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ORIGINAL ARTICLE

The treatment of childhood and adolescent chronic myeloid leukaemia in Nigeria

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Abstract:

Introduction: *The introduction of the tyrosine kinase inhibitors (TKI) has significantly improved the overall survival of Nigerian patients with chronic myeloid leukemia (CML). However, there have been concerns that the outcome for children and adolescents may be sub-optimal.*

Objectives: *To determine the overall survival (OS) of childhood and adolescent CML patients in Nigeria.*

Methods: *We retrospectively examined our records from 2003 to 2011, and identified all Ph⁺ or BCR-ABL1⁺ CML patients ≤ 18 years at diagnosis, and retrieved their clinical, haematological and biochemical parameters. They received imatinib at 260-340 mg/m²/day. Statistical analysis was done using SPSS 17, and survival studies using the Kaplan-Meier technique.*

Results: *Of the 410 patients diagnosed, 14 (3.4%; male/female = 5/9) paediatric cases were recorded, with a median age of 16.5 (range, 11 - 18) years. At presentation, nine and five patients respectively were in chronic and accelerated phases. As at April 2012, seven patients are known to be alive, one lost to follow-up and six dead from progressive disease. Overall survival at 1 and 2 years were 90% and 79% respectively; while estimated median survival is 48.2 months (95%CI = 42.3 - 54.1).*

Conclusions: *Imatinib continues to deliver impressive survival outcomes in Nigerian patients with CML. As compared to our previously reported data comprising mostly of adults, this cohort seems to suggest that survival outcomes are comparable in paediatric CML cases.*

Keywords *Chronic myeloid leukemia, imatinib, childhood, adolescent, Nigeria.*

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Introduction

Chronic myeloid leukemia (CML) is defined by the presence of the Philadelphia chromosome (Ph) which arises from the reciprocal translocation of the *ABL1* and *BCR* genes on chromosome 9 and 22 respectively.(1-2) It is characterized by the proliferation of a malignant clone containing the *BCR-ABL1* mutant fusion gene resulting in myeloid hyperplasia and peripheral blood leucocytosis and thrombocytosis. It is believed that paediatric CML is rare, accounting for less than 10% of all cases of CML and less than 3% of all pediatric leukaemias.(3) Incidence increases with age being exceptionally rare in infancy, it is about 0.7 per million/year at ages 1 – 14 years and rising to 1.2 per million/year in adolescents.(3-4) Generally, children are diagnosed at a median age of 11 – 12 years (range, 1 – 18 years) with approximately 10% presenting in advanced phases.(5) Similar to adults, children progress from chronic phase to accelerated phase and finally to blastic phase but up to 25% of the patients have been reported to progress from chronic phase to blastic phase.(3)

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only potentially curative treatment

available; however its role in the management of these patients has changed dramatically with the introduction of tyrosine kinase inhibitors (TKIs).(3, 6) While the results of HSCT for CML are best in pediatric patients, the convenience and tolerability profile of the TKIs has made them universally accepted as the first-line therapy in the management of CML for all ages.(7) With the introduction and availability of free TKIs in several resource-poor countries (through Novartis' Glivec international patient assistance program [GIPAP]), these drugs have also become the first-line therapy for CML in Nigerian paediatric patients.(8) Compared to our earlier report, the present study focuses on the survival outcomes of our paediatric patients receiving TKIs.

PATIENTS AND METHODS

Prior written informed consent had been given by the parents or guardians of all participants in this study. We reviewed all our pediatric and adolescent CML patients (age ≤ 18 years) diagnosed between August 2003 and April 2012. There were a total of 14 patients; and their clinical, haematologic and biochemical parameters were retrieved. All the patients received oral imatinib mesylate at 260-340 mg/m^2/day following confirmation of their cytogenetic (Ph-positive) or molecular (*BCR-ABL1* positive) status, as part of the ongoing GIPAP treatment programme. Of the 14 patients, 12 had been previously exposed to chemotherapeutic agents: (hydroxyurea, n = 9; busulphan, n = 2; α-interferon, n = 1). One patient had received multiple chemotherapeutic agents. Studied patients were from various parts of Nigeria.

Diagnosis and monitoring of patients

The diagnosis of CML was made according to the WHO standard clinical, hematologic and cytogenetic criteria.(9-10) Chromosomal analysis was done using cultured bone marrow aspirate samples with conventional cytogenetic, while *BCR-ABL1* status was determined by qualitative PCR. Patients were monitored with monthly blood counts, clinically every 3 months; and also had serial serum chemistry, cytogenetic analysis and *BCR-ABL1* status every 6 months, to evaluate response to imatinib. Information on adverse events was recorded.

Statistical analysis

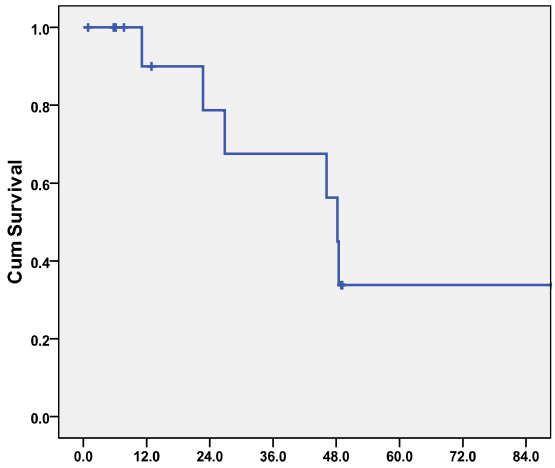
Data were collected into Microsoft Excel 2007 and analyzed using SPSS 17 software package. The survival analyses were done using the Kaplan-Meier technique.

RESULTS

There were a total of 14 patients (aged ≤ 18 years) out of the total 410 patients (3.4%) with Ph chromosome or *BCR-ABL1*-positive CML seen within the study period. Their ages ranged from 11 - 18 years (median 16.5 years) consisting of nine females and five males (M/F = 0.56). The median time from diagnosis to commencement of Glivec was 11.4 weeks (range, 0 - 128.3). At diagnosis, total leucocyte count was 11.0 - 618.8 x 10^9/l (median, 100 x 10^9/l). Eleven patients presented with splenomegaly, ranging from 4 - 26 cm (median, 18 cm; below the costal margin), while four had hepatomegaly. Eleven patients were in chronic phase (CP; one was in second CP, after chemotherapy for blastic phase) at diagnosis while three were in accelerated phase (AP). The median percentage Ph chromosome positivity at diagnosis was 50% (range, 10 - 65%).

After 90 days on imatinib, all 13 evaluable patients had attained complete hematologic response (CHR). At 6 months, two and three of the eight evaluable patients respectively, were in complete and partial cytogenetic remission (CCR, PCR). Seven patients (50%) were alive at the time of censorship (April 2012), one had been lost to follow-up , and the six others had died from progressive disease due to either non-compliance or imatinib resistance. Kaplan-Meier estimates of overall survival (OS) at 1 and 2 years were 90% and 79% respectively, while median survival was 48.2 months (95%CI = 42.3 - 54.1; Figure 1).

Figure 1. Overall survival of 14 CML patients



A plot of cumulative survival against overall survival (in months) from commencement of imatinib.

DISCUSSION

The relative frequency of childhood and adolescent CML in our cohort is 3.4%. With 14 patients over a 9-year period and an estimated population of 155 million people,(11) that gives an annual population incidence of approximately 1.0 per 100 million people; consistent with the earlier observation that pediatric CML is a rarity.(4-5)

Most experts believe that the optimal management of paediatric CML involves an initial period of oral therapy with a first-generation tyrosine kinase inhibitor (TKI; imatinib) to maximally reduce the tumor load and achieve an acceptably low level of minimal residual disease (complete cytogenetic or major molecular remission), followed by allogeneic haematopoietic stem cell transplantation (HSCT) in those patients with an HLA-matched related donor.(5, 12) In the absence of a matched

related donor however, continuation of therapy with a second-generation TKI (nilotinib, dasatinib, or bosutinib) is justified. Patients for whom a donor is unavailable may be candidates for experimental approaches such as newer TKIs (e.g. ponatinib) or other inhibitors that act through non-ATP-competitive mechanisms – DCC-2036, GNF-2.(13-16)

This approach is even more pertinent in our cohort, where the median leukocyte count at diagnosis was relatively high at 141.5 x 10^9/l. Even though initial response to imatinib was impressive for virtually all our patients, sustaining this level of response was a challenge due largely to disease progression and imatinib resistance, resulting from poor drug compliance, ignorance and miss-information on the part of parents/guardians. Moreover, access to TKIs other than imatinib is very limited in our setting. Likewise, local access to HSCT is virtually non-existent. However, similar to experiences reported from other centers, we also continue to receive valid concerns from caregivers about the possibility of serious late side effects.(17) This may partly explain the poor drug compliance we have noted.

Interestingly too, nine of these patients are females, a male/female ratio of 0.56, compared to 1.69 obtained from an earlier analysis of all 272 CML patients (adults inclusive).(18) It is still unclear why the gender distribution in this cohort is so skewed; though it could be mere coincidence from the small numbers. However, we may also need to explore other factors; socioeconomic, or cultural, before we begin to consider possible biological factors responsible. These are some of the questions that may be answered if we can pool data to study the pattern of childhood CML, in a multi-center study or a meta-analysis.

The median time from diagnosis to commencement of imatinib therapy of 11.4 weeks is relatively long, and this delay may also contribute to the presentation of these patients with bulky disease, which may presumably put the patient at risk for poor response.

Estimates of median overall survival of over 4 years (48.2 months) in this cohort is remarkable. Overall survival in the first two years of therapy were impressive, given that survival estimates were not significantly different from those reported for all CML patients from our center (90% and 79% vs 94% and 84%).(18) Additionally, the tolerability profile was also good, as only one of these patients reported side effects, which were mild and resolved with symptomatic care.

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