 and 60 years with the median age at diagnosis being 53 years in the Western world.[1]

In Nigeria, until 2003, CML was conventionally managed with cyclophosphamide, busulfan, and hydroxyurea. This was the basis of the first report from our center.[6] Similarly, a pilot study on the clinical utility of interferon alpha among newly diagnosed Nigerian patients with CML was conducted.[7] However, with the approval of the first TKI, imatinib mesylate (Glivec/Gleevec; Novartis Pharmaceuticals) by the US Food and Drug Administration in 2001, the natural history of CML changed dramatically.[8] The prognosis of CML significantly improved to the extent that several experts now consider hematopoietic stem cell transplantation as a distant second-line

option in the management of CML and only recommend when patients become resistant and/or intolerance to all TKI options.[8–11] Imatinib is now widely used as the first-line therapy of CML, particularly for patients in the chronic phase (CP).[12,13]

The Max Foundation was highly instrumental to the setting up of the Novartis Pharmaceuticals-supported Glivec International Patient Assistance Program (GIPAP), which provides free access to imatinib for many patients from several developing countries, including Nigeria. The program in Nigeria started in 2003, and this study is a review of our 10-year experience with Ph^+ or *BCR-ABL1*$^+$ Nigerian patients with CML receiving imatinib.

Patients and Methods

This is a prospective follow-up study designed to determine the cumulative overall survival (OS) of Nigerian patients with CML and to identify the significant predictors of OS. The study was conducted in accordance with the ethical standards of our institutional ethics review board, and all patients gave written informed consent. All patients were treated according to the Helsinki Declaration of 1975, as revised in Edinburgh 2000. All patients were originally part of a prospective cohort for the postapproval use of imatinib in Nigeria.

A total of 527 Ph^+ and/or *BCR-ABL1*$^+$ Nigerian patients with CML enrolled under the GIPAP and receiving imatinib (Glivec; Novartis Pharmaceuticals) upfront as first-line therapy from July 2003 to June 2013 were studied. Clinical and hematological parameters collected are as previously reported.[14,15] Data collection, cleaning, and validation were done in MS Excel, while statistical analysis was done using SPSS version 22 (IBM SPSS Statistics, 2013). Survival analysis was done using the Kaplan–Meier techniques, using definitions as previously reported in Refs. 14 and 15.

Results

Demographics. From 2003 to 2013, 527 patients were enrolled, with a median age of 37 (range 10–87) years, 320 males and 207 females. As at June 2013, 442 patients (84%) remained alive. Figure 1 is a multiaxis bar chart, showing both the total annual and total cumulative number of patients recruited. Even though patient accrual started in 2003 and this study technically covers 11 years, but because only one patient was recruited in 2003, we consider this study as a 10-year review. There was an immediate increase in the numbers enrolled until an early plateau of 33–35 patients per year from 2005 to 2007. A subsequent increase led to another plateau of 68–69 patients per year lasting from 2008 to 2010. In 2011 and 2012, the increases were less dramatic.

Survival outcomes for all 527 patients. Table 1 shows a summary of the clinical characteristics of all the patients studied. OS at one, two, and five years were 95%, 90%, and 75%, respectively (Table 2). The median OS was 106 months (95% confidence interval [CI] = 92–120). Using the log-rank statistical test, with the variables as individual predictors of OS, we found that CP disease at diagnosis ($P < 0.001$), male gender ($P = 0.04$), and hematocrit >0.3 ($P = 0.003$) were associated with significantly better OS (Table 3). When subjected to multivariable Cox regression analysis, using these three variables as predictors of OS, gender was no longer significant, while disease phase at diagnosis ($P = 0.001$, odds ratio = 1.576, 95% CI = 1.205–2.061) and hematocrit >0.3 ($P = 0.031$, odds ratio = 1.666, 95% CI = 1.047–2.649) were confirmed as independent predictors (Table 4).

The OS of the 472 patients in CP is better than the overall, at 96%, 92%, and 78%, respectively, at one, two, and

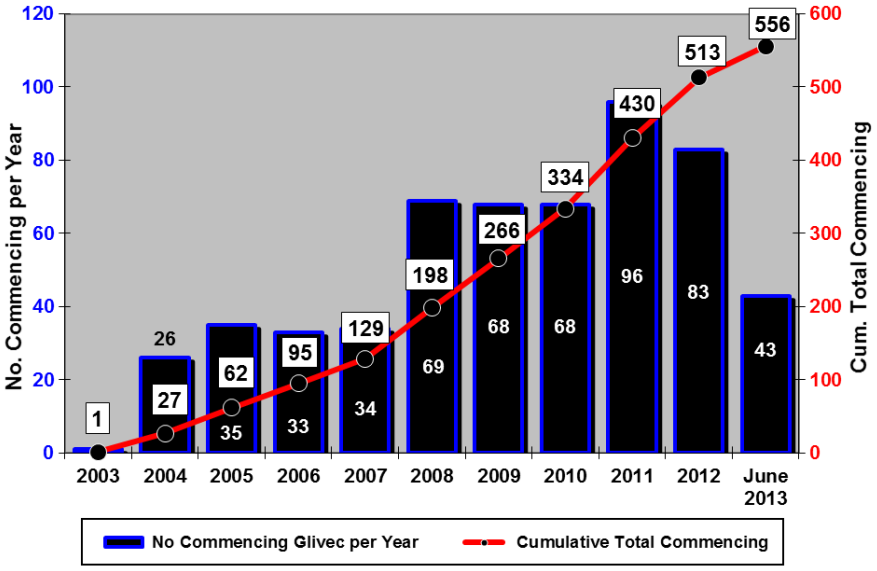

Figure 1. Annual and cumulative numbers of patients commencing imatinib. The bars show the total number of patients recruited each year (left axis), while the curve traces the cumulative total number of patients (right axis) as at the corresponding year.

Table 1. Summary of clinical parameters of all 527 patients at diagnosis.

VARIABLES	NO.	MEDIAN	(RANGE)
Age, years: patient	527	37	(10–87)
Gender: male/female (%)	320/207	(61/39)	
Splenomegaly (cm, BCM)	389	14	(2–36)
PCV (%)	499	30	(11–51)
WBC ($\times 10^9$/l)	500	78	(1.0–1060.0)
Platelet count ($\times 10^9$/l)	467	270	(10–1315)

Abbreviations: BCM, below the costal margin; PCV, packed cell volume; WBC, white blood cell.

five years. The median OS of this subgroup is 107 months (95% CI = 98–117) (Table 2).

Survival outcomes using a new scoring system. We then combined the two variables identified from our multivariate model, CP disease at diagnosis and absence of anemia (hematocrit > 0.30), to stratify our patients. The following four groups emerged: CP without anemia (group A, $n = 234$), CP with anemia (group B, $n = 212$), non-CP without anemia (group C, $n = 12$), non-CP with anemia (group D, $n = 39$). A Kaplan–Meier survival analysis using this scoring system revealed median OS of 123.3, 92.0, 53.7, and 78.9 months for groups A, B, C, and D, respectively ($\chi^2 = 22.874$, $P = 0.000043$). This analysis also showed, rather unexpectedly, that group C had the worst median OS. Interestingly, a subanalysis comparing only groups C and D showed no significant difference in their OS curves ($P = 0.496$), meaning that when patients are diagnosed with advanced disease (non-CP), the presence or absence of anemia has no impact on OS.

A second survival analysis was conducted, having combined the non-CP groups: CP without anemia (group A, $n = 234$), CP with anemia (group B, $n = 212$), and non-CP (group C, $n = 55$). The derived score revealed a median OS of 123.3, 92.0, and 74.7 months for groups A, B, and C, respectively ($\chi^2 = 22.042$, $P = 0.000016$) (Fig. 2).

Table 2. Overall survival of all 527 patients and of the 472 patients in chronic phase.

TIME POINTS	ALL 527 PATIENTS		472 CP PATIENTS	
	OS	SE	OS	SE
At 1 year	95%	0.011	96%	0.010
At 2 years	90%	0.016	92%	0.015
At 5 years	75%	0.030	78%	0.031
Median survival (95% CI)	106 mo; (92–120)		107 mo; (98–117)	

Abbreviations: CI, confidence interval; CP, chronic phase; mo, months; OS, overall survival; SE, standard error.

Table 3. Univariate analysis of all 527 patients' characteristics as predictors of overall survival.

PARAMETERS AT RECRUITMENT	NO.	*P*-VALUE
Sex: male/female	319/206	**0.040**
Age (years)		ns
≤30/>30	153/372	ns
≤35/>35	233/292	ns
≤37/>37	268/257	ns
≤40/>40	305/220	ns
≤45/>45	380/145	ns
Disease phase at diagnosis		
CP/AP/BP	470/47/7	**<0.0001**
Hematocrit at diagnosis (v/v)		
≤0.30/>0.30	251/254	**0.003**
≤0.33/>0.33	312/193	**0.048**
WBC count at diagnosis ($\times 10^9$/l)		
≤100/>100	288/210	ns
Platelet count ($\times 10^9$/l)		
≤270/>270	234/251	ns
≤330/>330	286/199	ns
≤100 & >450/others	316/149	ns
≤100 & >500/others	341/124	ns

Notes: *P*-values in bold type are significant, and those in regular type are close to significance. *The variables with the better outcomes are written first.
Abbreviations: CP/AP/BP, chronic, accelerated, and blastic phases; ns, not significant; OS, overall survival; WBC, white blood cell.

Discussion

It is believed that the annual incidence of CML is one per 100,000 people per year, and with a population of about 160 million people, this should ordinarily translate to an annual incidence of about 1600 new CML cases per year. Unfortunately, no one has been able to conduct community-level studies to either establish or refute these estimates. This is why the 527 patients seen over this 10-year period appears rather small, a mere 3.3% of an estimated 16,000 expected over this period. Several factors may account for this shortfall, such as limited awareness of the GIPAP scheme, especially during the first five years of the scheme, lack of a universal

Table 4. Multivariate analysis of all 527 patients, showing the outcomes of the significant predictors; disease phase at diagnosis and hematocrit as predictors of overall survival.

PARAMETERS AT RECRUITMENT	HR	95% CI	*P*-VALUE
Disease phase at diagnosis: CP	1.576	1.205–2.061	0.001
PCV at diagnosis: >30%	1.666	1.047–2.649	0.031

Abbreviations: CI, confidence interval; CP, chronic phase; HR, hazard ratio; PCV, packed cell volume.

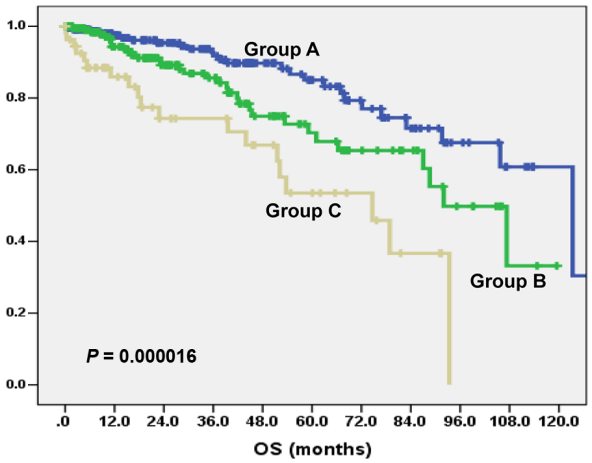

Figure 2. Kaplan–Meier curves of OS according to a new scoring system comprising disease phase at diagnosis and hematocrit. The figure shows a clear separation of the three groups: Group A, CP without anemia (blue); Group B, CP with anemia (green); and Group C, non-CP (brown).

health insurance (meaning that most patients pay for care out-of-pocket), and distance from our center, among other factors. There is also the remote possibility that CML incidence may exhibit real genetic/racial and/or environmental differences.

Using our hospital-based data over the preceding five years (2008–2012, when patient accrual attained the second plateau), there was an average of 76.8 new cases drawn from a population of 160 million people—approximately 0.48 new cases per million people per year.[16]

The median age of 37 years is similar to what we had reported in our earlier studies comprising fewer of these patients, 36 years in 2008 (n = 98) and 38 years in 2015 (n = 272),[14,15] and what has been reported from Ivory Coast but differs significantly from populations in the Western world.[17,18] Similar to incidence, it is equally unclear whether these are mere reflections of the younger population distribution as found in most developing countries or a true difference in CML biology.

Over the years, with increasing numbers and statistical power of our CML data, a trend of improving OS can be seen, which is best demonstrated with the two-year OS, 81%, 84%, and 90% with 98, 272, and 527 patients, respectively. Similarly, the five-year OS has increased from 63% (n = 272) to 75% in the current analysis.[14,15] It is to be noted that since this study has a much longer follow-up period and more patients, the survival outcomes are more reliable.

It is well known that patients with CP disease have better outcomes than those with later stages of disease. This has consistently been established in previous studies and in all reports from our cohort, including this study.[15,19]

In contrast to what has been reported from other CML studies including our earlier reports, this study has established that anemia at diagnosis is an independent prognostic factor predicting the poor OS. Indeed, the recent study by Saußele et al,[20] in which 1519 German CML patients were retrospectively studied for the impact of comorbidities on survival outcomes, found that OS was affected more by comorbidities than by CML and that hemoglobin level had no significant influence. We believe that the populations are fundamentally different especially as regards the tendency of our patients to present in late disease, which may influence their pattern of presentation, and the resultant statistical weighting of variables, such as hemoglobin, which tends to worsen with disease progression. Our study did not assess our patients specifically for comorbidities, so it is difficult to comment on its likely effect on survival. We do know, however, that the vast majority of our patients, being young, rarely present with comorbidities.

Combining the disease phase at diagnosis and hematocrit gave us a unique highly discriminatory scoring scheme that clearly delineates three groups of patients with significantly different OS over the long term. To our knowledge, no other group has been able to show this degree of difference in survival among patients with newly diagnosed CML managed using first-line imatinib.

The exact mechanism by which anemia can impart on the OS of patients with CML remains unclear. It is, however, well known that in several lymphoproliferative disorders, such as chronic lymphocytic leukemia and myelomas, anemia is recognized as a poor prognostic factor, though this has never been established for CML. In these conditions, anemia is typically an indication of the extent of marrow infiltration by the malignant cells and consequently a surrogate of tumor bulk. Similarly, in this case, it may also be a reflection of advanced disease, which is yet to meet the definition of disease progression. It may also be a reflection of how patients' premorbid state may affect disease outcome, as many of these patients may have been anemic long before CML was diagnosed.

In this study, we did not consider it necessary to further explore the Sokal and Hasford scoring systems, because in one of our recent studies, where we studied only patients in CP, we had established that neither of these scoring systems was predictive for differences in OS among our patients.[19]

This study would have been much better if we had access to cytogenetic and molecular data. Unfortunately, many of our patients are unable to afford the cost of these very important tests, and as such the data are incomplete and unsuitable for this analysis. Additionally, our in-house quantitative polymerase chain reaction for the *BCR-ABL1* transcript was established in 2012, and as at the time of this analysis, very few patients had done at least two tests, the minimum we need for a meaningful analysis.

Conclusion

This study shows that, for Nigerian patients with CML, the clinical phase of the disease at diagnosis and the hematocrit can be used to stratify patients into low, intermediate, and high risk groups, with significantly different survival outcomes.

This can be the basis for more individualized therapy particularly for those in CP with anemia (intermediate risk) for which the current guidelines dictate standard dose imatinib of 400 mg daily. We believe our results are likely to hold true in several developing countries with a population distribution similar to those of the patients studied and where access to second-line TKIs remains markedly limited.

Author Contributions

Conceived and designed the experiments: AAO and MAD. Analyzed the data: AAO. Wrote the first draft of the manuscript: AAO, RAB, and TO. Contributed to the writing of the manuscript: AAO, MAD, RAB, and TO. Agree with manuscript results and conclusions: TO, RAB, AAO, LS, NOA, and MAD. Jointly developed the structure and arguments for the paper: AAO, RAB, and MAD. Made critical revisions and approved final version: LS, NOA, and MAD. All authors reviewed and approved of the final manuscript.

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