A Review Article on Chronic Myeloid Leukaemia in Nigeria in the Era of Targeted Therapy

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Abstract

A Review Article on Chronic Myeloid Leukaemia in Nigeria in the Era of Targeted Therapy Chronic Myelocytic leukaemia is a myeloproliferative neoplasm and the first malignancy to be pathogenically related to an acquired genetic aberration involving reciprocal translocations between the long arms of chromosomes 9 and 22, with generation of the oncogenic BCR-ABL1 gene and the Philadelphia (Ph) chromosome. CML was incurable in the absence of a successful allogeneic stem cell transplantation that is available to less than 45% of the affected population. Curative potential came at the turn of the century with the discovery of imatinib, and other tyrosine kinase inhibitors (TKIs) that specifically kill the BCR-ABL1 oncoprotein. Today, survival of CML patients on therapeutic doses of TKI is no different from any other chronic disorder, with life span comparable to those of age-matched healthy controls in the general population. Imatinib targeted therapy has decreased the annual mortality of CML from 10%-20% to only 1%-2% in the USA between 2000 and 2017; and in Nigeria, the median survival of CML patients has risen from 31.7 months in 2006 to

176 months in 2021 following introduction of Imatinib in 2003, courtesy of the Max Access Solutions, Seattle, USA. This review summarizes our experience in the management of CML in Nigeria with reference to local and foreign publications through PubMed, Google Scholar and Google, on epidemiology, pathogenesis, diagnosis and differentials; we also considered disease staging, risk factors, treatment evolution and challenges of therapy, including pharmacokinetic studies, cost implications, adherence, host factors, parenting and pregnancy, associated disease(s), and survival.

Running Title: Targeted Therapy for chronic myeloid leukaemia in Nigeria
Key Words: Chronic myeloid leukemia (CML); Philadelphia chromosome (Ph); Breakpoint cluster region; Abelson murine leukemia (BCR-ABL); Tyrosine kinase inhibitors (TKIs); Imatinib

Introduction

Chronic Myelocytic leukaemia (CML) was the first leukaemia to be described in 1840 from similar autopsy findings in a number of patients presenting with hepatosplenomegaly, fever, gross leukocytosis, and "thick blood" by David Craigie, John Hughes Bennet, and Rudolph Virchow. [1,2] It is also the commonest of the leukaemic myeloproliferative neoplasms and the first known malignancy to be associated with a unique acquired genetic disorder, the Philadelphia chromosome (Ph).

Until the turn of the century, CML was a notoriously incurable cancer with the following general characteristics, "*80 % chance of dying in two years, 10 % chance of dying within six months, 10 % chance of living to 10 years. Nobody lived beyond 10 years. And there is no cure."* [3] Outside a successful allogeneic stem cell transplantation, which is available to less than 45% of patients, there had been no reliable potentially curative treatment until the arrival of the magic drug, imatinib, a tyrosine kinase inhibitor (TKI).

Adenosine Triphosphate (ATP)-Competitive BCR-ABL1 Tyrosine Kinase Inhibitors

The ATP-competitive BCR-ABL1 TKIs are the first to be synthesized. They act by targeting multiple kinases, inhibiting the interaction between the BCR-ABL1 oncoprotein and ATP, thus blocking cellular proliferation of the malignant clone. These drugs include imatinib, the first generation (1G), and the more potent 2G drugs including dasatinib (Sprycel), nilotinib (Tasigna), and bosutinib (Bosulif), with inhibitory activity against a broad spectrum of mutations resistant to imatinib.

The third generation TKIs include ponatinib (Iclusig) effective against newly diagnosed wild-type chronic phase CML, and mutant CM L and pan-resistant T315I mutation; and the recently approved olverembatinib for adults with chronic phase-CML resistant to and /or intolerant of 1G and 2G TKIs, as well as T315I-mutated CML.

Asciminib, the Non-ATP Competitive TKI

Asciminib is the first in-class of BCR-ABL1 TKI that 'Specifically Targets the ABL Myristoyl Pocket', hence the description, STAMP inhibitor. It is approved for the treatment of adults with chronic phase Ph+ CML, resistant or intolerant to two previous TKIs with or without T315I mutation as a 3rd - line therapy. Since asciminib targets a different domain, it is effective against all current mutations, including T315I, which are all from ATP-dependent inhibitors. [4]

Following the introduction of imatinib since 2000, the annual mortality from CML in the USA for instance, has decreased from 10% - 20% to only 1% - 2%, and the prevalence estimated at about 25–30 000 in 2000, is now as high as 80–100 000 plus in 2017; [5] and will reach a plateau of about 180 000 cases by 2030. [6] Currently, chronic phase CML in a patient compliant with standard dose of TKI has changed from a fatal disease to a chronic disorder, with life span comparable to those of age-matched controls in the general population. [7-9] However, success largely depends on patients' compliance to treatment, good monitoring for signs of resistance, for early switch to 2G or 3G TKIs and/or consideration for possible allogeneic-SCT before disease progression. [7]

Globally, the treatment modalities for CML long before imatinib and other small molecules are the non-specific cytoreductive agents, including busulphan, hydroxyurea, cyclophosphamide and cytarabine. [10-14] Interferon alfa, an immunotherapy was also adopted as the first line therapy for Ph+ CML before the era of TKIs. [15-16]

The TKI therapy of Ph+ CML effectively commenced at the OAUTHC, Ile-Ife, Nigeria in 2003, with only imatinib, and for a single patient. We now have all the aforementioned TKIs, except the olverembatinib, and over 1600 registered patients.

This review will discuss the epidemiology, pathogenesis, diagnosis and differentials, disease staging, risk factors, treatment evolution and challenges of therapy (pharmacokinetic studies, cost implications, adherence, host factors, fertility impairment and parenting, associated disease (s), including (COVID19) and survival studies of CML) with particular reference to our experience in Nigeria in the past two decades.

Epidemiology

Factors responsible for development of CML include exposure to radiation [17] treatment with DNA topoisomerase inhibitors such as etoposide, [18] smoking, [19] obesity [20] and occupational exposure to benzene. [21]

CML has no familial association; monozygotic twins and patients' relatives are not at risk of acquiring the disease. The cancer does not appear to have any hereditary causes. [22] However, individuals with CML have an increased frequency of HLA antigens CW3 and CW4, suggesting that these may be markers for susceptibility genes for this leukaemia. [23] The same HLA antigens CW3 and CW4 protect against CML development in Mexican populations. [24]

Mendizabal, et al [25] had suggested that the median age at diagnosis of CML and its incidence vary by region, and that geographic and income heterogeneity have significant environmental effects on disease outcome. Generally, the global incidence is 1-2/100,000 population, with a slight male predominance. Age at presentation in the western nations is around 60 years compared to the median age of 30 to 40 years in the low- and middle-income countries (LMICs) of Asia, Africa, Latin America, Southern and Eastern Europe. [14, 26-27] CML is rare in children ≤ 18 years (3.8%). [28] The median age for a cohort of 1,550 Ph+ve CML Nigerians accessing imatinib was 38 years (range, 3 - 87 years) with male: female ratio of 1.5:1; 136 (10%) were 60 years and above as previously reported by Fleming in 1993. [13]

Pathogenesis

In 1960, Nowell and Hungerford identified a tiny chromosome in two CML patients, which they named Philadelphia chromosome (Ph), after the city of discovery. Later in 1973, Janet Rowley showed that the Ph chromosome results from a balanced reciprocal translocation between the long arms of chromosomes 9 and 22 [t (9; 22) (q34; q11)] [29, 30], (Fig. 1). It was further shown by Groffen and others in 1984 that the characteristic Ph chromosome breakpoints are clustered within a specific region (BCR) on chromosome 22. [31]

The fusion of the *Abelson murine leukemia* (*ABL*) gene on chromosome 9 with the *breakpoint cluster region (BCR)* gene on chromosome 22 generates the oncogenic *BCR-ABL1* fusion gene. The fusion gene is a persistently active tyrosine kinase that enhances continuous stem cell replication, inadequate differentiation, and resistance to apoptosis, with development of the cancer, CML, [32] which leads to additional cellular mutation.

The BCR-ABL1 oncoprotein varies in size from 185/190 kDA to 230 kDA, depending on the site of the breakpoint in the BCR gene, however, each fusion gene encodes the same portion of the Abl tyrosine kinase, but differs in the length of BCR sequence retained at the N terminal.

The three breakpoint cluster regions in the BCR gene are the major (M-BCR) 210- kDA, minor (m-BCR) 185/190 kDA and micro (u-BCR) 230-kDA. [33-34]

- The *BCR-ABL1* P210 is expressed mostly in typical CML (95%), and about a third of Ph+ve acute lymphoblastic leukaemia (Ph+ve ALL); most (97–98%) of the CML cases express a chimeric mRNA in which BCR exon 13 or exon 14 joins ABL1 exon 2 (e13a2 and e14a2 to form the fusion proteins, respectively). The remaining 2–3% express diverse atypical mRNA fusions involving other exons of BCR (usually e1, e6, e8, e19) or ABL1 (a3). [35]

- *BCR-ABL1* P185/190 (e1a2) is most often associated with B-ALL/LBL, but found only in about 1% of CML.

- *BCR-ABL1* P230 (e19a2) is expressed in the chronic neutrophilic leukaemia (CNL)

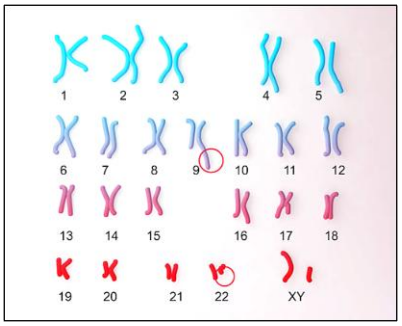

Fig1. Karyotype of a Male Ph+ CML Patient Showing Translocations Between Chr 9 and Chr 22. (https://www.istockphoto.com/photos/cml-leukemia)

Of the 230 Nigerian CML patients whose transcripts were typed, the frequencies of individuals expressing the major (M-BCR) 210 kDA (p210 BCR-ABL1) and exon 2 of ABL, e13a2, e14a2 and both e13a2 & e14a2 were 30 (13.0%), 114 (49.6%) and 82(35.7%), respectively. The other variants: minor (185/190) in Ph+ ALL and micro (230-KDA) in CNL were rare at only 0.4% and 1.3%, respectively. [36] Nigeria has the largest burden of combined e13a2 and e14a2 (35.7%) compared to other populations. [37-38]

In CML, 90%-98% of patients have the diagnostic cytogenetic abnormality, t (9; 22) (q34; q11) mutation, thus confirming Ph chromosome as the main pathogenetic basis for the leukaemia. [39] The Ph abnormality arises from the pluripotent stem cell with its presence in cells of myeloid, megakaryocytic, and erythroid lineages, but is absent in normal lymphocytes. [40]

However, in rare cases, about 5% of patients present with signs and symptoms of CML including, leukocytosis with left shift, splenomegaly, and marked myeloid dysplasia, but are negative for both Ph and *BCR-ABL1* fusion gene, this is atypical CML (aCML), which is characterized by very poor prognosis. [41-42] The emergence of resistance to TKIs therapy has led to the development of new drugs including immunotherapy. [43]

Clinical Features

Diagnosis of CML is based on clinical history, physical examination, and laboratory findings, including CBC, cytogenetic and molecular tests. Evaluation of the findings will both confirm the diagnosis and establish the disease stage and determine the approach to therapy. [44]

Several patients are diagnosed during routine medical checks in the absence of any symptoms, which is very common in the chronic phase of the disease. However, asymptomatic cases are very unusual in our environment but constitute close to 30% to 50% of patients in the USA. In most populations, about 85% of CML is diagnosed in the chronic treatable phase (CP). The chronic phase is followed by the accelerated phase (AP), and finally, the rapidly progressive and almost incurable blastic phase (BP); and a minority of patients progress directly to BP from CP (Table 1). [45]

The very successful outcome of TKI therapy of Ph+ CML in the western nations, wherein the incidence of progression from CP-CML to AP-CML and patients presenting in AP-CML are now having similar good responses with those in CP-CML had persuaded the WHO to abolish the hitherto triphasic staging of CML to a biphasic disease, comprising CP-CML and BP-CMP, with elimination of intermediate AP-CML in its 2022 classification of haematologic cancers. [46] Apparently, the panel failed to consider the role of additional chromosomal abnormalities that remain high-risk for progression to accelerated and blastic phase disease in the previous classifications, including the 2016 WHO CML staging system, such as a complex karyotype, extra Ph translocation, trisomy 8, trisomy 19, etc. [47] The new WHO CML classification system may not be applicable in the low-income countries.

Clinically, over 60% of patients in CP present with splenomegaly, hepatomegaly is found in 20-30%, a large majority suffer from fatigue, weight loss, easy satiety and fullness, or pain in the upper left quadrant, and less commonly, priapism, bleeding, thrombosis, and retinal hemorrhage. In accelerated phase are more severe clinical symptoms including anaemia, bone pain, skin infiltration, lymphadenopathy, fever, arthralgia, and abdominal pain, usually from splenic infarction. The blastic phase is characterized by signs and symptoms of acute leukaemia including

severe anaemia, thrombocytopenic bleeding, fever, and secondary infections.

Table 1. WHO Clinical Phases of CML. [52]

Disease Phase	*Criteria*
Chronic	No criteria for accelerated or blast phase are present
Accelerated	Blasts 10% to 19% in the peripheral blood or bone marrow; Basophilia ≥ 20% in the peripheral blood; Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy; Persistent thrombocytosis (>1,000 × 10^9/L) unresponsive to therapy; Increasing spleen size and leucocyte count unresponsive to therapy; and Cytogenetic clonal evolution
Blastic	Blasts ≥ 20% in the peripheral blood or bone marrow; Extramedullary blast proliferation, apart from the spleen large foci or clusters of blasts in the bone marrow biopsy

Laboratory Confirmation of CML

This is guided by clinical findings and or accidental blood count features, even in apparently asymptomatic individuals. The presence of mild-moderate anaemia, leucocytosis with left shift, and a presence of myelocytosis, compared to metamyelocytes, promyelocytes or blasts, absolute basophilia in over 90% of patients and monocytosis (but rarely greater than 3%), and platelets may be normal, low or high, and less commonly presence of isolated thrombocytosis; the presence of splenomegaly are suggestive of CML. [45, 48]

The hyperleucocytosis in CML is often associated with an elevation in the serum levels of Vit B-12 along with unsaturated B-12 binding capacity. The levels of circulating basophil, histamine, or both are often raised during the transition to CML-BP; although, the underlying reasons and significance of these events remain unknown. [49] Untreated CML is characterized by elevated uric acid, hyperuricemia and hyperuricosuria. [50]

CML patients in the chronic phase have normal immunity like any healthy individuals and may go for extended periods of time without showing any signs of illness; however, with symptoms appear signs of hyper-catabolism including fatigue, night sweats, fever, poor appetite and splenomegaly related abdominal pain. [49]

Cytogenetics and Molecular Confirmatory Diagnostic Tests

a. Bone marrow (BM) aspiration for cytogenetic analysis (karyotyping)
b. Peripheral blood Reverse transcriptase polymerase chain reaction (RT-PCR) for qualitative confirmation of BCR-ABL1 fusion gene
c. Real time PCR (qRT-PCR) for quantification of the copies of BCR-ABL1 transcripts for monitoring of CML therapy
d. Fluorescence in situ hybridization (FISH), a molecular cytogenetic technique that uses commercial single stranded DNA probes labelled with fluorochrome stain

In addition to cytogenetics studies, BM cytology and histology are invaluable for appropriate staging of the CML as determined by the levels of blasts, promyelocytes, myelocytes, eosinophils and basophils. BM aspirate and histology show hypercellularity [7, 51-52]. Histology will confirm the degree of BM fibrosis, which worsens prognosis because it hastens disease progression to AP and BP. [53]

A major differential diagnosis of CML is infection, inflammation or cancer related leukaemoid reaction, characterized by leucocytosis, usually about 50 x 10^9/L or higher with toxic granulocytic vacuolation, and granulocytes with Döhle bodies, absence of basophilia (< 2%), and normal or increased leucocyte alkaline phosphatase (LAP) levels. LAP score is always markedly reduced in CML.

Less common differential diagnosis of CML includes atypical CML (aCML), Ph negative myeloproliferative disorders, chronic myelomonocytic leukemia (monocytes >1.0 × 10^9/L and <20% myeloblasts), and proliferative myelodysplastic syndrome.

In our practice, peripheral blood, bone marrow cytology and trephine, including marrow karyotyping, as well as peripheral blood levels of BCR-ABL1 reverse transcriptase-quantitative (qRT-PCR) confirmatory and monitoring tests are available on site. [54-55]

Therapy of CML

The aims of therapy in CML

The frontline therapies today are TKIs and the major aims are to:

a. Achieve an enduring remission with normal survival and good quality of life without life-long treatment
b. Achieve complete haematologic remission (CHR) within 3 months of initiating imatinib therapy
c. Achieve complete cytogenetic remission (CCyR) within 12 months of initiating therapy, and remain in CCyR thereafter, on the standard dose of imatinib, as defined in table 2.
d. Achieve major molecular response (MMR) within 18 months, with further progression to deep molecular response (DMR) until complete molecular response in (CMR) as shown in Table 3

The primary therapy of CP CML with TKI should always start upfront with imatinib rather than any of the 2GTKI, in that studies had shown no differences in overall survival (OS) after 5 years of follow up. [35]

However, where feasible, upfront 2GTKI may benefit the following group of CP CML:

i. Patients with high or intermediate EUTOS long-term survival (ELTS) score or Sokal score in whom a reduction in disease progression has been demonstrated with a first-line 2GTKI;
ii. Women who wish to have children, where the more rapid molecular response achieved with a 2GTKI is desirable; and
iii. Younger patients, (i.e., the under 30s, and children), who are excellent candidates for stem cell transplantation if the need arises, and in whom concerns have been raised regarding more aggressive disease at presentation.

The major treatment milestones in TKI treatment of CML for patients on first-line or 2L TKI therapy are at 6 and 12 months. Patients with complete cytogenetic response (CCyR) (Ph+ 0%); and/or BCR-ABL1 ≤ 1% at 6 months have optimal response to first line TKI therapy. However, Ph+ > 35% and/or BCR-ABL1 > 10% at 6 months indicate treatment failure. At 12 months into therapy, optimal response is CCyR and major molecular response (MMR) BCR-ABL1 ≤ 0.1%; a failed response is BCR-ABL1 > 1% and/or Ph+ > 0%. [9].

Failed TKI or loss of response at any time may be due to development of kinase domain mutations or intolerance to the drug. Such candidates require a switch of therapy, the choice of alternate must be based on the mutation profiles and patients comorbidities, as determined by outcome of the following repeat investigations a) bone marrow examination to confirm CML phase (chronic, accelerated or blastic), marrow fibrosis and karyotyping for any clonal evolution; as well as peripheral blood for BCR-ABL1 kinase domain mutations, to guide selection of the most appropriate TKI. However, there is no basis for a change of TKI therapy in patients in CCyR but without MMR. [5, 9]

Table 2. Definition of Cytogenetic Response to TKI Therapy of CML (% of Ph+ cells in ≥ 20 Marrow Metaphases)

Cytogenetic Response	*%Ph+ Marrow Cells*
Complete cytogenetic Response (CCyR)	0% Ph+ cells
Partial Cytogenetic Response (PCyR)	1-35% Ph+ cells
Major Cytogenetic Response (MCyR)	0- 35% Ph+ cells
Minor Cytogenetic Response (MnCyR)	36-95% Ph+ cells
No Cytogenetic Response (NCyR)	> 95% Ph+ cells
Monitoring: 6 monthly until CCyR, then Yearly	

***Baccarani, et al. Blood 2006; 108: 1809; Martin MG, et al, Leukemia & Lymphoma 2009; 50(1): 14*)**

Table 3 Definition of Molecular Response of CML Patients to TKI Therapy

Molecular Response	BCR-ABL1 log Reduction or BCR-ABL/ABL ratio on the 'IS' scale
Major molecular response (MMR)	≥ 3-log reduction; ratio < 0.1% IS
Deep molecular response (DMR)	≥ 4 / 4.5-log reduction; ratio < 0.01%/0.0032% IS
Complete molecular response (CMR)	Undetectable by qRT-PCR / BCR-ABL/ABL; ratio < 0.001% IS
3 monthly Monitoring: mutation analysis in case of failure, suboptimal response, or increase level of transcripts	

TABLE 4 Criteria for Response/Failure and Change of TKI Therapy in CML (Jabbour & Kantarjian 2018) [5]

Months	*Imatinib*		*2G TKIs*	
3–6	MCyR; 10% [IS]	PCR	CCyR; 1% [IS]	PCR
12	CCyR; 1% [IS]	PCR	CCyR; 1% [IS]	PCR
Later	CCyR; 1% [IS]	PCR	CCyR; 1% [IS]	PCR

Challenges of TKIs Therapy in Nigeria

a. Imatinib Failure and Limitations of Targeted Therapy of Ph+ CML

A major limitation to the Success of the tyrosine kinase therapy, especially in resource-constrained populations that depend on donor medications, is the development of resistance and/or intolerance to the drugs. The second line and 3L TKIs are not readily available; leading to disease progression and death since AlloSCT are not accessible to most of the patients.

Primary/refractory resistance to imatinib is haematologic in 2-4 % of cases, but it is more often, cytogenetic in 15-25%. Secondary/ acquired resistance is the loss of haematologic and/or cytogenetic responses after initial response. Primary resistance is a major risk factor for the development of secondary resistance. BCR-ABL1 Kinase domain mutations very rarely cause primary resistance.

Acquired resistance occurs from

i. Point mutations of KN domain even after 2GTKIs, occurring in 50% to 90% of patients
ii. Amplification of the BCR-ABL1 gene at the genomic and transcript levels
iii. Overexpression of SRC-related kinases; and
iv. Emergence of new chromosomal aberrations in the resistant clone. [56-57]

Development of resistance and intolerance is the basis for the second-generation ABL kinase inhibitors that are capable of binding and inhibiting the activities of imatinib- resistant BCR-ABL1 KD mutants, and are several folds more potent than imatinib, including, in order of potency nilotinib x 30, bosutinib x 20-50, and dasatinib x 300. Dasatinib and Bosutinib enhance better leukaemic cell kill by targeting both the ABL1 & SRC kinases. The new generations of TKIs are active against most imatinib resistant kinase domain mutations, except T315I mutation. [58-59]

Thirty-three of our patients who became resistant /intolerant to Glivec between 4th Dec 2001 and 30th Jan 2020 were enrolled into the 2L TKIs after a median follow up period of 47 months (range, 4 – 137 months). There were 17 males and 16 females; 29 (88%), 3 (9%) and 1 (3%) presented in chronic, accelerated and lymphoblastic phases, respectively. Majority of the patients (81. 8%) carried the standard-risk e13a2, e14a2 or both e13a2/e14a2 transcripts. Only 14 (42.4%) of the patients achieved complete haematologic response (CHR) within 3 months into imatinib. The indications for switching were imatinib intolerance, progressive disease and hepatotoxicity. [60]

Kinase domain mutations were evaluated for the identification of the mutant genes and the choice of most suitable second generation (2G) TKIs. Mutations were confirmed in 22 (66.7%) of the patients including E255K in 7 and M244V in 4 patients; however, mutation status was not available for 11 (33.3%) individuals, it was negative in 7 but not tested in another 4 (Table 5). Mutations were not even confirmed in some cases; nonetheless, such patients have been shown to also benefit from second line drugs. [61-62]

Table 5 Mutations requiring 2nd generation tyrosine kinase inhibitors in Nigeria

Kinase Domain Mutations	*Frequency (%)*
E255K	7 (21.2)
M244V	4 (12.1)
M255V	2(6.10)
G250E	2 (6.10)
Q252H	2 (6.00)
F359V	1(3.00)
M351T	1(3.00)
M255V	1(3.00)
Q252R	1 (3.00)
Y253H	1 (3.00)
No Mutations	7 (21.2)
Mutations not evaluated	4 (12.1)
Total	33 (100)

The 2G-TKIs used included dasatinib (20; 60.6%), nilotinib (7; 22.6%) and bosutinib (6; 18.2%). The mean survival time for patients on 2G-TKIs was 55.3 months (± 15.1 SE; 95% CI = 25.7-85.0), better in males (52.5 (± 15.1 SE) than in the females, 45.1(± 17.1 SE) months. Poor adherence to therapy and the cost of monitoring tests are limitations to achieving the desired goals of TKI therapy for CML in LMICs.

Patients with ABL1 mutations related-resistance were managed with the most appropriate 2G TKIs (nilotinib, dasatinib and bosutinib) [61], while the 3G TKI, ponatinib (Iclusig; the multi-kinase inhibitor) is active against unmutated and all mutated BCR-ABL1 kinases, including T315I (Table 6). [62] Some of the TKIs targeting multiple kinases, such as, Src, PDGFr and C-kit are used for the treatment of all kinase- induced malignancies. [62, 63] Table 6 summarizes treatment of kinase domain mutations dependent imatinib resistance.

Table 6 Treatment options based on BCR-ABL1 kinase domain mutation status [35]

Mutation	*Recommended treatment*
T315I	Ponatinib/AlloSCT/Asciminib\Clinical Trial
T315A, F317L/V/I/C	Consider nilotinib, bosutinib or ponatinib rather than dasatinib;
Y253H, F359V/C/I, E255K/V	Consider dasatinib, bosutinib or ponatinib rather than nilotinib;
V299L	Consider nilotinib or ponatinib rather than dasatinib or bosutinib
Any other mutation	Clinical significance unclear: consider high-dose TKI, alternative TKI, allo-SCT, investigational drugs

Immunotherapy in CML

Although TKI therapy can eradicate the majority of the leukaemic cells, the most primitive quiescent leukaemic stem cells (LSCs) are preserved; leading to development of disease relapse if treatment is discontinued. Residual LSCs are best eradicated by allogeneic SCT, where the grafted donor cells mediate the graft versus leukaemia (GvL) effect, through the alloreactive T-cells in the unrelated HLA-matched or partially-HLA mismatched transplants. HSCT use is hindered by the very high cost, difficulty getting suitable donors and the potentially serious complications including GVHD.

Interferon, an immunotherapeutic agent was the first line therapy for CML before the emergence of TKIs, and it has been associated with achievement of complete cytogenetic remission. A successful trial of interferon alpha for chronic phase CML was also conducted in Nigeria some 20 years ago. [16, 64] Even, in the TKIs era, interferon is still available as a rescue measure, often used in combination with TKIs [65]. Interferon alpha induced immune activation in a CML patient with disappearance of the T315I mutated clone and discontinue TKI therapy without disease relapse has been reported. [66]

b. Costs of Diagnostic and Treatment Monitoring Tests

Imatinib and all other TKIs are supplied gratis by a donor agency, the Max Access Solutions; otherwise imatinib would cost about US$3000.00 per month for each person, which is out of reach for the majority. The cost of hospital services such as, blood counts, chemistry, microbiology/parasitology, imaging techniques, bone marrow and karyotyping, as well as molecular diagnostic, confirmatory and monitoring tests (RT-PCR/qRT-PCR of BCR-ABL1transcripts), are borne by the patients. These tests are also too expensive for most of our patients to afford the ideal 3-monthly monitoring qRT-PCR protocol, therefore, 6 or 12 monthly tests are done!

All these tests have been domesticated, qRT-PCR of BCR-ABL1transcripts is expressed in percentages rather than in International Scale 'IS', since we stopped using the very expensive unaffordable Gene Expert cartridges.

c. Pharmacokinetic Studies and Imatinib Intolerance/Resistance:

Imatinib-related moderate-severe recurrent cytopenias are serious complications of therapy often requiring drug suspension or even withdrawal for days or weeks and may eventually lead to the development of drug resistance and disease progression. The problems are those of

pharmacokinetic variability, nonadherence to drug, suboptimal dosing of imatinib (< 300 mg in adults), drug-drug interaction with imatinib, and clonal evolution of cytogenetic abnormalities. [56-57]

In Nigerians, pharmacokinetic studies identified two groups of aberrant imatinib metabolisers, slow and fast metabolisers. The slow metabolisers are individuals with higher trough of plasma concentration (TPC) of imatinib and low clearance of the drug, and with longer exposure to the drug, induction of cellular toxicity, recurrent cytopenias, drug intolerance and suboptimal response to the medication. Often the cytopenias in the patients require treatment suspension or dose reduction. The recurrent drug reduction/suspension frequently results in disease progression, and ultimately, development of blastic transformation. However, with effective control of cytopenias with growth factors (e.g., filgrastim; neupogen) for neutropenia or thrombopoietin and platelet transfusion for thrombocytopenia that keep the platelets persistently above 75 x 10^9/L, the normal dosage of imatinib may be maintained, but at a great cost.

The fast metabolizers on the other hand, have rapid clearance of the drug from the plasma, shorter exposure of leukaemic cells to imatinib, suboptimal disease response, treatment failure, disease progression and high risk of resistance. [67-68]

d. Therapy Adherence and Resistance to Imatinib

TKIs for Nigerians are only accessible from a single centre in Ile-Ife, southwest Nigeria; this remains a strong impediment to adherence, the only approach to successful therapy and achievement of treatment goals. The WHO defines adherence as "the extent to which a person's behaviour at taking medication corresponds with agreed recommendations from a health care provider". [69] A successful treatment of CML with imatinib or any other TKI requires more than 95% adherence. Poor adherence to therapy is the most important cause of treatment failure and development of resistance. It has been shown that major molecular response (BCR/ABL1 ≤ 0.1%) or deep-MR4 (≤ 0.01%) is achieved in individuals with adherence of ≥ 80% or ≥ 90%, respectively. [70-71] Adherence to Glivec therapy in Nigeria is abysmally low at 47% as against the expected 95% and above [72]. A large majority of the patients could not conveniently afford the cost of transportation to the treatment centre in Ile-Ife, especially those domiciled over 200 km away who present a significant non-adherence rate when compared to those who reside less than 200 km (p = 0.008). [72] The donor agency, *Max* Access Solutions, had graciously approved an additional treatment centre at the National Hospital, Abuja in 2020

e. Fear of Possible Fertility Impairment: Pregnancy, Low Sperm Count and Therapy Adherence to Imatinib in Nigerian Patients

The teratogenicity of Imatinib in pregnancies has been confirmed in lower animal and human foetuses exposed to the drug during the first trimester of pregnancy [73]. Some of the Imatinib-related congenital abnormalities include premature closure of the skull sutures (craniosynostosis), hypoplastic lungs, exomphalos, duplex left kidney, absent right kidney, and right renal agenesis, hemivertebrae, exomphalos and scoliosis, etc. [74]

Alternates to imatinib in early pregnancies include IFN-a, which is not teratogenic [75]. Hydroxyurea is suitable from the 2nd trimester, while leukapheresis can be used all through pregnancy. [75]

It is unfortunate, CML is a disease of young adults of child-bearing ages in Africa; therefore, issues of raising family during treatment are normally discussed as part of the pre-therapy counseling. This probably explains why some young women and men who are desirous of raising family in the future often show poor adherence to therapy. However, a recent publication by George Nesr et al from the UK did not confirm fertility impairment in male patients after TKI therapy. [76]

Seventeen women, ages 16 to 36 (median, 27) years at initiation of Glivec therapy, got pregnant during treatment. All but one, were on imatinib at 400mg daily for CML-CP, except one Mrs P. I., who has been on imatinib since 2012, but switched to dasatinib following development of *E255K* mutation in July 2019. All the women

stayed off TKI (imatinib & dasatinib) during the first trimesters of their pregnancies, but Mrs P.I, and U.C who were never aware of their pregnancies until after the first trimesters. The babies were delivered after duration of 11-154 (median, 31) months into TKI therapy. All the pregnancies were successful. There were a total of 20 children, eight males and 12 females (including a set of twins); three women had successful pregnancies twice, consisting of two females and two males by each of two women, respectively, and one male and one female by the third lady. However, seven of the patients had delivered children prior to the diagnosis of CML. It would appear that imatinib was associated with abortions in one of the patients, Mrs. P. I, who lost three pregnancies. There was a maternal death, Mrs A. A, who stayed off therapy immediately she missed her period in February 2005, and never showed up until her delivery on the 5th of November 2005! Apparently, she did not want the drug to injure her unborn child. She died on the 3rd of December 2006, most likely from her disease.

f. Imatinib and COVID-19 Pandemic

The COVID-19 associated inter- and intra-city lockdown worsened the already abysmally low adherence to TKIs amongst Nigerian Ph+ CML patients on TKIs, especially during the total lockdown period of 30th March to 27 July 2020. Courier services had to be engaged for door-step delivery of drugs across the country.[77] The programme is still on, but patients must be physically present twice in the year for follow up laboratory monitoring, while the host haematologists supervise treatment at the referral hospitals. The lockdown adversely affected the follow up of patients for karyotyping and BCR-ABL1 monitoring, with possibility of delay in detecting development of sub-optimal response or resistance to the drugs.

At international level, CML patients on TKIs recorded significant mortality and morbidity as confirmed in the 2020/2021 multicentre international COVID-19 study on 642 CML patients, including Nigerians, median age 53 years (18-94). There were 48 (8%) deaths and 558 (92%) survivors of the 606 (94.4%) fully documented patients. Mortality was higher among older patients above age 75 years, patients with cardiovascular or pulmonary comorbidities and individuals who were poorer in the low and low-middle income brackets with inadequate supportive facilities. As expected, mortality was also higher in patients presenting in the advanced accelerated or blastic phases of the disease, as well as in individuals that failed to achieve a major molecular response (MMR). [78]

g. Survival Estimates in Nigerians CML Patients on Glivec

As at the end of 2021, there were 1,550 patients, 879 (56.7%) were alive, status of 385 (24.5%) was not known and 286 (18.5%) were dead. The median overall survival (OS) was 179.0 ± 16.7 (SE) months (95% CI = 146-211.7). Using log rank, the median survival was greater in males, than in the females at 201.0 ± 55.8 and 160.0 ± 19.4 months, respectively but the difference was not statistically significant (p = 0.93) (Fig 2). The 176 months (15 years) OS of CML patients on this drug compared to the 32-43 months survival reported for patients treated with conventional chemotherapy in Africa, Europe and N. America in the past confirmed the potential curability of the cancer by imatinib. [14,79, 80]

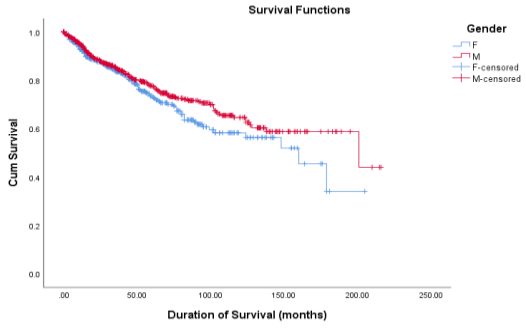

Fig 2 OS Survivals of Female and Male CML Patients on Imatinib

4. Conclusion

Despite the challenges identified, the feasibility of Imatinib as the frontline therapy for CML in Nigeria has been established. The treatment is available to patients from every part of the country. Donations of 2GN and 3GN ATP-competitive TKIs and non-ATP-competitive STAMP inhibitor, Asciminib, are now available to Nigerians. The recognition of the drugs as donated anticancer medications by the Government has greatly facilitated Customs and

NAFDAC clearance from the Ports. The domestication of the CML diagnostic and treatment monitoring has greatly enhanced the development of the hospital cytogenetics and molecular laboratory facilities. However, the donor-dependent supply of these novel TKIs to patients in our parts of the world, together with other deficiencies, including poor compliance to therapy, inability to effectively monitor treatment response using QR-PCR, lack of the stem cell transplant facilities and other factors are limitations to achievement of normal life expectancy as for the general population which is now the norm in the high-income populations on these medications. However, the overall survival of 15 years in CML patients on imatinib remains very impressive compared to our previous experience of less than 50 months reported globally before TKIs.

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