Distribution of *BCR-ABL1* Transcript Variants in Nigerians with Chronic Myeloid Leukemia

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Abstract The distribution of *BCR-ABL1* transcript variants e13a2 (“b2a2”) and e14a2 (“b3a2”) in Nigerians with chronic myeloid leukemia (CML) had not been previously studied. In addition, there is paucity of data on the impact of *BCR-ABL1* transcript variants on clinical presentation and survival in CML patients in Nigeria. The *BCR-ABL1* transcript variants were analyzed in 230 Imatinib-treated CML patients at diagnosis. Patients with incomplete data (n = 28), e19a2 (n = 3) and e1a2 (n = 1) were excluded from analysis of transcript variant on disease presentation and survival leaving only 198. The frequencies of *BCR-ABL1* transcript variants were 30 (13.0%), 114 (49.6%), 82 (35.7%), three (1.3%) and one (0.4%) for e13a2, e14a2, co-expression of e13a2/e14a2, e19a2 and e1a2, respectively. A significantly higher platelet count was found in patients with e13a2 variant ($531.1 \pm 563.4 \times 10^9/L$) than in those expressing e14a2 ($488.2 \pm 560.3 \times 10^9/L$) or e13a2/e14a2 ($320.7 \pm 215.8 \times 10^9/L$); $p = 0.03$. No significant differences were found between the variants with regards to gender, age, phase of disease at diagnosis, total white blood cell count, neutrophil percentage, hematocrit, splenomegaly or hepatomegaly. Overall survival was higher but not statistically significant ($p = 0.4$) in patients with e14a2 variant (134 months) than in e13a2 (119 months) and co-expression of e13a2/e14a2 (115 months). Nigerian CML

patients have the highest incidence of co-expression of e13a2 and e14a2. Distinct disease characteristics which contrast with findings from the Western countries were also identified in Nigerians which may be due to genetic factors.

Keywords Chronic myeloid leukemia · *BCR-ABL1* · transcript variants · Nigerians

Introduction

Chronic myeloid leukemia (CML) is a clonal malignant disorder characterized by the proliferation of myeloid cells in the bone marrow with spillage into the peripheral blood. The disease results from the reciprocal translocation t(9;22)(q34;q11) which produces the *BCR-ABL1* oncogene that encodes the aberrant protein tyrosine kinase BCR-ABL1 [1]. The mutant oncogene is found on the shortened chromosome 22 which is called the “Philadelphia (Ph) chromosome” and can be detected by cytogenetics in patients with CML [2]. The BCR-ABL1 protein induces malignant proliferation of hematopoietic cells resulting in diseases such as CML. The *BCR-ABL1* oncogene is found in over 95% of Ph-positive CML patients and in about 50% of Ph-negative CML patients [3].

There are many variants of the *BCR-ABL1* oncogene which encode proteins with different molecular sizes depending on the location of the *BCR* and *ABL1* genomic breakpoints [4]. Generally, the recombination points may be any of exon 1, exon 13, exon 14, or exon 19 of *BCR* which can fuse with a 140-kb region of *ABL1* between exons 1b and 2. The three breakpoint cluster regions in the *BCR* gene include major (M-BCR), minor (m-BCR) and micro (μ -BCR) [4, 5]. The fusion of exon 13 of *BCR* and exon 2 of *ABL1* (e13a2, originally called b2a2) or e14a2

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(originally called b3a2) constitute the major *BCR-ABL1* transcript (M-*BCR*). Both transcripts result in a hybrid 210-kDa protein (p210^{*BCR-ABL1*}) which is the variant detected in the majority of CML patients and occasionally in acute lymphoblastic leukemia (ALL) or acute myeloblastic leukemia (AML) [4]. The minor *BCR-ABL1* transcript (m-*BCR*) results from fusion of *BCR* exon 1 with *ABL1* exon 2 (e1a2) and it encodes a hybrid 190-kDa protein (p190^{*BCR-ABL1*}) which is rare in CML but commonly detected in B-cell ALL (B-ALL) and occasionally in AML. The fusion of *BCR* exon 19 with *ABL1* exon 2 (e19a2, originally called c3a2) is the micro *BCR-ABL1* transcript (μ-*BCR*), it encodes a larger hybrid 230-kDa protein (p230^{*BCR-ABL1*}) which is typically found in neutrophilic-CML (CML-N) but rare in classical CML [4]. Most CML patients express one of the two major *BCR-ABL1* transcript variants e13a2 or e14a2 [5–9]. However, in some patients, both are expressed due to alternative splicing [10]. The e14a2 oncoprotein is longer than the e13a2 variant by the presence of 25 amino acids which results in differences in secondary structure elements between the two variants [6, 11].

About 50% of CML patients are asymptomatic, being diagnosed after a routine physical examination or blood test. There are three phases of CML, chronic, accelerated and blastic. Clinical features include fatigue, malaise, pallor (in patients with anemia), early satiety, left hypochondriac fullness or pain (suggestive of splenomegaly), bleeding, thrombosis, priapism, retinal hemorrhages, gouty arthritis and weight loss. Blood counts usually show anemia and leukocytosis while the platelet count may be normal, increased or decreased depending on the phase [2].

Significant progress has been made in the management of CML with the discovery and subsequent approval of Imatinib, the first of a class of drugs that specifically inhibit tyrosine kinases (called tyrosine kinase inhibitors or TKIs) and block their effects on cellular proliferation of malignant clones [2, 12]. Imatinib produces significantly favorable clinical, hematologic, cytogenetic and molecular responses in CML patients [12, 13]. Most patients improve with Imatinib but some do not, either due to Imatinib-intolerance or resistance [2, 14]. Second-generation (2G) TKIs like Nilotinib and Dasatinib were subsequently developed providing relief for such patients [14, 15]. The frequencies of the different *BCR-ABL1* transcripts vary in different populations [5–8]. Previous studies have demonstrated that the variant of *BCR-ABL1* transcript in CML patients affects the clinical presentation, response to Imatinib and other TKIs and disease progression [6, 16]. Researchers also explored the prognostic significance of *BCR-ABL1* transcript variants [16, 17]. Patients with the e14a2 variant have been observed to have better response

rates to Imatinib compared to those with the e13a2 variant [6, 16].

The distribution of *BCR-ABL1* transcript variants had not been previously studied in Nigerians with CML. Nigerians diagnosed with CML have access to Imatinib (Glivec®, Novartis Pharmaceuticals, Basel, Switzerland) free-of-charge at our institution through the Glivec International Patient Assistance Program (GIPAP) which is a collaboration between the non-governmental, non-profit organization, the Max Foundation and Novartis Pharmaceuticals. The objectives of this work were to determine the distribution and investigate the effects of *BCR-ABL1* transcript types on disease presentation and survival in Nigerian CML patients treated with Imatinib.

Methods

A follow-up study to determine the distribution and impact of *BCR-ABL1* transcript variants on clinical presentation and survival in Nigerian CML patients treated with Imatinib.

Ethical Approval

The study was conducted in accordance with the standards of our institutional ethics committee and in compliance with the Helsinki Declaration of 1964 and subsequent revisions.

Informed Consent

Written informed consent was obtained from all the patients who were originally part of a prospective cohort enrolled for Imatinib therapy under the GIPAP in Nigeria between November 2004 and May 2017 [18].

Sample Collection for *BCR-ABL1* Analysis

Peripheral blood (PB) samples were collected into ethylenediamine tetra acetic acid (EDTA) anticoagulated tubes. Genomic mRNA was extracted from patients' fresh peripheral blood (PB), either directly from whole blood using ZR® Whole-Blood RNA MiniPrep™ kit (Zymo Research, Irvine, California, USA) or from the buffy coat using Quick-RNA buffy coat MiniPrep™ Plus kit (Zymo Research, Irvine, California, USA) according to the manufacturer's instructions. The RNA concentration was determined using the BioPhotometer® Plus Spectrophotometer (Eppendorf, Hamburg, Germany). Genomic cDNA was generated from the extracted mRNA using the standard protocol for QuantiTect® reverse transcription kit (Qiagen, Hilden, Germany). The cDNA was then subjected

Fig. 1 Multiplex PCR of *BCR-ABL1* transcript variants in CML patients visualized on agarose gel. Lane M: DNA marker; Lanes 1 and 2: e13a2; Lanes 3 and 4: e14a2; Lane 5: negative control; Lane 6:

positive control; Lane 7: negative control; Lane 8: e13a2 + e14a2, Lane 9: e14a2; Lanes 10, 11 and 12: no *BCR-ABL* transcript detected; Lane 13: negative control; Lane 14: positive control

to real-time polymerase chain reaction (RT-PCR) using the Seeplex® Leukaemia *BCR/ABL1* transcript kit (Seegene, Seoul, Korea). The *BCR-ABL1* variants generated were resolved and analyzed in 2% agarose gel (Fig. 1). Included in our analysis were transcript variants of patients done at molecular laboratories within and outside Nigeria and in the molecular laboratory of our department (from September 2014).

Data Analysis

Demographic, clinical and laboratory data were collected at baseline. Kaplan–Meier technique was used to determine survival studies in 198 patients with full data. The effects of transcript types on spleen size, liver size, hematocrit (PCV), total white blood cell count (WBC), platelets and neutrophil percentage at presentation were also investigated in the same group of patients using analysis of variance (ANOVA) and the chi-squared (χ^2) test. Patients with e19a2 ($n = 3$) and e1a2 ($n = 1$) variants were excluded from the statistical and survival analysis due to small number of samples. SPSS Statistics for Windows, version 16.0 (SPSS Inc., Chicago, Ill., USA) was used for all statistical calculations.

Results

There were 230 patients, aged 10–87 (median age 38 years) comprising 124 males and 106 females (M: F, 1.2: 1). All were TKI-naïve at presentation and subsequently treated with Imatinib. The P210^{*BCR-ABL1*} transcript variants were more prevalent than the P190 and the P230 variants. The frequencies of e13a2, e14a2 and both e13a2 (b2a2) and e14a2 (b3a2) were 30 (13.0%), 114 (49.6%) and 82 (35.7%) respectively. The e19a2 (c3a2) variant was

seen in three (1.3%) patients while the rare e1a2 transcript variant was recorded in only one (0.4%) patient. The full data of 28 patients could not be retrieved and they were subsequently excluded from further analysis. The four patients with variant transcripts e19a2 and e1a2 were also excluded from the analysis leaving 198 patients with full data expressing e13a2 or e14a2 variants or a combination of both. Among those with full data, 179 (90.4%), 15 (7.6%) and four (2.0%) were in chronic, accelerated and blastic phases respectively. Transcript variants had no significant association with gender ($p = 0.34$) (Fig. 2), phase at diagnosis ($p = 0.64$) (Fig. 3), age ($p = 0.69$), PCV ($p = 0.72$), WBC ($p = 0.71$), neutrophil percentage ($p = 0.50$), spleen size ($p = 0.56$), hepatic size ($p = 0.53$) (Table 1). The e13a2 transcript variant was associated with significantly higher platelet counts ($531.1 \pm 563.4 \times 10^9/L$) than e14a2 ($488.2 \pm 560.3 \times 10^9/L$) and both e13a2/e14a2 ($320.7 \pm 215.8 \times 10^9/L$) ($p = 0.03$). There were 18 (9.1%) deaths among the patients, 14 (7.1%) occurred in chronic phase and two (1.0%) each occurred in accelerated

Fig. 2 Gender distribution of *BCR-ABL1* transcript variants

Fig. 3 Association between transcript variant and disease phase at diagnosis

and blastic phases. The 5-year survival rates were 89%, 92%, 89% and 87% for all the 198 patients, e13a2, e14a2 and combined e13a2/e14a2 respectively; while the mean overall survival (OS) estimates were 119, 134 and 115 months for e13a2, e14a2 and e13a2/e14a2, respectively ($\chi^2 = 1.86$, $p = 0.40$) and 127 months for all patients (Fig. 4).

Discussion

This study analyzed the distribution and impact of *BCR-ABL1* transcript variants on the clinical presentation and survival of Nigerian CML patients treated with Imatinib. Majority of the CML patients expressed the p210^{*BCR-ABL1*} tyrosine kinase transcript variant, either e13a2 or e14a2 or a combination of both while the e19a2 and e1a2 variants were very rare. The e14a2 was the most commonly expressed variant in the present study which is similar to findings from previous studies [5–9]. The frequencies of e13a2, e14a2 and both e13a2 (b2a2) and e14a2 (b3a2) were 13.0%, 49.6% and 35.7%, respectively, compared to 32%, 68% and 0.36%; 42%, 41% and 18%; 41%, 45% and 14%

Fig. 4 Survival according to *BCR-ABL1* transcript variant

among Koreans, Americans and Europeans respectively [5–7].

The Nigerian patients carry the largest burden of combined expression of e13a2 and e14a2 (35.7% of 230) compared to other populations [5–8]. The mechanisms for these differences are unknown, but they could be due to genetic and/or ethnic peculiarities in the Nigerian population. In a recent international study by Baccarani et al. [8] the average worldwide frequency of co-expression of e13a2 and e14a2 was 7.6%, ranging from 2.4% in Asia, 6.5% in Africa, 8.9% in South America, 9.3% in Europe to 18.7% in Australia. In the Baccarani study, patients with co-expression of e13a2 and e14a2 transcript variants were grouped together with those who expressed only the e14a2 variant for the data analysis [8]. This is because the e13a2/e14a2 co-expression occurs due to alternative splicing in patients with e14a2 variant [8, 10]. The African data was pooled from Algeria, Egypt, Nigeria and Tunisia [8]. The

Table 1 Association between *BCR-ABL1* transcript variants and patients' parameters

Parameter	e13a2	e14a2	e13a2/e14a2	<i>p</i> value
Age in years (mean ± SD)	38.5 ± 13.2	40.7 ± 13.4	49.2 ± 15.4	0.69
PCV (%) (mean ± SD)	29.1 ± 7.0	30.3 ± 6.0	30.1 ± 8.1	0.73
Platelet ($\times 10^9/L$)	531.1 ± 563.4	488.2 ± 560.2	320.8 ± 215.8	0.03*
WBC ($\times 10^9/L$)	171.5 ± 225.7	143.5 ± 125.5	147.8 ± 163.2	0.71
Neutrophil percent	50.2 ± 20.5	45.7 ± 18.9	49.2 ± 20.5	0.50
Spleen (cm below left costal margin)	12.8 ± 13.5	14.5 ± 8.2	13.0 ± 8.6	0.56
Liver (cm below right costal margin)	2.5 ± 3.1	3.8 ± 4.5	4.2 ± 4.7	0.52
Lymphocyte percent	14.0 ± 11.5	10.8 ± 8.3	12.8 ± 12.4	0.60

SD standard deviation, PCV packed cell volume, WBC total white blood cell count, cm centimeters

*Statistically significant i.e. *p* value less than or equal to 0.05

wide disparity observed between the Nigerian rate and overall African rate for the frequency of co-expression of e13a2 and e14a2 might be due to possible genetic similarities in Algerian, Egyptian and Tunisian populations which may not be present in Nigerians. The rates of co-expression of e13a2 and e14a were 2.0%, 3.4%, 4.8%, 5.4%, 7.3% and 18.0% in Brazil, northern India, Syria, eastern India, Sudan and Italy respectively [10, 17, 19–22].

The e19a2 (c3a2) variant was seen in 1.3% of our patients compared to 0.7% among Korean patients, 0.4% among Europeans and 1.8% among eastern Indians [5, 7, 21]. The rare e1a2 variant was recorded in 0.4% of our patients which is much higher than 0.002% among Koreans and 0.2% among Europeans but substantially less than 1.8% among eastern Indians [5, 7, 21]. The frequency of rare transcripts from the international study ranged from 0.9% to 13.0%, the e1a2 was the commonest variant with overall frequency of 0.91% worldwide while that of the e19a2 variant was 0.31% [8]. These differences in frequencies of *BCR-ABL1* transcript variants could be caused by ethnic and/or genetic influences which require further studies to identify [5]. The e19a2 variant in CML patients had been found to be associated with thrombocytosis, higher Sokal scores at diagnosis and better response to 2G-TKIs than to Imatinib [23–25]. Similarly, expression of the e1a2 transcript in CML was associated with poor response to TKI therapy and poor outcomes in CML patients [9, 25].

This study found no association between *BCR-ABL1* transcript variants and age or sex, similar to findings by other researchers [6, 7, 17, 19]. However, a study of 559 patients in Italy found that e13a2 was more commonly found in males [16]. In the international study, e13a2 was also found to be commoner in males and in younger patients [8]. In this study, e13a2 was associated with a higher platelet count than e14a2 or combined e13a2/e14a2, similar to findings in Iraqi patients [26]. Although, this contrasts with findings from studies in Western countries in which e14a2 was associated with higher platelet counts [6, 7, 27]. These conflicting results may also be due to ethnic and/or genetic factors which are yet to be identified. The prognostic importance of this finding in Nigerian patients also requires further study. There was no significant difference in WBC with respect to transcript variants in this study. Reports on the association between transcript variants and WBC have been controversial. Some studies found no significant association [6]. In contrast, others showed that the e14a2 variant was associated with a lower WBC count [7, 27, 28]. There was no significant difference in the other hematological parameters such as PCV, splenic size or hepatic size. This is similar to findings by other researchers [7, 17, 28]. The e14a2 transcript was associated with better (but non-significant) OS estimates compared with e13a2 and combined e13a2/e14a2. Some studies

showed that e14a2 was associated with a significantly better event-free-survival (EFS) than e13a2 [6]. However, other researchers did not detect any difference in survival with regards to *BCR-ABL1* transcript variants [7, 17]. Cytogenetic and molecular responses could not be evaluated in this study as few patients complied with recommended follow-up tests due to financial constraints. The differences in disease characteristics and survival outcomes in association with transcript variants have been linked to a higher tyrosine kinase activity in e13a2 variant, as measured by higher levels of phospho-CT10 regulator of kinase-like (pCrKL) which is a surrogate marker of tyrosine kinase activity, this results in more effective inhibition of tyrosine kinase activity in e14a2 by any given TKI [6, 16]. The presence of additional 25 amino acids in e14a2 variant is associated with differences in *SRC* homology domain (*SH1-SH3*) and DNA-binding domains which affect the tyrosine kinase activity [11].

Conclusions

The frequency of co-expression of e13a2 and e14a2 variants in Nigerian CML patients is the highest in literature. The e1a2 and the e19a2 variants were rare in Nigerian CML patients. The *BCR-ABL1* transcript type influences disease characteristics and survival in CML patients. Nigerians with CML exhibit distinct disease characteristics which may be due to ethnic-specific genetic factors.

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Author Contributions Study conception and design were performed by MAD. Material preparation, data collection and analysis were performed by MAD and TOO. The first draft of the manuscript was written by TOO. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animals Rights The study was approved by the institutional ethics committee (Ethics and Research Committee, OAUTHC) and was performed in accordance with the ethical standards as laid down in the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in this study.

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