

Chronic Myeloid Leukaemia at the University Hospital of the West Indies A 17-Year Review

LM Buchner-Daley, DC Brady-West

ABSTRACT

Objective: To determine the presenting features and evolution of patients diagnosed with chronic myeloid leukaemia between 1983 and 1999 at the University Hospital of the West Indies.

Methods: Forty-one records were retrospectively analyzed for the patients' demographics, reasons for referral, clinical features, laboratory investigations and the time to blast transformation and death.

Results: Seventy-one per cent were males and 29% were females. The male to female ratio was 2.4:1. The median age at presentation was 37 years (range 14–81 years). Seventy-eight per cent of the patients presented in the chronic phase. Weight loss and splenomegaly were the most frequent presenting features being seen in 54 and 83 per cent respectively. The median survival was 36 months.

Conclusion: In this study, the clinical features and evolution were comparable to existing data. Improved accrual and routine Philadelphia chromosome testing would provide a more accurate reflection of the status of CML in our population.

Leucemia Mieloide Crónica en el Hospital Universitario de West Indies Un Estudio de 17 Años

LM Buchner-Daley, DC Brady-West

RESUMEN

Objetivo: Determinar los rasgos presentes y la evolución de los pacientes diagnosticados con leucemia mieloide crónica entre 1983 y 1999 en el Hospital Universitario de West Indies.

Métodos: Cuarenta historias clínicas fueron analizadas respectivamente en busca de los datos demográficos de los pacientes, las razones para la remisión de casos, las características clínicas, las investigaciones de laboratorio y el tiempo hasta la transformación blástica y la muerte.

Resultados: El setenta y uno por ciento eran varones y el 29% eran hembras. La proporción varones-hembras fue 2.4:1. La mediana de la edad en el momento de la presentación fue de 37 años (rango 14–81 años). Setenta y ocho por ciento de los pacientes se presentaron en la fase crónica. Pérdida de peso y esplenomegalia fueron las características más frecuentemente observadas en el 54 y el 83 por ciento respectivamente. La mediana de la supervivencia fue 36 meses.

Conclusión: En este estudio, las características clínicas y la evolución fueron comparables con los datos existentes. El mejoramiento de la acumulación y las pruebas de rutina para identificar el cromosoma Filadelfia, reflejarían con mayor precisión el estatus de la LMC en nuestra población.

West Indian Med J 2008; 57 (5): 493

INTRODUCTION

Chronic myeloid leukaemia (CML) is a clonal stem cell disorder with features of granulocytic hyperplasia at all stages of differentiation. It is primarily a disease of adults and accounts for less than 10% of leukaemias in patients under 20 years of age. The median age at diagnosis is 50–60 years with a male to female ratio of 1.4:1 (1, 2). Incidence figures

of CML are not locally available but an average incidence of 24/100 000 is quoted for myeloid leukaemias (3). Fatigue, weight loss and splenomegaly are reported as the most frequent presenting clinical features. Median survival from diagnosis is approximately 4 years if treated with conventional chemotherapy [busulphan or hydroxyurea] (1, 4). This 17-year review is the first report on the clinical presentation and outcome of CML in our population.

From: Department of Pathology, University Hospital of the West Indies, Kingston 7, Jamaica

Correspondence: Dr LM Buchner-Daley, Department of Pathology, University Hospital of the West Indies, Kingston 7, Jamaica.

SUBJECTS AND METHODS

Patients diagnosed with chronic myeloid leukaemia (CML) were identified retrospectively from the files of the Medical

Records Department and the Haematology Laboratory of the University Hospital of the West Indies (UHWI). During the period of study, January 1, 1983 to December 31, 1999, one hundred and twelve cases were identified but only 41 records were accepted for analysis. Seventy-one patients were excluded because 57 records were not located in the Medical Records Department and 14 records were incomplete. Patients with juvenile chronic myeloid leukaemia were not included in the study.

The 41 records were examined for the patients' demographics, reasons for referral, clinical features, laboratory investigations and the time to blast transformation and death. The diagnosis of CML was based on history, physical examination findings, peripheral blood counts and smear as well as leukocyte alkaline phosphatase (LAP) results and where available, bone marrow assessment was included to aid in the exclusion of other differential diagnoses. The patients did not have karyotyping performed due to the unavailability in the earlier years and the high cost in the latter years.

Patients were classified as anaemic if the haemoglobin level was < 11.5 g/dL in women and < 13.5 g/dL in men. Leukocytosis was defined as a white blood cell (WBC) count $> 11 \times 10^9/L$. Thrombocytosis was considered to be present if the platelet count was $> 400 \times 10^9/L$ and thrombocytopenia if the platelet count was $< 150 \times 10^9/L$.

The criteria for the diagnosis of chronic myeloid leukaemia in the chronic phase were persistent leukocytosis $> 20 \times 10^9/L$, WBC differential showing neutrophilic granulocytosis with immature cells, basophilia and eosinophilia, LAP score < 35 , packed cell volume < 55 l/l and platelet count $< 600 \times 10^9/L$ in the absence of a secondary aetiology for the leukocytosis.

Patients who met one or more of the following criteria were classified in the accelerated phase (5):

1. $> 10\%$ blasts in the peripheral blood or bone marrow
2. $> 20\%$ blasts plus promyelocytes in the peripheral blood or bone marrow
3. $> 20\%$ basophils in the peripheral blood

The blast phase was defined as $> 30\%$ blasts in the peripheral blood or bone marrow.

RESULTS

Chronic myeloid leukaemia was discovered incidentally during routine physical examination or laboratory investigation in 10 patients (24%). The incidental diagnosis was made during routine blood testing (4 patients), preliminary work-up for trauma (2 patients) and other medical disorders (4 patients). The reasons for referral to the UHWI were due to an abnormal haematological blood result, most commonly an elevated WBC count (37%) and/or splenomegaly (17%).

Seventy-eight per cent of patients presented in the chronic phase while 17% and 5% presented in the accelerated and blast phases respectively. There was a male pre-

dominance with a male to female ratio of 2.4:1. The ages ranged from 14 to 81 years with a median age of 37 years and nine patients (22%) were older than 60 years (Fig. 1).

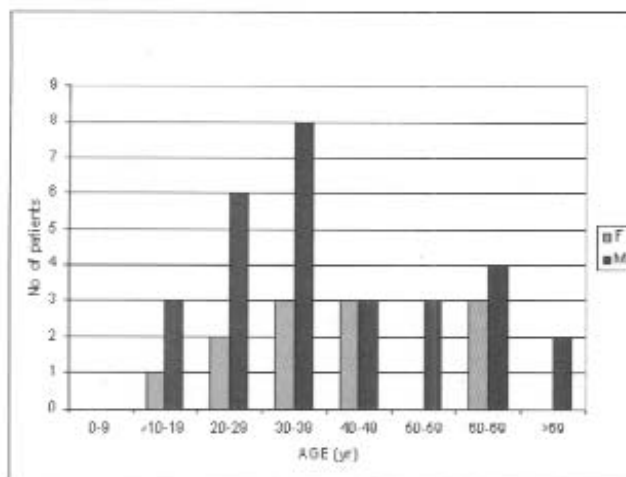


Figure: Age and sex distribution of chronic myeloid leukaemia patients

Ninety per cent of the patients presented to the Haematology clinic within 12 months of the onset of symptoms. These symptoms are displayed in Table 1 and did not differ

Table 1: Presenting clinical features of chronic myeloid leukaemia

Clinical feature	No	%
Symptoms		
Weight loss	22	54
Anorexia	4	10
Lump on self-exam	10	24
Left upper quadrant pain	9	22
Fatigue	9	22
Night sweats	7	17
Fever	7	17
Bleeding	7	17
Priapism	2	5
Other	26	63
Signs		
Splenomegaly	34	83
Hepatomegaly	14	34
Lymphadenopathy	13	32
Bleeding	4	10
Skin nodules	2	5
Ascites	1	2

between patients presenting in the chronic phase and those in the more advanced phases. The commonest symptoms at onset were those secondary to hypermetabolism and splenomegaly. Purpura, gum bleeding, menorrhagia and haemoptysis characterized the bleeding of the seven affected patients of whom five had normal or elevated platelet counts.

The physical findings included splenomegaly in 83% of patients with moderate to severe enlargement in 66%. Hepatomegaly was noted in 34% of the patients all of whom had splenomegaly. Of the 13 patients (32%) who had lym-

phadenopathy, nine were in the chronic phase, three in accelerated and one in the blast phase.

Leukocytosis was manifested in all patients (range 20–800 x 10⁹/L) with two of the nine patients who had hyperleukocytosis (WBC >300 x 10⁹/L) exhibiting priapism. Forty-seven per cent of the patients had normal platelet counts (range 150–400 x 10⁹/L) and the seven patients who were thrombocytopenic were proportionately distributed among the three phases of the disease. Clinical features of thrombosis were not evident in the three patients who had marked thrombocytosis (platelet count >1000 x 10⁹/L) but bleeding occurred in one. Thirty-one patients were anaemic and the majority (72%) were in the chronic phase. Four of the five patients who had haemoglobin levels below 7 g/dl (Table 2) were in the advanced phases of the disease.

Table 2: Haematological results in chronic myeloid leukaemia

Laboratory Result	No	%
WBC count x 10 ⁹ /L		
< 100	11	27
100–299	21	54
> 299	9	19
Platelet count x 10 ⁹ /L		
< 150	7	17
150–399	19	48
> 399	14	35
Haemoglobin g/dL		
< 7	5	12
7–12	26	64
> 12	10	24

The time from presentation to transformation of the disease to the accelerated and blast phases was available for 24 patients. Two patients were in the blast phase at presentation. The time ranged from 5 to 73 months for transformation to the blast phase and 7 to 104 months for the accelerated phase with a median time of 30 and 44 months respectively. In 17 patients who developed blast transformation, the acute leukaemia was morphologically designated as myeloid in 53%, lymphoid in 12% and not specified in 35%. This designation was not confirmed by cytochemistry or flow cytometry.

Survival, calculated from the time of referral to our institution, ranged from 1 to 84 months with a mean of 43 months for females and 34 months for males. The overall median survival was 36 months. Survival information was lacking for 25 patients (61%) who were either lost to follow-up or had no recorded date of death.

DISCUSSION

This is the first report of the clinical features, at presentation, and evolution of patients with CML in Jamaica. Although several limitations were apparent, the information gleaned reflect in many ways the published data on this disease (1, 2, 6).

Incidence figures of CML are not locally available but the reported annual incidence for CML in the United States of America (USA) is 1–1.5/100 000 population. Even though the incidence in the USA may not directly correlate with our population, the potential study population would approximate 425 patients. The fact that the UHWI is one of three major referral centres in the island as well as the lack of awareness and referral by physicians may account for the lower than expected numbers in the study. Also, the absence of computerization of the Medical Records Department prior to 1996 and the inadequate filing of inactive records limited the number of records available for analysis.

The diagnosis of CML is made on the basis of neutrophilic granulocytosis with immature cells, basophilia and splenomegaly coupled with cytogenetic examination of the blood or bone marrow for the confirmatory Philadelphia chromosome (7). The absence of cytogenetic analysis is a limiting factor of the study in the differentiation of CML from other myeloproliferative disorders because in each of the latter diseases, the absence of the BCR rearrangement is a key distinction from CML. Given that the majority of the study patients did not have cytogenetic analysis and some did not have bone marrow examination, the presence of a low LAP score as a unique laboratory finding in CML in conjunction with the basophilia helped in the differential diagnosis of the leukocytosis from other myeloproliferative diseases.

There were some interesting points to note in the present study. Firstly, CML is a disease of older patients with a median age at diagnosis of 50 years (1, 2) but in the population analyzed the age was lowered by a decade for both sexes. Of course one must bear in mind that this may be skewed as only about 30% of medical records were found. It may be related to the biology of the disease but this requires justification. Secondly, several authors have suggested that patients with CML are frequently asymptomatic at diagnosis and those who are symptomatic have symptoms related to hypermetabolism and splenomegaly predominantly (1, 7). This was in keeping with what was identified in the present study population. Bleeding was predominantly mucocutaneous. In the presence of normal or elevated platelet counts, this suggests platelet dysfunction. However this was not confirmed. Thirdly, lymphadenopathy was evident in 32% of patients most of whom were in the chronic phase. This is discordant with the literature that reports lymphadenopathy as being uncommon in chronic phase CML and its appearance suggests either the accelerated or blastic phase of the disease (2). The lymphadenopathy ranged in size from shotty to significant which would suggest other non-neoplastic causes such as concurrent infection or inflammation; however, this was not confirmed. Therefore, the presence of lymphadenopathy in the chronic phase in this population warrants further evaluation.

Chronic myeloid leukaemia is a disorder that usually progresses from an indolent, chronic phase through an

accelerated phase to a rapidly fatal blast phase and most patients, in this limited series, presented in the chronic phase. Again, this information could be quite biased since only a small percentage of patients identified were actually analyzed. The time from diagnosis to blast transformation was consistent with reported interval of three to five years. Patients who transformed to the blast phase have a reduced survival of three to six months (2) and the two patients who presented in the blast phase died at one and three months after presentation. One group of researchers reported a median survival of 39 months that was similar to our data (8). However, the absence of follow-up data in a significant proportion of patients makes meaningful analysis difficult. Disease progression and survival will be studied prospectively in order to have a valid comparison with international data.

The treatment of CML has evolved over time with the use of the tyrosine kinase inhibitor imatinib mesylate as standard first-line therapy for all phases of CML. Although allogeneic stem cell transplantation (ASCT) is traditionally viewed as the only curative option for CML, its associated mortality and morbidity has altered its role in the era of targeted therapy. It should be noted that imatinib therapy was not yet in clinical use during the period of study and ASCT was not feasible due to the prohibitive cost and unavailability of the procedure in this region (9).

In this limited study of patients with CML, the clinical features and evolution were similar to other populations.

However, one pertinent recommendation would be the routine testing for the Philadelphia chromosome as a means of improving the accuracy of the diagnosis of CML and facilitating the use of targeted therapy that would afford patients improved survival.

REFERENCES

1. Cortes J, Kantarjian HM, Giralt S, Talpaz M. Natural history and staging of chronic myelogenous leukaemia. *Bailliere's Clinical Haematol* 1997; **10**: 277–90.
2. Kantarjian HM, Giles FJ, O'Brien SM, Talpaz M. Clinical course and therapy of chronic myelogenous leukaemia with Interferon-alpha and chemotherapy. *Hematol Oncol Clin North Am* 1998; **12**: 31–80.
3. Hanchard B, Blake G, Wolff C, Samuels E, Waugh N, Simpson D et al. Age-specific incidence of cancer in Kingston and St Andrew, Jamaica, 1993-1997. *West Indian Med J* 2001; **50**: 123–9.
4. Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK et al. Randomized comparison of busulphan and hydroxyurea in chronic myelogenous leukaemia: Prolongation of survival by hydroxyurea. *Blood* 1993; **82**: 398–407.
5. Hoffmann R, Benz EJ, Shadtil SJ, Furie B. *Hematology: Basic Principles and Practice*, 3ed. Pennsylvania: Churchill Livingstone; 2000
6. Kolibaba KS, Druker BJ. Current status of treatment for chronic myelogenous leukaemia. *Med Gen Med* 2000; **2**: 1–20.
7. Lichtman MA, Beutler EB, Kipps TJ, Williams WJ. *Williams Manual of Hematology*, 6ed. New York: McGraw-Hill; 2003
8. Kantarjian HM, Smith TL, McCredie KB, Keating MJ, Walters RS, Talpaz M et al. Chronic myelogenous leukaemia: A multivariate analysis of the associations of patient characteristics and therapy with survival. *Blood* 1985; **66**: 1326–35.
9. Milojkovic D, Apperley J. State-of-the-art in the treatment of chronic myeloid leukaemia. *Curr Opin Oncol* 2008; **20**: 112–21.