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ABSTRACT

Objective: **To determine the clinical and haematological factors associated with treatment and outcome of chronic myeloid leukaemia (CML) at Kenyatta National Hospital.**
Design: **Retrospective survey of patients treated for chronic myeloid leukaemia.**
Setting: **Kenyatta National hospital, Nairobi, Kenya, between April 1990 and August 2000.**
Subjects: **Patients with chronic myeloid leukaemia.**
Results: **One hundred and four patients, 55 males and 49 females, age range 10-72 years with a median age of 35 years. Treatment with busulphan getting less popular in favour of hydroxyurea. Median follow-up 20 months with none of the clinical and haematological parameters impacting significantly on duration of follow-up.**
Conclusion: **CML occurs at a younger age-group in Kenya, and none of the clinical or haematological parameters appears to impact on follow-up duration.**

INTRODUCTION

Chronic myeloid leukaemia (CML) results from neoplastic proliferation of a multipotential haematopoietic stem cell, with resultant proliferation of all myeloid elements in the bone marrow and peripheral blood. Massive enlargement of the spleen is its most frequent clinical manifestation and profuse neutrophil leukocytosis its most distinctive finding on peripheral blood examination, The bone marrow picture is a reflection of what is seen in the peripheral blood.

CML is diagnosed by the demonstration of Philadelphia (Ph) chromosome on leukaemic cells both in peripheral blood and the bone marrow(1). This chromosome results from reciprocal translocation between the long arms of chromosomes 9 and 22 – t (91; 22) (q34; q11) (2), which results in fusion of the ABL gene from chromosome 9 with BCR gene from chromosome 22. This hybrid (chimeric) gene, encodes an oncoprotein of 190, 210 or 230 kilodaltons, depending on the breakpoint on the BCR gene. The bcr-abl fusion protein products have enhanced tyrosine kinase activity which is critical for leukaemogenesis(3). Demonstration of Ph chromosome or the characteristic ber-abl message is critical in diagnosis of CML in close to 100% of the cases. The chronic stable phase of CML lasts on average 24-36 months after which the acute (blastic) phase sets in. Some cases transform first into the accelerated phase before finally assuming the blastic phase which is rapidly fatal within 3-6 months. The current standard of care for CML is a combination of interferon-alpha and cytosine arabinoside in the majority of cases. Young patients, especially those aged less than 45-50 years are best treated with allogeneic haematopoietic stem cell transplantation. Other agents used are hydroxyurea or busulphan. Currently indications are emerging that the inhibitor of the signal transduction mediated by BCR- ABL kinase activity, STI 571 (imatinib mesylate - glivec, gleevec), should be the standard first-line therapy for patients with CML(4,5).

We set out to evaluate in a retrospective study, the clinical and haematological features, treatment and outcome amongst CGL, patients at Kenyatta National Hospital between April 1990 and August 2000 inclusive.

MATERIALS AND METHODS

Case records of patients with CML seen at Kenyatta National Hospital between April 1990 and August 2000 were studied. Information obtained included patients' sex, age at diagnosis and date of diagnosis, residence and occupation. The size of the spleen at diagnosis was noted as massive, moderate, tipped (mild), not palpable-haemoglobin level, total white blood cell count at diagnosis (with differential counts of neutrophils, monocytes, eosinophils and the blast count as a percentage), platelet counts, and mean corpuscular volume. Treatment given upfront was noted with response, also second-line treatment with response. The last date of follow-up and disease status or date of death were also recorded.

From the information obtained, duration of follow-up was derived, and also survival duration for cases with dates of death recorded.

Attempts were made to find out if there were any

statistical correlations between survival or follow-up durations with spleen size, residence, occupation, and the various haematological parameters using the Chi-squared and student's t-tests.

RESULTS

Records were available for a total of 104 patients, 55 males and 49 females. The age range was 10-72 years, the median age being 35 years (Table 1). Sixty-five patients (62.5%) were aged less than 40 years. Eighty-eight patients out of 97 evaluable (90.7%) had massive splenomegaly, four (4.1%) had moderate splenomegaly, two (2.1%) had mild splenomegaly and three (3.1%) had the spleen not palpable.

Table 1

Clinical and haematological features at diagnosis

Feature/Parameter	Value/Number
Total number of patients:	104
Demographic Features:	
- Number of males	55
- Number of females	49
- Median age (years)	35
- Age range (years)	10-72
Clinical Features:	
- Splenomegaly (n=97)	
- Massive	88 (90.7%)
- Moderate	4 (4.1%)
- Mild	2 (2.1%)
- Not palpable	3 (3.1%)
Haematological parameters (Blood):	
- Total wbc x 10^9/litre (n=92)	
<50	7 (7.6%)
50-99.9	9 (9.8%)
100-299	41 (44.6%)
300-499	16 (17.4%)
≥ 500	19 (20.7%)
- PB blast count % (n=68)	
0	2 (2.9%)
1-5	48 (70.6%)
≥6 <15	18 (26.5%)
- PB basophil count % (n=35)	
<3	29 (82.9%)
≥3	6 (17.1%)
- PB eosinophil count % (n=42)	
<4	16 (48.5%)
4-9.9	14 (42.4%)
≥10	3 (9.1%)
- Haemoglogin level-g/dl (n=42)	
<10	14 (33.3%)
≥10	29 (66.7%)
Treatment Upfront (n=98):	
Busulphan	65 (66%)
Hydroxyurea	33 (33.7%)

Table 2

Demographic, clinical and haematologic parameters in relation to duration of follow-up

Follow-up duration-months	(n=98)	
Median	20	
Range	<1 - 72 (312)	
Follow-up duration at ≥ 2 years VS age-group (years)		
<40 years	67.5%	
≥ 40 years	47.5%	P>0.I NS
Follow-up duration at ≥ 2 years VS wbc count x 10^9/litre (n=92)		
<100	62.5%	X^2 = 4.937
≥ 100	39.4	P≈ 0.2 NS
Follow-up duration at ≥ 2 years VS eosinophil count % (n=33)		
< 4	37.5%	P> 0.2 NS
≥ 4	23.5%	
Follow-up duration at ≥ 2 years VS basophil count % (n=35)		
<3%	27.6%	
≥3%	0%	
Follow-up duration at ≥ 2 years VS blast count % (n=68)		
<6	47.9%	P> 0.1
≥6	50%	NS
Follow-up duration at ≥ 2 years VS haemoglobin (n=42)		
<10g/dl	78.6%	P > 0.1
≥ 10g/dl	60.7%	NS
Follow-up duration at ≥ 2 years VS treatment upfront (n=98)		
Busulphan	44.6%	P >0.1
Hydroxyurea	45.5%	NS

Sixteen out of 92 patients evaluable (17.4%) had total white blood cell counts less than 100 x 10^9 /litre at diagnosis, 57 (62.1%) had counts ranging between 100-499x 10^9 /litre. Two out of 69 patients (2.9%) evaluable for peripheral blood blast counts at diagnosis had no blasts, 48 (70.6%) had blasts of 1-5% and 18(26. 5%) had blasts of ≥6% but <15%. Twenty-seven out of 33 evaluable patients (81.8%) had peripheral blood eosinophil counts of 4% and above, and six out of 35 (17.1%) had monocyte counts of 3% and above. Fourteen out of 42 patients evaluable (33.3%) had haemoglobin levels less than 10g/dl at diagnosis and 28 (66.6%) had levels of 10g/dl and above.

From 1990 -1995, 78.4% of patients were treated with busulphan upfront and 21.6% were treated with hydroxyurea upfront. From 1996-2000, 53.3% of the patients were treated with busulphan upfront and 46.7%

with hydroxyurea upfront. This shift in treatment was significant (78.4% Vs 53.3% - P ≈ 0.0l). No patients were treated with interferon-alpha or cytosine arabinoside.

Twenty nine out of 98 patients evaluable (29.6%) were followed up for 36 months and above six (6.1%) were followed up for 60 months and above. The median follow-up time was 20 months, range <1-72 months. About 46% of patients on busulphan upfront were followed up for less than one year compared with 33% on hydroxyurea. At 24 months an equal percentage of patients on both treatment groups (44.6% Vs 45.8%) were still on follow-up. Recorded time to transformation ranged from de-novo to 36 months. Only three deaths were recorded, the majority of the patients having been lost to follow-up.

Twenty nine out of 61 patients aged under 40 years (47.5%) were followed up for under two years compared with 27 out of 40 (67.5%) of those aged 40 years and above, but this difference was not statistically significant (P> 0.1). Thirty-two out of 61 patients aged less than forty years (52.5%) were followed up for two years and above compared with 13 out of 40 (32.5%) aged forty years and above, but again the difference was not statistically significant. There was no significant difference in follow-up duration between male and female patients, either at less than 24 months or 24 months and above (X^2 = 2.499; P>0.05). When the possible impact on total peripheral blood white cell count on duration of follow-up was assessed, there was no difference between those who had counts below 100 x 10^9/litre and those who had counts of 100 x 10^9/litre and above (X^2 = 4.937, P ≈ 0.2). Similarly, there was no correlation between follow-up duration and peripheral blood eosinophil, basophil and monocyte counts. Only two patients had no baseline peripheral blood blast counts. Those with blast counts of 1-5% and those with 6% and above were compared and out of the 68 cases evaluable there were no significant differences in follow up for less than two years and follow-up of two years and above (P > 0.1). Haemoglobin levels of 10g/dl and above or below 10g/dl were tested against duration of follow up, but again there was no significant difference. Platelet counts below 100 x 10^9/litre and those of 100 x 10^9/litre and above did not correlate with duration of follow-up either.

DISCUSSION

The median age of occurrence of CML at KNH of 35 years is a decade younger than the age of 45 years described amongst whites. The male-to-female ratio of 1.1:1 is a known fact. Massive splenomegaly amongst 90.7% of the patients is just on the higher side of what is expected, possibly because our patients are likely to present late or have health care workers delay in making the diagnosis. Tropical conditions that lead to massive splenomegaly such as visceral leishmaniasis and chronic malarial infection could resemble CML clinically and since they are more common this could lead to delays in diagnosis. One can not assume that a good peripheral blood examination is possible in all local health institutions where these patients report first. One should also be aware that in a retrospective study such as this one, the accuracy of rating the spleen size is limited.

It would appear that it is taking unnecessarily long to set up facilities for routine chromosome banding in our major health institutions. In absence of the capacity to demonstrate the Philadelphia chromosome, leave alone molecular probes for BCR/ABL fusion, our diagnosis of CML, is based on the presence of neutrophil leukocytosis, with full spectrum of myeloid maturation in the peripheral blood and bone marrow. Diminished neutrophil alkaline phosphatase score assists in making the diagnosis. The others are serum vitamin B12 levels, transcobalamin 1 levels and lysozymes, but they are not assayed in our institution routinely.

The haematologic parameters in peripheral blood in this study did not correlate with duration of follow-up. This is not surprising since this was a retrospective study and the follow-ups were haphazard, with the majority of patients being lost to follow-up. On the other hand, the peripheral blood parameters are not believed to be of much prognostic value except for persistently elevated peripheral blood blast counts. These did not correlate with duration of follow-up amongst our patients either.

Despite the fact that several models have been established that could categorize patients into groups with distinct survival characteristics(6-8), their reproducibility and utility is doubted because they were tried in certain generally restricted therapy regimens(9-10). There is now evidence that histologic characteristics of bone marrow in CML, may yield important predictors for disease progression in Philadelphia chromosome positive CGL(11,12). Unfortunately, bone marrow biopsies are not routinely performed for CML patients not only in our institution, but also in most institutions all over the world.

Traditionally, conventional chemotherapy for CML has utilized mostly two agents, busulphan and hydroxyurea as the standard of care. These two have been favoured in community practice because they are administered orally and also are relatively cheap. Most recently, hydroxyurea has been shown to be superior to busulphan in terms of survival duration whether as a single agent or pre-transplant(12-14). Busulphan is non-cell-cycle-dependent hence affects cells in G0 phase, bone marrow stem cells included. This is believed to trigger off myelodysplasia and enhance transformation to acute leukaemia earlier. Hydroxyurea on the other hand acts mainly during

the DNA synthetic phase of the cell cycle, with minimal influence on non-proliferating early haematopoietic progenitor cells. Its use is gaining popularity in our institution as compared with busulphan. Conventional cytotoxic drugs do not significantly cause cytogenetic remissions in CML. Interferon-alpha mono-therapy in maintenance on the other hand has been shown to have significant(15,16) or only questionable(12,13) survival advantage over conventional chemotherapy. It induces cytogenetic remissions in about one third of the cases of CML. Because of high cost none of the patients in our institution which serves mainly the poor, were treated with interferon-alpha. Combination of cytosine arabinoside at low doses with interferon-alpha which has been shown to confer some survival advantage (16) was not offered to any of these patients. Other workers claimed survival advantage when interferon-alpha was combined with other cytotoxic agents either at low doses or in intensive doses, but the value of this approach has remained questionable(17,18).

Definitive treatment for young, fit chronic phase CML patients with HLA - identical siblings has been pegged on myeloablative chemotherapy with allogeneic haematopoietic progenitor cell transplantation with 40-70% long-term disease survivals realised. This facility is not available to us. Luckily, imatinib mesylate (glivec, gleevec, STI-571) is poised to become the standard of care even in chronic stable phase CML (4,5). Even if the cost of this agent which is currently pegged at Kenya shillings four hundred thousand per month (US$5335) will be a problem, this drug has the advantages of a low side effect profile and the oral route of administration that does not require technically sophisticated and expensive equipment.

In conclusion, chronic myeloid leukaemia in Kenya occurs in patients a decade younger than in the white counterparts in Europe and North America. Clinical and haematological parameters are similar to those described elsewhere. The diagnostic facilities are grossly lacking and all of our patients at KNH are treated with conventional chemotherapies. Follow up and probably median survival may not exceed that for untreated patients.

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