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Research Article

Epidemiology of Chronic Myeloid Leukemia in Tunisia

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Abstract

Chronic myeloid leukemia (CML) is a rare clonal myeloproliferatives disorder characterized by enhanced proliferative capacity and prolonged survival of hematpoietic stem cells.The pathogenesis of CML is driven by a bcr-abl fusion oncoprotein formed by a balanced translocation between chromosomes 9 and 22. Prevalence rate of CML has increased by use of tyrosine kinase inhibitors that transformed CML into a chronic disease.

Reliable epidemiological information on CML in Low and Middle income countries is limited. Geographic and/or ethnic variation might contribute to the variability of incidence among registries.

To retrospectively review characteristics of CML Tunisian patients, we followed up newly diagnosed chronic myeloid leukemia patients in Tunisia between January 2011 and December 2019.

A total of 801 cases entered this study. which corresponds to an annual incidence of 0.79 /105 habitants mean age at diagnosis was 47 years, 16 % of patients had more 65 years ,5% of patients had less than 20 years. CML was slightly more frequent in male than in females sex ratio 1.1. More than 85% of the patients were in chronic phase when diagnosed. Mean WBC was 176 835 elts/mm3, 54% of patients had WBC between 50 000 and 200 000 /mm3, mean platelet count was 463 000/mm3, 49 % of patients had b3a2 isoform. Differential age patterns would suggest the presence of a risk factor that predisposes individuals to CML at an earlier age.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder due to a clonal pluripotent stem cell disorder. Virchow & binnet described it for the first time in 1845 [1]. and it was the first malignant disease with a genetic marker involved in its etiology. The genetic marker is represented by the Philadelphia chromosome described in 1960 [2] which results from a reciprocal exchange of material between two chromosomes: 9 and 22 chromosomes t (9 ;22) (q34; q11).

This translocation produces the juxtaposition of abl gene on chromosome 9 with BCR gene from chromosome 22 resulting in a fusion gene which encodes the bcr-abl transcript and the fusion proteins with abnormal tyrosine kinase activity. This activity is responsible for the proliferation mechanisms in CML [3].

Clinical management and outcome in CML have improved dramatically since the introduction of imatinib and other tyrosine kinase inhibitors (TKIs) that molecularly specifically targets and inhibits the tyrosine kinase activity [3]. CML implies long term treatment with expensive drugs. patients up to 60-70 years with CML diagnosed in chronic phase and treated within a health care setting have a 5-year survival close to that of the age matched general population [4].

Etiological factors are not well understood with the exception being an increased incidence of CML among survivors of the atomic bombings of Hiroshima and Nagasaki 5. Agriculture and occupational exposures have been considered as potential etiological factors, but a strong association has yet to be established [6].

The epidemiology of CML in low and middle income countries is limited. differences in age at diagnosis and overall survival exist between regions [7]. epidemiological studies should be conducted to assess for possible environmental factors associated with clinical and outcome characteristics. The primary objective of this study was to determine epidemiological parameters and clinical characteristics at diagnosis across tunisian patients diagnosed with CML between January 2011 and December 2019.

Design & Methods

Design

Between January 2011 and December 2019 Hematology department of institut Pasteur de Tunis has been the reference center for the molecular diagnosis of leukemia.

all suspected CML Tunisian patients are referred to our laboratory. cytogenetic analysis was performed on bone marrow aspirates according to the standard laboratory protocol. Total RNA was extracted from EDTA anticoagulated bone marrow or blood samples for detection of the bcr-abl transcript by multiplex RT-PCR. Informed consent is signed by all patients. when the diagnosis of CML is confirmed by RT-PCR; clinical and biological data including sex, date of birth, date of diagnosis, stage of disease at diagnosis (chronic phase, accelerated phase or blastic phase), white blood cell count, platelet count at diagnosis and bcr-abl isoforms are registered.

Statistical methods

The T test and ANOVA were used to compare means. Comparison of percentages was performed using the Chi-square or the Fisher exact Test. A p value less than 0.05 was considered statistically significant.

Incidences rates were calculated for each year of the study period and throughout the nine years of the study as follows:

(Number of new cases over the observation period)/ (Midterm Tunisian population over that observation period ×Time frame)

Estimates of Tunisian population size were provided by the Tunisian National Institute of Statistics. Rates were expressed per 1 million Person years.

Data were analyzed using Epi-InfoTM (version 7.2.3.1).

Results

Between January 2011 and December 2019, a total of 801 newly diagnosed patients with CML (415 men and 376 women) were registered in Tunisia. this corresponds to an annual incidence of 7,9 per 10^6 inhabitants. The diagnosis of CML was confirmed by karyotyping and/or RT-PCR in all cases. Median age at diagnosis was 49 years, 16% of patients had more than 65 years and 5% were less than 20 years (Figure 1). Mean WBC was 176 835 [5200 - 928 000], 54.1 % of patients had WBC between 50 000 and 200 000 elts/mm^3, 33.3% had WBC > 200 000 elts/mm^3 and 12.5% had WBC < 50 000 elts/mm^3.

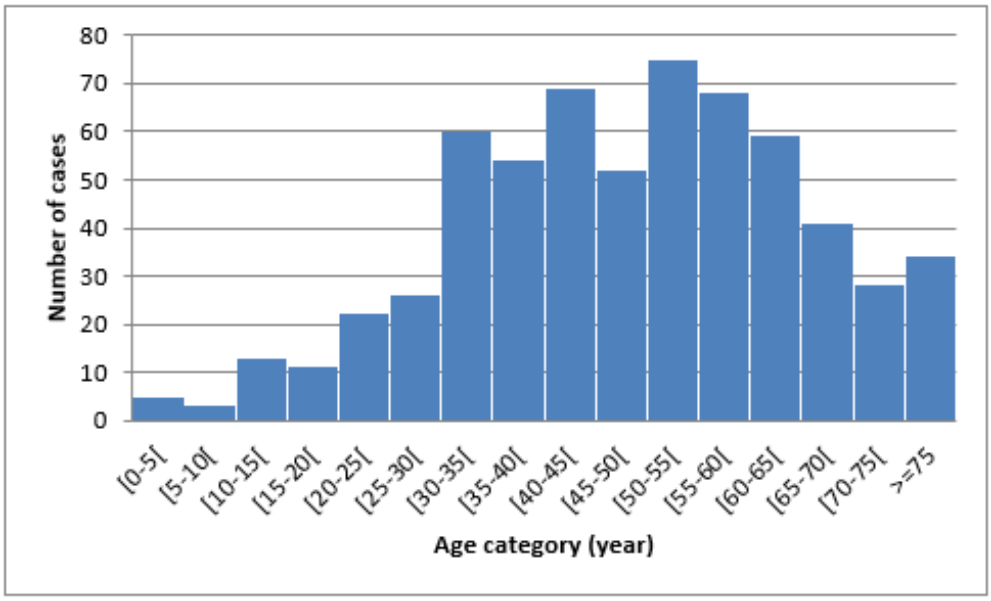

Figure 1: repartition of age category

Mean platelet counts at diagnosis was 463 000/mm^3 15 patients presented with pronounced thrombocytosis and who were referred with a suspected diagnosis of essential thrombocythemia E14a2 and e13a2 were identified in 52 % and 46 % of patients unusual or atypical transcripts were identified in 2 % of the patients (e1a2; e13a3; e6a2; e19a2) were the most frequently identified transcripts (Figure 2). the incidence of these atypical transcripts was higher in females and the proportion decreased with age in both genders. A large majority, 93 % of patients was diagnosed as being in chronic phase, 4% of patients were in accelerated phase and 2% of patients were in blastic phase.

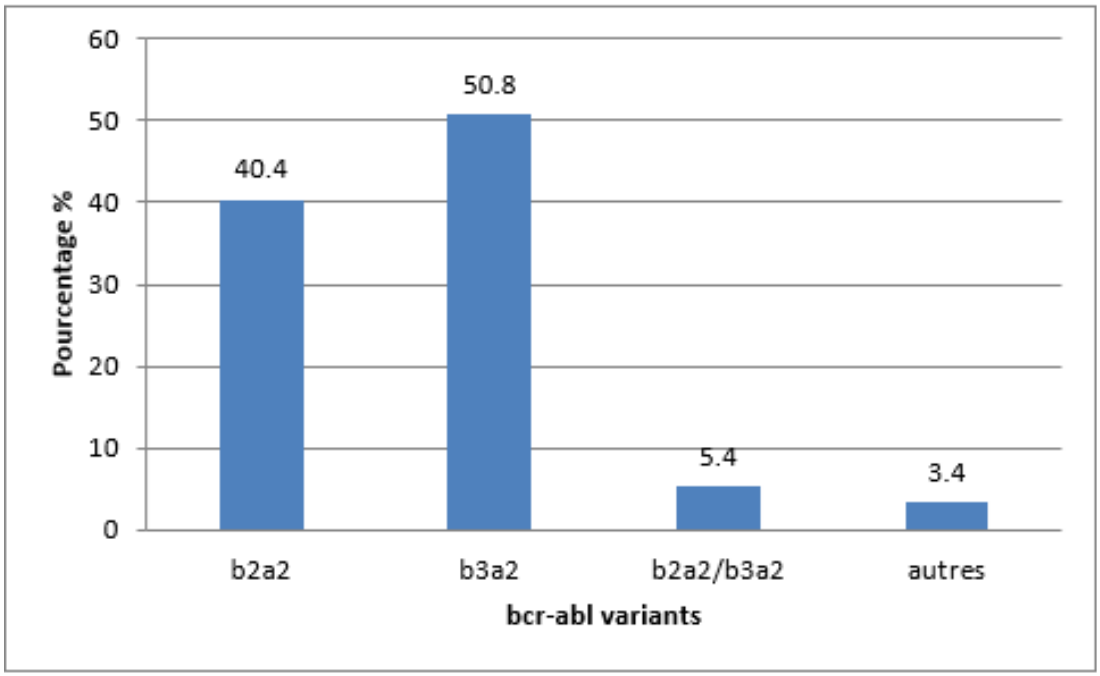

Figure 2: Distribution of bcr-abl variants

Discussion

Chronic myeloid leukemia accounts for 15% of adult leukemia's, an increasing annual prevalence rate of CML is observed in Tunisia and all over the world, this is due to the use of TKI therapy positively influencing survival and life expectancy of CML patients [8].

Between January 2011 and December 2019, A total of 801 Patients with CML have been diagnosed in Tunisia. This corresponds to an annual incidence of 0.6/100 000. The worldwide incidence of CML is considered to range between 0.6 and 2 per 100 000, increase with age and are higher in men than in women [8].

With no known geographic or ethnic variation etiological factors are not well understood with the exception being an increased incidence of CML among survivors of the atomic bombings of Hiroshima and Nagasaki [5]. As previous reports, Male incidence rates of CML in Tunisia are higher than those of females with a male to female ratio: 1.2 [8].

This study confirms that an earlier age of diagnosis exists in Tunisian CML patients. This difference may be due to the effect of biological, environmental, or socioeconomic factors 9. Further studies should determine if a possible specific environmental mechanism can be elucidated.

An earlier age at diagnosis of CML in developing countries has been previously reported with median age ranging between 32 and 44 years [9]. In Tunisia Patients older than 65 years of age at diagnosis made up 10 % of the cohort and only 5% of the patients had less than 18 years of age at diagnosis. Older age has been considered a poor prognostic factor in patients with CML [10], the 2 more widely used prognostic score for CML, namely the sokal and Euro risk scores identified older age as a variable predicting lower response rates and worse outcome [11].

The finding of regional differences in age at diagnosis demonstrates that there exists a possible environmental factor that may be impacting the pattern of CML. Agriculture and occupational exposures have been considered as potential etiological factors, but a strong association has yet to be established.

As described in other populations Stage of CML at diagnosis was predominantly in the chronic stage (93%) followed by 4% in the accelerated stage and 2% in blastic crisis [12]. Bcr-abl isoforms as identified by RT-PCR found that 52 % of patients had b3a2 isoform, 46 % had b2a2 and 2% had rare variants such as e19a2, e6a2 [13]. Only 12.5% of patients had WBC < 50 000 elts/mm^3, 33.3% had WBC > 200 000 elts/mm^3 15 patients presented with pronounced thrombocytosis and moderate leucocytosis and who were referred with a suspected diagnosis of essential thrombocythemia [14]. CML prevalence is anticipated to increase due to therapeutic advancements, continuous evaluation of adherence to CML guidelines and treatment results is of key importance.

For many years, CML was associated with a poor life expectancy, but the 2001 introduction of tyrosine kinase inhibitors (TKIs) has profoundly changed the CML curative-intent treatment from increasing survival to improving quality of life and attempting treatment free remission.

Subsequent to the development and global availability of BCR/ABL–targeted tyrosine kinase inhibitors (TKIs), the prognosis of patients with chronic myeloid leukemia (CML), at least those in the chronic phase, has markedly improved [15], and in the developed world, the average lifespan of these patients is now close to that of age- and sex-matched subjects without the disease [13]. However, the situation in low- and middle-income countries (LMICs) may not be so rosy.

Many important differences in hematological cancers, including CML, have been highlighted in various publications in developing countries vs developed countries [16]. These include differences in incidence and prevalence rates, age, and stage of disease at diagnosis, response rates, and survival. Some of the possible reasons proposed for these are varying socioeconomic milieu (impacting availability of effective drugs and essential monitoring), environmental factors (mainly exposure to viral infections and pesticides), nutritional factors with interplay of malnutrition and diet on drug absorption and blood levels, and possible unknown genetic factors.

Although generic first-generation TKIs (imatinib) are available in many parts of the world, several challenges remain in providing optimal treatment to patients with CML in resource-poor countries [17]. Some of these include availability of optimal and high-quality BCR/ABL testing, availability and expense related to use of second- and third generation TKIs (nilotinib, dasatinib, bosutinib, and ponatinib) and hematopoietic stem cell transplantation, issues with compliance and toxicities of drugs, and ensuring a minimal standard-of-care treatment and monitoring for every patient diagnosed with CML [18]. Future studies will focus on the use of second generation TKIs in different age groups, outcome in terms of molecular response and continuous evaluation of adherence to established guidelines on the management of patients with CML.

Conflict of Interest

On behalf of all authors the corresponding author states that there is no conflict of interest.

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