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CHRONIC MYELOID LEUKEMIA: FROM MOLECULAR UNDERSTANDING TO THERAPEUTIC ADVANCES

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INTRODUCTION

Chronic myeloid leukemia (CML) is a rare malignant hematologic disorder classified among myeloproliferative neoplasms (MPN) or chronic myeloproliferative syndromes, according to the WHO classifications from 2008 and their updates in 2016 and 2022.[1–3] It was notably the first neoplastic disease for which genotype identification enabled the development of targeted therapy.[4] Due to its clearly understood pathophysiology, straightforward diagnostic process, well-defined prognostic factors, and causative treatment, CML has been extensively studied beyond its epidemiological significance, thereby serving as a model for other cancers.[5]

This hematopoietic stem cell disorder results from a reciprocal translocation between the long arms of chromosomes 9 and 22 (T(9;22)(q34;q11)), known as the Philadelphia chromosome. This translocation leads to juxtaposition of the ABL gene from chromosome 9 and the BCR gene from chromosome 22, forming a BCR-ABL fusion gene. The resulting fusion transcripts and proteins possess deregulated tyrosine kinase activity.[5]

Significant advances in understanding this mechanism have led to targeted therapies employing tyrosine kinase inhibitors (TKIs), revolutionizing CML treatment and substantially improving patient survival outcomes.[4] Indeed, many patients treated with TKIs achieve a near-normal quality of life.[6]

Before TKI therapy, untreated CML typically exhibited a biphasic or triphasic progression: an initial indolent chronic phase (CP) followed by a blast phase (BP), possibly preceded by an intermediate accelerated phase (AP). With TKI therapy and careful disease monitoring, the progression rate to advanced phases has significantly decreased, resulting in an improved 10-year overall survival rate of 80–90% (10, 11). Consequently, the term 'accelerated phase' has become less relevant. Current classifications thus omit the AP, focusing instead on high-risk features associated with CP progression and resistance to TKIs, such as mutations in the ABL1 kinase and additional cytogenetic abnormalities (1).

Patients newly diagnosed with CML now have a nearly normal life expectancy. Nonetheless, regular monitoring of BCR-ABL1 transcript levels, along with surveillance for genetic evolution and treatment resistance, remains essential for early detection of disease progression (2). Recent studies have also suggested that continuous TKI therapy may no longer be necessary for all patients, as approximately half maintain remission even after discontinuation of treatment.[7]

Study Description

Study Design and Duration This is a retrospective descriptive study of 61 cases of chronic phase chronic myeloid leukemia (CML-CP) conducted over a 5-year period, from January 2019 to December 2023.

Study Location The study was conducted in the Clinical Hematology Department of Mohammed VI University Hospital in Tangier.

METHODOLOGY AND TECHNIQUES

Inclusion Criteria Patients aged over 15 years diagnosed and monitored for chronic phase chronic myeloid leukemia (CML-CP) at the Clinical Hematology Department of Mohammed VI University Hospital in Tangier between January 2019 and December 2023 were included.

Exclusion Criteria Incomplete or unusable medical records of patients with CML-CP.

Data Collection Clinical data were collected from archived medical records and the computerized database of the Clinical Hematology Department of Mohammed VI University Hospital in Tangier. Data were recorded using a structured extraction form (Appendix 1), detailing sociodemographic, clinical, paraclinical, therapeutic, and evolutionary aspects for each patient.

Data Entry and Analysis Data analysis was performed using Excel 2021 software. Text and tables were prepared using Word 2021, while graphics were generated with Excel 2021. We conducted descriptive analyses of sociodemographic, clinical, biological, therapeutic, and evolutionary patient characteristics, calculating means and percentages for quantitative variables and percentages for qualitative variables.

Study Limitations The retrospective nature of this study posed challenges, particularly missing information in medical records. Additionally, some patients were lost to follow-up, and others were unreachable by telephone during the study period.

RESULTS

Epidemiology A total of 61 patients diagnosed with CML-CP were studied over 5 years. The average age was 48 years (range: 15–94 years), with 50% of patients aged between 40 and 59 years. Sex distribution showed a female predominance (59%) with a sex ratio of 0.72.

Clinical Diagnosis Most patients (78%) had no significant past medical history. Fatigue was the predominant initial symptom (62%), followed by left flank heaviness (16%), abdominal pain (7%), abdominal distension (5%), and dizziness (5%). Physical examination revealed splenomegaly in 85% of patients. At diagnosis, 51% of patients had an OMS score of 0, while only a minority had higher scores (13% with OMS score 2, and 4% with scores 3–4).

Laboratory Findings All patients presented with hyperleukocytosis (average 241 G/L), predominantly neutrophils (average 121,620/mm³), and moderate anemia (mean hemoglobin 9.61 g/dL). Thrombocytosis was noted in 44% of patients. Cytogenetic analysis showed the Philadelphia chromosome (T(9;22)) in 93% of patients. Additional chromosomal abnormalities were noted in 23% of these cases. RT-PCR confirmed BCR-ABL positivity in 100%, predominantly M-BCR-ABL (86%).

Therapeutic Management and Response First-line therapy with Imatinib (400–600 mg/day) was administered to 98.3% of patients. Optimal molecular responses according to ELN 2020 criteria were achieved at 6, 12, and 18 months in approximately half of the cases. Treatment failure at 12 and 18 months occurred in 26% and 30% of patients, respectively.

Toxicity Toxicity occurred in 28% of patients treated with Imatinib, predominantly hematologic (56% thrombocytopenia, 19% neutropenia, 25% bicytopenia). Non-hematologic toxicity was rare, with a single case of severe hepatic cytolysis. Second-line therapy with Nilotinib resulted in optimal responses in 47% of patients but was associated with agranulocytosis in 9% of cases.

Disease Progression Only 3.3% of patients progressed to blast phase (AML type), with one fatality due to complications from AML treatment. One patient was lost to follow-up.

DISCUSSION

Our patients presented at a mean age of 48 years, younger than reported in European studies but consistent with North African studies.[10–13] This demographic difference reflects regional variations in population age structure and highlights the need for age-adapted clinical protocols. Additionally, the observed female predominance (sex ratio 0.72) contrasts with the general international data but aligns with specific Moroccan cohorts, suggesting possible epidemiological or genetic influences specific to our region.[14]

Clinically, the high prevalence of splenomegaly (85%) and common symptoms like fatigue (62%) underline late-stage diagnoses in our patient population. These findings align with regional data, highlighting diagnostic delays due to limited routine hematologic screening,[14-16] Improved early detection strategies could significantly alter the clinical presentation and reduce advanced disease burden at diagnosis.

Laboratory findings showed marked hyperleukocytosis and frequent anemia, aligning with regional data, indicating advanced disease at presentation compared to European cohorts,[14-17] The higher incidence of additional chromosomal abnormalities (23%) further emphasizes the advanced stage of the disease in our population, possibly linked to delayed diagnosis or biological factors.

First-line treatment with imatinib remains standard practice due to accessibility and affordability, consistent with other North African countries,[14,18] However, notable hematologic toxicity observed in 28% of patients underscores the importance of careful monitoring and management of side effects to ensure optimal treatment adherence and outcomes.

Second-line nilotinib therapy provided moderate effectiveness (optimal response in 47%), but the substantial resistance rate (42%) contrasts significantly with data from developed regions, where second-generation TKIs generally show higher efficacy and tolerability,[19,20] This difference could be attributed to genetic variability, disease biology, or potential suboptimal adherence related to socioeconomic constraints.

Limited use of third-line therapy (dasatinib) due to availability constraints further emphasizes gaps in therapeutic access. Despite significant advancements, our findings illustrate persistent obstacles, such as treatment affordability, availability, and required rigorous molecular monitoring, limiting treatment-free remission strategies in our setting.

CONCLUSION

Chronic myeloid leukemia (CML) has long served as an emblematic model in onco-hematology, demonstrating significant advances resulting from a deep understanding of its molecular mechanisms and the development of targeted therapies. The identification of the Philadelphia chromosome and BCR-ABL fusion gene marked a transformative moment in treatment, notably with the introduction of first-generation tyrosine kinase inhibitor (TKI), imatinib, which significantly improved patient outcomes. Despite these advances, resistance to treatment remains a challenge, leading to the development of second- and third-generation TKIs, which provide more personalized therapeutic approaches.

However, complete eradication of CML remains elusive due to persistent resistant clones, underscoring the need for innovative therapeutic strategies. Our study contributes to this evolving context by highlighting the effectiveness and limitations of TKIs in our patient population, emphasizing challenges such as treatment costs and the necessity of frequent molecular monitoring. The retrospective nature and sample size limitations further underline the importance of optimizing clinical practices. Continuous efforts are essential to improve patient follow-up, treatment accessibility, and explore new avenues toward potential cures.

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