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A Ten-Year Experience of Treating Chronic Myeloid Leukemia in Rural Rwanda: Outcomes and Insights for a Changing Landscape

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PURPOSE In describing our ten-year experience with treating chronic myeloid leukemia (CML) as part of the Glivec Patient Assistance Program (GIPAP) in rural Rwanda, we evaluate (1) patient characteristics and treatment outcomes, (2) resource-adapted management strategies, and (3) the impact of diagnostic capacity development.

METHODS We retrospectively reviewed all patients with BCR-ABL–positive CML enrolled in this GIPAP program between 2009 and 2018. Clinical data were analyzed using descriptive statistics, Kaplan-Meier methods, proportional hazards regression, and the Kruskal-Wallis test.

RESULTS One hundred twenty-four patients were included. The median age at diagnosis was 34 (range 8–81) years. On imatinib, 91% achieved complete hematologic response (CHR) after a median of 49 days. Seven (6%) and 12 (11%) patients had primary and secondary imatinib resistance, respectively. The 3-year overall survival was 80% (95% CI, 72 to 87) for the cohort, with superior survival in imatinib responders compared with those with primary and secondary resistance. The median time from imatinib initiation to CHR was 59 versus 38 days ($P = .040$) before and after in-country diagnostic testing, whereas the median time to diagnosis ($P = .056$) and imatinib initiation ($P = .170$) was not significantly different.

CONCLUSION Coupling molecular diagnostics with affordable access to imatinib within a comprehensive cancer care delivery program is a successful long-term strategy to treat CML in resource-constrained settings. Our patients are younger and have higher rates of imatinib resistance compared with historic cohorts in high-income countries. High imatinib resistance rates highlight the need for access to molecular monitoring, resistance testing, and second-generation tyrosine kinase inhibitors, as well as systems to support drug adherence. Hematologic response is an accurate resource-adapted predictor of survival in this setting. Local diagnostic capacity development has allowed for continuous, timely CML care delivery in Rwanda.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder that affects approximately one to two in 100,000 people annually worldwide.¹ CML is characterized by a Philadelphia chromosome and BCR-ABL fusion gene product, leading to unregulated tyrosine kinase activity and proliferation of myeloid cells.^{2,3} With the advent of tyrosine kinase inhibitors (TKIs), CML has transformed from a near fatal condition into a chronic manageable disease.^{4,5} However, prohibitive drug pricing has limited TKI use in low- and middle-income countries (LMICs), and therefore, patients in high-income countries (HICs) have derived much of the benefit of TKIs, whereas those in LMICs continue to suffer and die of untreated disease.^{6,7}

To address this stark inequity and make TKIs accessible in LMICs, the Glivec Patient Assistance Program

(GIPAP) was created in 2001. A partnership between Novartis and the Max Foundation, GIPAP, provides imatinib (Glivec), a first-generation TKI, to patients with BCR-ABL–positive CML or GI stromal tumor free of charge. GIPAP requires a molecular diagnosis of CML and enrollment in a care delivery program capable of treating and monitoring patients on TKIs.⁸ A recent GIPAP program evaluation showed that between 2001 and 2014, 63,000 patients in 93 countries were treated with imatinib, with a 5-year overall survival (OS) of 89%.⁹ Numerous individual studies have demonstrated the efficacy and safety of GIPAP-facilitated CML treatment in LMICs; however, most care delivery programs have been implemented in private sectors or urban academic centers, with few in sub-Saharan Africa.^{10–14}

In Rwanda, a CML care delivery program was developed at two rural public hospitals, Rwinkwavu and

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CONTEXT

Key Objective

With the advent of imatinib therapy, chronic myeloid leukemia (CML) has been transformed from a fatal to a chronic disease. This CML care delivery program has made imatinib available to rural Rwandan patients who would otherwise not have access. In this study, our objective is to evaluate CML management strategies and outcomes from this program in Rwanda.

Knowledge Generated

Resource-adapted molecular diagnostics, affordable imatinib therapy, and hematologic response assessment facilitated timely CML care over a decade through the support of the Glivec Patient Assistance Program and a long-term international collaboration. Still, our patients experienced worse outcomes than those receiving imatinib in high-resource settings.

Relevance

The feasibility of CML care coupled with suboptimal outcomes in our setting is a call to action for increased access to resistance testing and second-generation tyrosine kinase inhibitors to close the gap in CML outcomes between low-resource and high-resource settings.

Butaro Hospitals, in 2009 through collaboration between GIPAP, the Rwanda Ministry of Health (RMOH), the organization Partners In Health (PIH), and advisors from Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC).^{15,16} Initially, in-country diagnostic testing was unavailable, and blood and bone marrow specimens were shipped to DF/BWCC for diagnostic confirmation of CML. Imatinib was then initiated in patients with confirmed CML. A preliminary report of patients in this program from 2009 to 2014 showed promising early outcomes.¹⁶ At a median follow-up of 22.6 months, 32 of 43 patients (74%) were in hematologic remission and the OS was 94.7%, with 11.8% lost to follow up (LTFU).¹⁶ To our knowledge, this study was among the first to demonstrate the feasibility of treating CML with imatinib in a significantly resource-constrained rural setting.

Through local investment and longitudinal international collaboration, this program has significantly expanded since this early study. In 2012, the Butaro Cancer Center of Excellence (BCCOE) was established through partnership between the RMOH, PIH, and DF/BWCC.^{15,17} BCCOE uses a task-shifting model in which nononcologist clinicians and nurses deliver protocol-guided cancer care in consultation with international advisors.¹⁷ Implementation of this care model has facilitated a standardized approach to high-quality CML treatment at both hospitals. In March 2015, molecular diagnostics for CML were implemented at Rwinkwavu Hospital using GeneXpert (Cepheid, Sunnyvale, CA), an automated polymerase chain reaction test that is widely used in LMICs for tuberculosis diagnosis and drug resistance testing.¹⁸ The GeneXpert platform can diagnose CML from peripheral blood samples potentially within hours, transforming the timeline to treatment initiation.

To evaluate this evolving CML care delivery program, real-world data from a larger cohort with an extended follow-up were needed. In this study, we aim to (1) describe patient characteristics and treatment outcomes, (2) validate

resource-adapted CML management approaches using hematologic response assessment, and (3) evaluate the impact of molecular diagnostic capacity development on care delivery over a ten-year period.

METHODS

CML Care Delivery Program

This study was conducted at Rwinkwavu and Butaro Hospitals, two GIPAP-registered rural district hospitals in Rwanda serving catchment areas of about 210,000 and 300,000 people (in addition to country-wide referrals to BCCOE), respectively. Patients with confirmed CML receive protocol-directed treatment as outlined in [Figure 1](#). Before March 2015, CML diagnosis was confirmed by send-out BCR-ABL testing at DF/BWCC as indicated in [Table 1](#). After March 2015, CML diagnosis was confirmed using in-country GeneXpert at Rwinkwavu Hospital; Butaro patients with suspected CML were sent to Rwinkwavu for testing. Imatinib was the only treatment available for CML beyond hydroxyurea. The CML treatment protocol included counseling on contraception, which is accessible to all through the Rwandan public health insurance system, and confirmation of contraception at each visit.

Study Patients

The study cohort consisted of all patients with documented BCR-ABL-positive CML who were enrolled in the GIPAP program from July 2009 to March 2018. Patients in the previously published study were included with updated follow-up if records were available. Patients who enrolled in this program but received a CML diagnosis and/or treatment with imatinib elsewhere (private sector hospitals or another GIPAP program) were included if diagnostic, treatment, and hematologic response and vital status were available.

Data Collection

Data were abstracted from paper and electronic medical records using the Ona database platform (Ona Systems, Nairobi, Kenya). Chart abstraction was conducted twice by

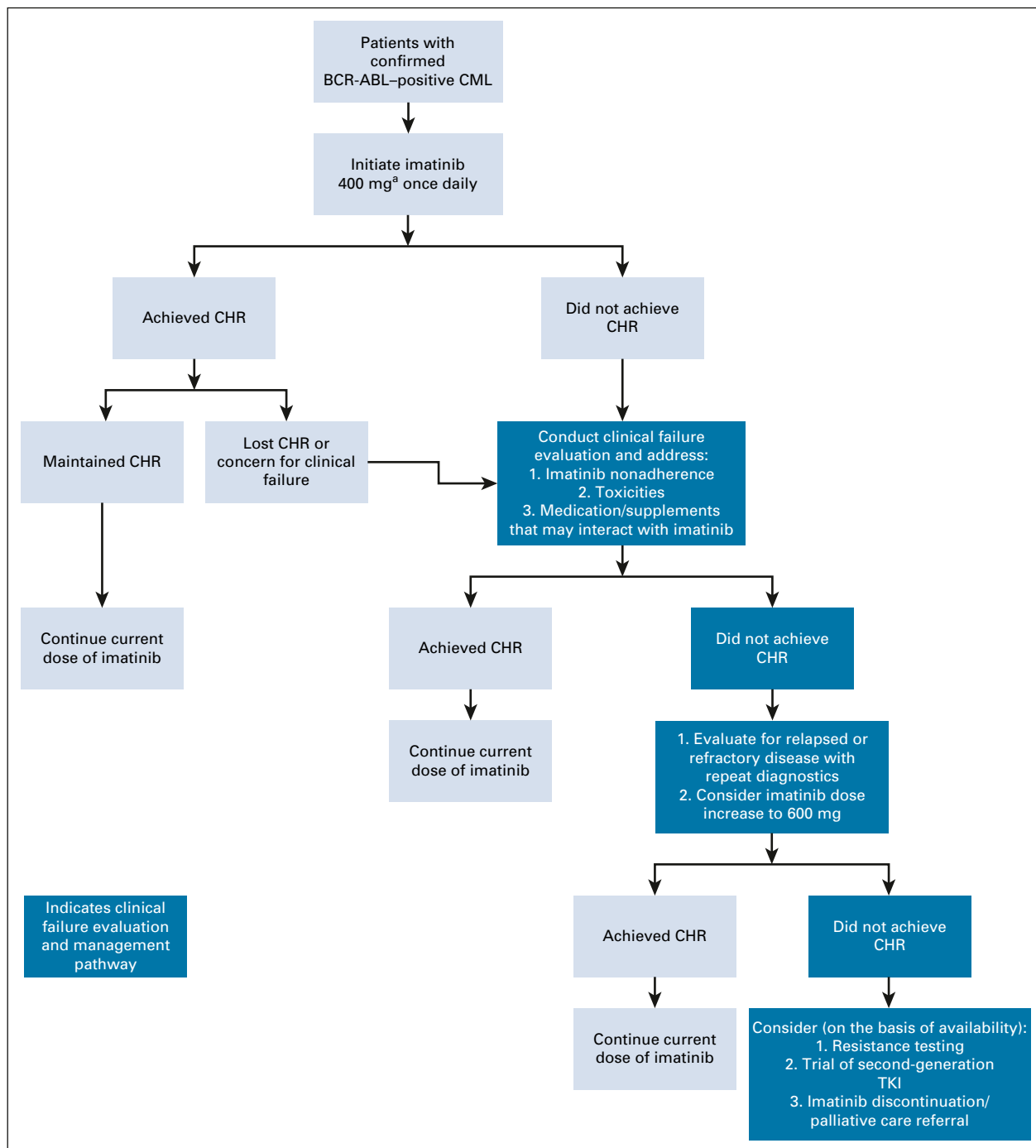


FIG 1. Treatment algorithm for CML as per the Rwinkwavu and Butaro Hospital protocol. ^aPatients with chronic phase CML were initiated on imatinib 400 mg once daily. Few patients with an accelerated/blast phase were initiated on 600 mg once daily. After imatinib initiation, evaluation for treatment response was conducted every 2-4 weeks until CHR was achieved and every 3 months thereafter. CHR, complete hematologic response; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

independent observers with discrepancies resolved by a third observer. Variables included patient demographics, diagnostic evaluation, treatment details, and vital status. Splenomegaly was evaluated as present or absent on the basis of documented physical examination or imaging. The CML disease phase according to 2016 WHO criteria

(Table 1) was determined by available laboratory studies, biopsy results, and clinician documentation.¹⁹

The primary outcome, complete hematologic response (CHR), was defined as WBC < 10 × 10⁹/L, no circulating immature myeloid cells (if differential available), platelets < 450 × 10⁹/L, no clinical findings of disease, and absence of

TABLE 1. Baseline Characteristics of Patients With CML Enrolled in a GIPAP Program in Rural Rwanda From July 2009 to March 2018

Characteristic	Total (N = 124) ^a
Age, years, median (IQR; range)	34 (28-44; 8-81)
Sex, No. (%)	
Male	74 (60)
Female	50 (40)
Presenting hospital, No. (%)	
Butaro	71 (57)
Rwinkwavu	53 (43)
Country of residence, No. (%)	
Rwanda	94 (76)
Outside Rwanda (includes DRC and Burundi)	30 (24)
ECOG, No. (%)	
0-1	81 (65)
≥ 2	11 (9)
Unknown	32 (26)
HIV status, No. (%)	
Negative	96 (77)
Positive	4 (3)
Unknown	24 (19)
Duration of symptoms, months, median (IQR; n = 104)	11 (4-24)
Laboratory studies before imatinib therapy	
WBC count, 10 ⁹ /L, median (IQR; n = 104)	226 (118-309)
Hemoglobin, g/dL, median (IQR; n = 100)	9.9 (8.3-11.5)
Platelet count, 10 ⁹ /L, median (IQR; n = 101)	339 (231-530)
Splenomegaly (n = 113)	97 (86)
Test used for diagnostic evaluation, ^b No. (%)	
Bone marrow biopsy	83 (67)
Peripheral blood smear	29 (23)
GeneXpert	54 (44)
Other BCR-ABL testing ^c	67 (54)
Phase of disease at diagnosis, ^d No. (%)	
Chronic	88 (71)
Accelerated	4 (3)
Blast	2 (2)
Not documented	30 (24)

Abbreviations: CML, chronic myeloid leukemia; DRC, Democratic Republic of Congo; ECOG, Eastern Cooperative Oncology Group; GIPAP, Glivec Patient Assistance Program; IQR, interquartile range.

^aN = 124 unless specified.

^bDoes not add to 100%, given that patients can receive > 1 diagnostic test.

^cIncludes karyotyping, fluorescence in situ hybridization, or reverse transcriptase polymerase chain reaction on peripheral blood and/or bone marrow specimens.

^dDefined by 2016 WHO Criteria as follows: chronic phase if < 10% blasts present in the bone marrow or peripheral blood; accelerated phase if 10%-19% blasts present in the peripheral blood or bone marrow, ≥ 20% peripheral blood basophils, platelets < 100,000/μL unrelated to therapy, platelets > 1,000,000/μL unresponsive to therapy, and/or progressive splenomegaly and increasing WBC count unresponsive to therapy; or blast phase if ≥ 20% blasts present in the peripheral blood or bone marrow, presence of large foci or clusters of blasts on the bone marrow biopsy, and/or extramedullary blast proliferation

palpable spleen.²⁰ Clinical failure was defined as (1) failure to achieve CHR, (2) no longer meeting criteria for CHR, and/or (3) progression from the chronic phase to the accelerated or blast phase.²⁰ Treatment response on the basis of CHR status was assigned as follows: (1) primary imatinib resistance: patients who never achieved CHR; (2) secondary imatinib resistance: patients who achieved CHR and subsequently met criteria for clinical failure despite appropriate management; and (3) imatinib response: patients who achieved and maintained CHR or achieved and regained CHR with appropriate management after meeting criteria for clinical failure.

Survival status was determined by medical records and contact with patients, families, or community health workers. Patients were considered LTFU if they missed their most recent appointment, had no contact with hospital staff for 1 year, and were not reachable.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics and treatment response. OS was measured from diagnosis to last follow-up or death from any cause. Kaplan-Meier methods with log-rank tests were used to compare OS among patient groups. Independent effects of clinical characteristics and treatment response on the risk of death were evaluated using multivariate Cox proportional hazards models and included variables with a *P* value < .1 in univariate analyses or high clinical significance. All tests were two-sided, and a significance level of $\alpha = .05$ determined statistical significance. Time to diagnosis was calculated from the enrollment to diagnostic result date in patients who presented without a prior CML diagnosis. Time to treatment initiation was calculated from enrollment to first imatinib dose in patients who had not previously received imatinib. Time to CHR was calculated from first imatinib dose to the date of CHR. Differences in time to diagnosis, to treatment initiation, and to CHR were compared among patients receiving out-of-country (before March 1, 2015) and in-country (after March 1, 2015) diagnostic testing using the Kruskal-Wallis test. Analyses were performed using Stata Statistical Software (College Station, TX). This study was approved by the Rwanda National Ethics Committee (Kigali, Rwanda) and the Inshuti Mu Buzima Research Committee (Kigali, Rwanda).

RESULTS

Patient and Disease Characteristics

A total of 152 patients were suspected to have CML from July 2009 to March 2018. Ten patients with missing charts and 18 patients with inconclusive BCR-ABL testing were excluded. Ultimately, 124 patients were analyzed. Baseline demographic and clinical information is presented in [Table 1](#). The median age was 34 (range 8-81) years; the age distribution is illustrated in [Figure 2](#). Most patients were

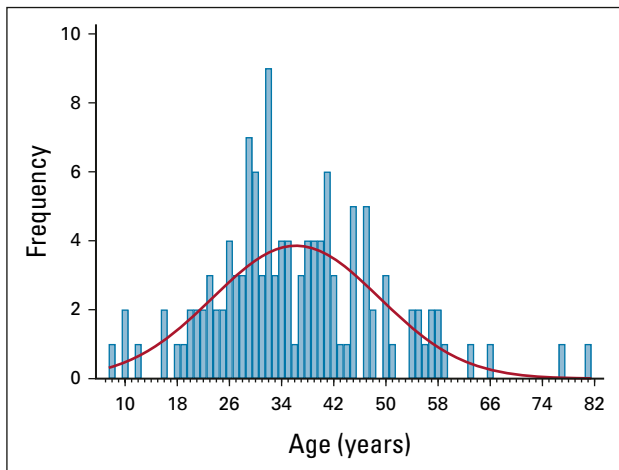


FIG 2. Age distribution of patients with CML enrolled in a GIPAP program in rural Rwanda from July 2009 to March 2018. CML, chronic myeloid leukemia; GIPAP, Gleevec Patient Assistance Program.

male (60%), resided in Rwanda (76%), and had no other comorbidities (86%). Four patients (3%) were HIV-positive.

The median duration of symptoms before enrollment was 11 (interquartile range [IQR], 4-24) months. Most (n = 88;

71%) presented in chronic phase, four (3%) in accelerated phase, two (2%) in blast phase, and 30 (24%) without documented phase. Before enrollment, 69 patients (56%) had received no treatment, 42 (34%) had received hydroxyurea, and 22 (18%) had received a CML diagnosis and imatinib elsewhere.

Treatment Outcomes

Treatment response is summarized in Figure 3. Most patients (n = 113; 91%) experienced CHR, with a median time to CHR of 49 (IQR, 29-91) days. Of these, 76 patients (67%) experienced CHR within 90 days. Fifty-three patients (47%) were still in their initial CHR at last follow-up, with a median CHR duration of 23.5 (IQR, 8.5-50.6) months. Of the 51 patients (45%) who ceased to meet criteria for CHR at any point, 34 patients durably regained CHR after appropriate management (Fig 1) and were considered to have imatinib response. Twelve patients (11%) demonstrated secondary imatinib resistance. Seven patients (6%) had primary imatinib resistance, all of whom were male with a median age of 30 (IQR, 26-33) years. In total, 58 patients (47%) met criteria for clinical failure at any point. The median duration on imatinib for the cohort was 31 (IQR, 15-55) months.

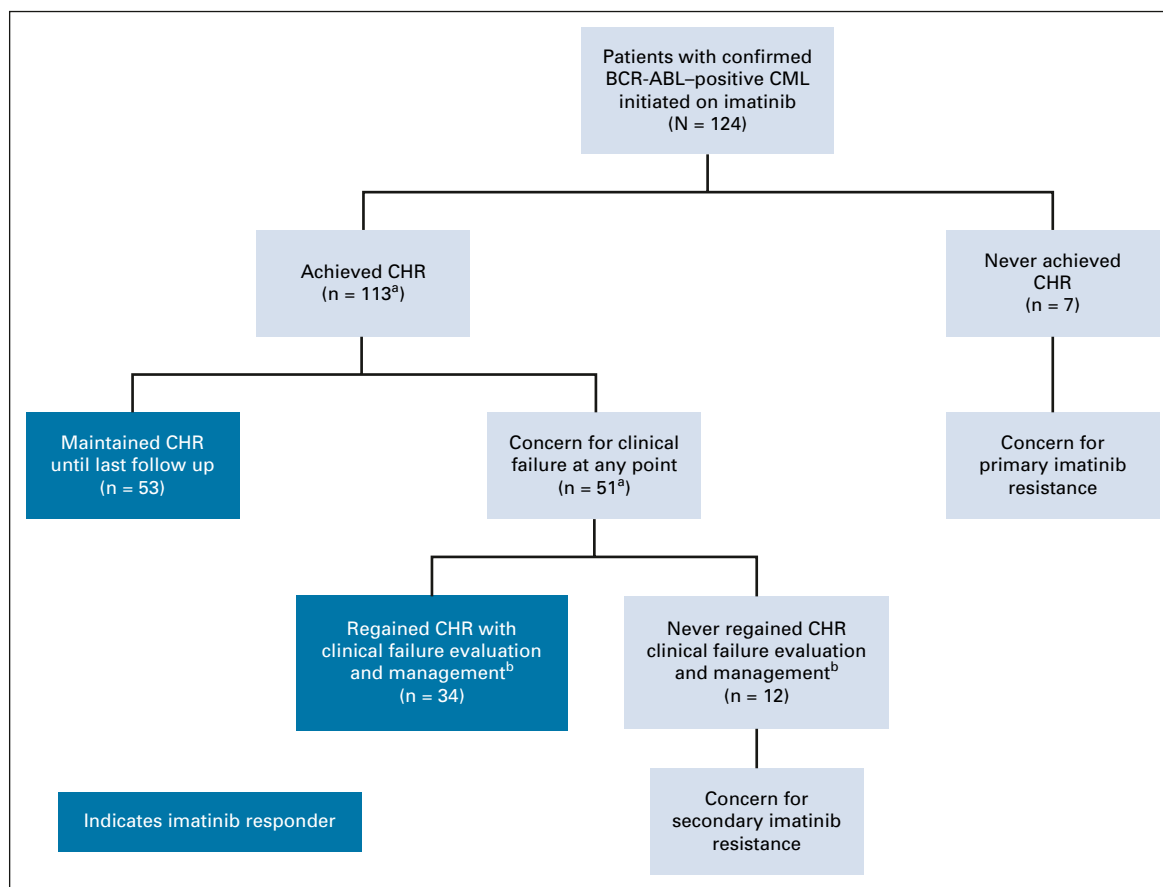


FIG 3. Treatment response among patients with CML enrolled in a GIPAP program in rural Rwanda from July 2009 to March 2018. ^aDoes not add to the previous total because of patients with unknown response. ^bClinical evaluation and management pathway as per Figure 1. CHR, complete hematologic response; CML, chronic myeloid leukemia; GIPAP, Gleevec Patient Assistance Program.

Survival

The estimated 3-year OS for the overall cohort was 80% (95% CI, 72 to 87). OS significantly varied by treatment response (Fig 4). The 3-year OS was 91% in patients with imatinib response (n = 87), 51% with secondary imatinib resistance (n = 12), and 17% with primary imatinib resistance (n = 6; $P < .001$). The median follow-up for the cohort was 32 (IQR, 16-58) months. Seven patients (6%) were LTFU.

Multivariate Analysis

Age ≥ 45 years (hazard ratio [HR], 101; $P = .002$), WBC count (HR, 1.01; $P = .006$), residence inside Rwanda (HR, 24.3; $P = .04$), primary imatinib resistance (HR, 5,505; $P < .001$), and secondary imatinib resistance (HR, 392; $P = .003$) were associated with increased mortality (Fig 5). Sex, initial hemoglobin and platelet count, and duration of symptoms were not statistically significant but were retained for model fit using Akaike's information criteria.

Time to Diagnosis, Treatment Initiation, and Response

Among 99 patients who presented with neither a prior CML diagnosis nor prior imatinib therapy, the median time to diagnosis was 32 (IQR, 10-73) days and to treatment initiation was 42 (IQR, 18-119) days. Subgroup comparison of patients diagnosed before versus after implementation of in-country diagnostic capacity at Rwinkwavu Hospital demonstrated no significant difference in median time to diagnosis (23 v 38 days; $P = .056$) or time to treatment initiation (33 v 49 days; $P = .170$), yet median time to CHR was reduced (59 v 38 days; $P = .040$). The median time to CHR was 47 days in patients with imatinib response versus 57 days in those with secondary imatinib resistance ($P = .507$).

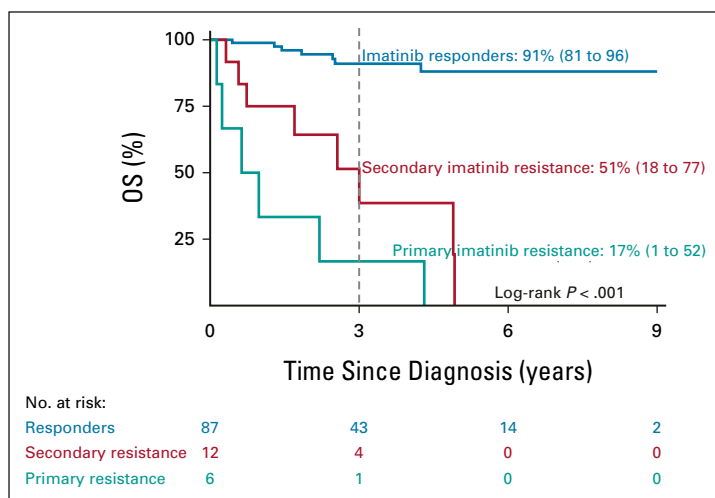


FIG 4. OS among patients with CML enrolled in a GIPAP program in rural Rwanda from July 2009 to March 2018, on the basis of imatinib treatment response. CML, chronic myeloid leukemia; GIPAP, Gilec Patient Assistance Program; OS, overall survival.

Pregnancy During Treatment

Despite a protocol for contraception and counseling, two patients became pregnant during imatinib treatment. One patient developed a molar pregnancy and was treated with oral methotrexate. One patient became pregnant twice, resulting in one delivery and one termination. In all cases, imatinib was temporarily held until the patient was no longer pregnant, and CHR was attained upon reinstitution of imatinib. Information on fetal outcomes was not available.

DISCUSSION

In this study, we demonstrate how a GIPAP care delivery program in rural Rwanda has created treatment opportunities for patients with CML where none previously existed. With continuous investment in local capacity building and international collaboration, this program has significantly evolved over 10 years and offers insight into strategies for improving CML care delivery programs in LMICs.

Our patients were strikingly young with a median age of 34 years (35 years when including adults only) compared with a median age of 50 years in major imatinib clinical trials from HICs.²¹⁻²⁴ This younger age distribution may reflect the younger overall population in Rwanda, health care system selection bias for young versus old patients with symptomatic disease, or biologic differences that warrant further investigation.²⁵ Our patients also had higher rates of primary imatinib resistance, slower time to CHR, and higher rates of clinical failure than historical cohorts from HICs.²¹⁻²³ Nearly half (47%) met criteria for clinical failure at any point, compared with 20%-40% of patients in HICs.²²⁻²⁴ These disparities may also indicate biologic differences or more advanced disease at presentation. Less subclinical diagnostic recognition given that blood counts are evaluated less often, delays in presentation to care after symptoms onset, and barriers in the referral process from primary to specialty care may lead to more advanced, treatment-resistant disease at diagnosis. In addition, this cohort included categories of patients that were excluded from major clinical trials in HICs, such as patients with HIV, age below 18 years, an Eastern Cooperative Oncology Group performance status of ≥ 3 , and platelet counts ≤ 100 , which may contribute to outcoming disparities with historical cohorts.²¹⁻²⁴ Finally, 24% of our patients did not have documented phase of disease at presentation, and thus, rates of accelerated and blast phases may be under-reported and contribute to poorer treatment responses.

The 3-year OS was 80% for our cohort, whereas the 5-year OS was 89% and the 10-year OS was 83% in the hallmark IRIS study.²¹⁻²³ These results, while inferior, demonstrate that patients with CML in rural Rwanda can successfully be treated and no longer must die of untreated disease as they did a decade ago. In our multivariate regression analysis, age ≥ 45 years and living inside Rwanda (compared with outside Rwanda) were associated with increased mortality. Patients from outside Rwanda in our program likely

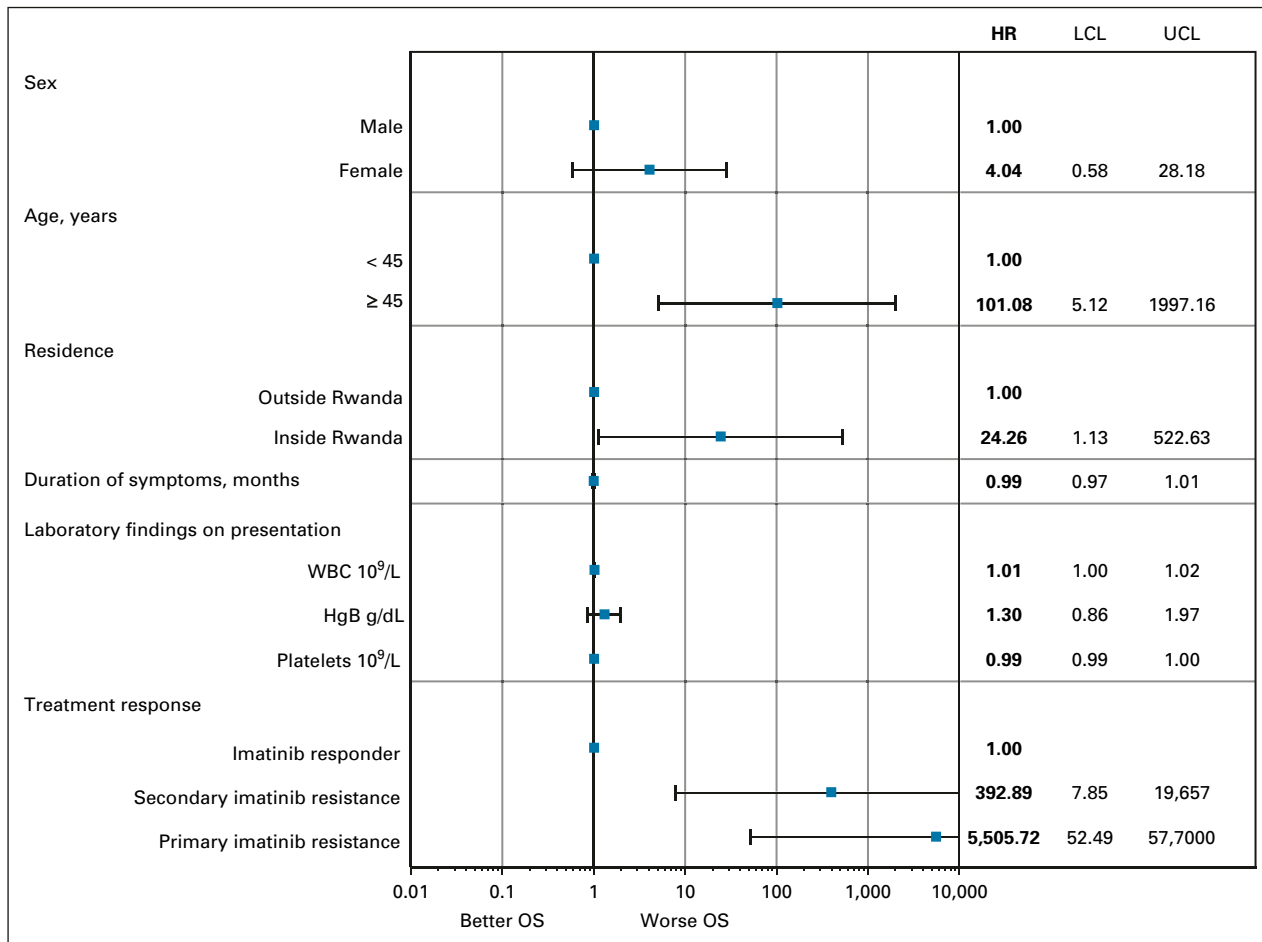


FIG 5. HRs for mortality among patients with CML enrolled in a GIPAP program in rural Rwanda from July 2009 to March 2018. CML, chronic myeloid leukemia; GIPAP, Gleevec Patient Assistance Program; HgB, hemoglobin; HR, hazard ratio; LCL, lower control limit; OS, overall survival; UCL, upper control limit.

represent a unique population with access to resources for travel and care that can affect survival. Initial hemoglobin and platelet counts and duration of symptoms were not significant, suggesting that advanced presentations alone may not account for increased mortality, and thus, biologic differences should be investigated. Validated prognostic scores (eg, Sokal and Hasford scores) could not be applied in our study because of inconsistent reporting of splenomegaly.^{26,27}

Hematologic response proved to be an accurate predictor of survival in our study. In HICs, routine molecular monitoring is recommended for patients with CML on TKIs, with molecular response predicting long-term survival.^{28,29} However, hematologic and molecular response assessment cannot distinguish between imatinib resistance and poor medication adherence, and relapse should trigger mutational testing to investigate imatinib resistance and selection of secondary TKIs. In Rwanda and many other LMICs, routine molecular monitoring has been cost-prohibitive, limiting our evaluation of clinical failure.³⁰ Recently, although, second-generation TKIs have

become available through GIPAP, making the case for investment in routine molecular monitoring and resistance testing to identify patients early on who are most likely to benefit from switching TKIs.⁹ Various strategies could be implemented to incorporate newly available second-generation TKIs within a low-resource CML care delivery program. Routine hematologic response assessment with clinical failure triggering molecular evaluation could be a resource-adapted strategy for prioritizing costly molecular studies and second-generation TKIs. Alternatively, patients with clinical failure could be treated empirically with a second-generation TKI and followed closely using hematologic response assessment. In either scenario, TKI adherence assessments and supportive measures must also be implemented.

A significant number of patients (n = 34) experienced CHR, met criteria for clinical failure, and then, with appropriate management, regained CHR. These patients had a similar OS to those who achieved and maintained CHR from the beginning. This temporary loss of CHR may reflect instances of disease relapse because of imatinib

nonadherence or unrelated causes of blood count abnormalities, such as acute illness, which may be seen even with well-controlled CML. Across many settings including HICs, TKI nonadherence is a major cause of clinical failure, has been reported to be as high as 50%-80%, and is known to increase with time on TKIs.^{31,32} Imatinib nonadherence has been attributed to adverse drug reactions; side effects such as edema, gastrointestinal upset, myalgias, and rash; and challenges of chronic medication usage over many years.³¹⁻³³ Our study highlights the need to identify barriers and facilitators of imatinib adherence in our patients who are young and have the potential to take TKIs for many years, to design effective implementation strategies for long-term adherence.

This study also highlights the importance of implementing effective measures for avoiding pregnancy during TKI treatment in a young patient population with high parity. Recently, TKI discontinuation has become a standard option for select patients with deep molecular response, allowing patients to avoid side effects associated with TKIs.³⁴ Approximately 50% of patients who meet clinical criteria for a trial of treatment-free remission can remain in remission.³⁴ Access to routine molecular monitoring in reproductive-age patients in our cohort could inform clinical decisions about treatment discontinuation and family planning.

Time to diagnosis and time to treatment initiation were not significantly different before and after implementation of in-country GeneXpert diagnostic testing. We attribute this to GeneXpert testing being implemented only at Rwinkwavu Hospital during this study period, whereas most (n = 71) patients presented initially to Butaro Hospital, on the opposite side of the country. The

delay between enrollment at Butaro and diagnosis at Rwinkwavu likely contributed to these intervals being comparable with out-of-country testing. Since this study period ended, however, GeneXpert testing has also been implemented at Butaro, and we anticipate that this has expedited times to diagnosis and to treatment initiation. Time to CHR was reduced after implementing in-country diagnostic testing, and, although, without concurrent reduction in time to diagnosis or treatment initiation, this finding remains difficult to interpret. With increasing awareness of CML and the GIPAP care delivery program among patients and referring providers over time, patients may present with less advanced, more treatment-sensitive disease at enrollment.

Limitations of this study are related to the retrospective design in which incomplete data limited our assessment of initial prognosis, clinical failure, imatinib toxicity, and treatment adherence. Specifically, rates of imatinib discontinuation in the setting of clinical failure were poorly documented.

In conclusion, we have demonstrated that patients with CML in a rural resource-constrained setting can be successfully treated with imatinib and experience extended survival through the support of a GIPAP care delivery program. Still, there is much work to do to further close the gap in CML outcomes between HICs and LMICs. Suboptimal responses and resistance to imatinib in our cohort highlight the need for improved access to routine molecular monitoring, second-generation TKIs, and implementation strategies to promote long-term treatment adherence. With continuous investment into programs like ours, it is possible to achieve cancer care equity for patients with CML around the world.

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PRIOR PRESENTATION

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Lawrence N. Shulman

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