Int J Biol Med Res. 2012; 3(3): 2099-2102

BioMedSciDirect Publications

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International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Original article

Factors affecting survival in chronic Myeloid leukemia patients

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ARTICLE INFO

Keywords:
Accelerated Phase
Blast Crisis
Leukocytosis
Splenomegaly

ABSTRACT

Introduction: Chronic myeloid Leukemia is categorised into Chronic Phase(CP), Accelerated Phase(AP) and Blast Crisis(BC). Poor prognostic factors for survival include the presence of splenomegaly, hepatomegaly, older age, leukocytosis, increased blast counts and expansion of paratrabecular seams of myeloblasts, increased basophil counts, thrombocytopenia, or thrombocytosis and cytogenetic clonal evolution. We have made an attempt to find out the factors affecting survival of chronic myeloid leukemia patients. Materials and Methods: Present study was carried out on forty-six patients (30 males and 16 females) of CML. Staining of peripheral smears was done with Leishman's stain. Cytochemistry of peripheral smears was carried out with Leukocyte Alkaline Phosphatase (LAP) in thirteen cases. Staining for myeloperoxidase, Sudan Black and PAS reaction was done in cases of CML with blast crisis. Bone marrow aspiration and biopsy was also done in 33 cases. Observations: Out of 46 cases; 89% of cases were in CP, 7% in AP and 4% in BC and 3 cases of CML-chronic case were of adult type of juvenile CML. 90% of patients of CML-CP and 100% in CML-AP and CML-BC were anaemic . All of them had increased leukocytosis. Platelet count in CML-CP was decreased in 7% of cases, normal in 49% of cases and increased in 12%.Haemoglobin, total leukocyte count and platelet counts were lower in cases of accelerated phase and blast crisis phase as compared to those in chronic phase. Conclusion: Eleven out of thirteen patients had low LAP score. All the patients who progressed to higher grade leukaemia had spleen size > 10 cm at presentation. Patients who had high LAP scores, died. Two patients who had grade-III fibrosis progressed to blast crisis and one patient who progressed to accelerated phase had grade-II fibrosis. 29% CML-G patients progressed to blast crisis and 4% of CML-GM progressed to accelerated phase.

1.Introduction:

Chronic myeloid leukemia (CML) is a clonal myeloproliferative expansion of transformed, primitive hematopoietic progenitor cells. It was first Leukemia in which a specific abnormality of the karyotype- the Philadelphia (Ph) chromosome could be linked to the pathogenetic events of leukemogenesis. CML has an incidence between 1 and 1.5 cases per 100,000 population [1]. Although the disease can occur in all age groups, the median age at diagnosis is somewhere between 39 and 48 years [1, 2, 3]. CML results from malignant transformation of a single stem cell [4]. Recent studies with FISH have demonstrated that bcr-abl fusion is present in all mature hematopoietic cells, including all myeloid elements, B and T cells and even natural killer cells [1], though molecular fusion of the bcr gene on chromosome 9 with the proto oncogene abl on chromosome 22 is considered to be the initiating event in CML. The abl gene also has motifs for action and DNA binding, and a domain for nuclear localisation [5].

The most common presentation is with symptoms of anemia: loss of energy, fatigue, dyspnoea, anorexia, weight loss and pallor [6]. The spleen is palpable in 80% to 90% of patients and is usually nontender [6, 7,8].

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The clinical course of CML patients is heterogenous with hydroxyurea or busulfan therapy, the median survival is 3.0-4.2 years, and risk of death is 10%-12% in first 2 years and 15%-25% subsequently [9]. Consistent pre-treatment poor prognostic factors for survival include the presence of splenomegaly, hepatomegaly, older age, leukocytosis, increased blast counts and expansion of paratrabecular seams of myeloblasts [10], increased basophil counts, thrombocytopenia, or thrombocytosis and cytogenetic clonal evolution [11].

1.1.Different phases of CML

CML is a heterogeneous disease with marked variability in individual prognosis [4], the course of CML may be biphasic or triphasic [12]. The chronic phase either changes to an acute phase that later progress to the blast phase. Blast phase is defined as the presence of 20% or more blasts in peripheral blood or bone marrow [1, 13].

Three subcategories of CML which are based on the relative numbers of granulocytes and megakaryocytes in the biopsy have been proposed.

1. CML-Granulocytic type- this is characterized primarily by granulocytic proliferation with diminished; normal or only slightly increased numbers of megakaryocytes.

2. CML-Granulocytic megakaryocytic type- in this subtype there is increase in the number of both megakaryocytes and granulocytes.

3. CML-Megakaryocytic type- in this rare subtype, there is prominent increase in the number of megakaryocytes, often with increased numbers of megakaryocytes and accompanying marked fibrosis [14].

Reticulin fibrosis whether it is primary or secondary event in the pathophysiology is closely linked to progression of disease [15,16].

1.2.Accelerated phase

The latest criterion proposed by World Health Organization is based upon the identification of one or more of the following:

1. 10-19% blasts in blood or bone marrow.

2. Peripheral basophilia more than 20%.

3. Persistent thrombocytopenia with platelets less than 100x 109 per litre, not related to therapy [13].

Aim of present study is to find out the factors affecting survival of chronic myeloid leukemia patients.

2.Materials and Methods:

Forty-six patients (30 males and 16 females) who fulfilled the clinical and haematological criteria of CML were included in the study. Haematological investigations were done; peripheral smears were stained with Leishman's stain to observe the following: Morphology regarding Anisopoikilocytosis, Polychromasia, nrbc and Dyserythropoiesis in rbc.100 leukocytes were counted and differential count was done to see:

Blasts, Promyelocytes, Myelocytes, Metamyelocytes, Basophils, Eosinophils, Hypersegmented forms, Dyspoiesis in WBC, Platelet count and their morphology.

Cytochemistry of peripheral smears was carried out with Leukocyte Alkaline Phosphatase (LAP) [17].The normal range of LAP is wide 14-100. In the chronic phase of the disease, the score is invariably low.

Staining for myeloperoxidase, Sudan Black and PAS reaction [17] was done in cases of CML with blast crisis in order to differentiate between myeloid and lymphoid blasts. Bone marrow aspiration was also done from the ileum, by Salah's needle.3-4 smears were made and stained with Leishman's stain from aspirated material without delay. Bone marrow biopsy was also done and was fixed in Bouin's fluid and decalcified. Biopsy was processed; blocks were made and on an average 3 sections in each case were stained with H&E and one section with Gomori's reticulin stain. In Gomori's reticulin stain, reticulin fibres and nuclei were stained black. Reticulin stain is graded from I to III based on the degree of fibrosis of the marrow.

3.Observations:

The classification of the 46 cases was based on the clinicohematologic profile and study of the bone marrow histomorphology. Out of 41 cases; 89% of cases were in chronic phase, 7% in accelerated phase and 4% in blast crisis (myeloid type) and 3 cases of CML-chronic case were of adult type of juvenile CML.

3.1.Haematological Profile in cases of CML:

90% of patients of CML-CP and 100% in CML-AP and CML-BC were anaemic (standard taken-Hb 12%). All of them had increased leukocytosis. The highest total leukocyte count was seen to be 547x109/L. Platelet count in CML-CP was decreased in 7% of cases, normal in 49% of cases and increased in 12%. The highest platelet count was 666000/cu mm. Haemoglobin, total leukocyte count and platelet counts were lower in cases of accelerated phase and blast crisis phase as compared to those in chronic phase.

3.1.1.Differential leukocyte count

The percentage of blasts in CML-CP, CML-AP and CML-BC was an average 3.36%, 11% and 55.5% respectively. Basophila was seen in 100% of CML-CP, CML-AP and CML-BC. Eosinophila was seen in 55% cases of CML-C, 33% cases of CML-AP but not in cases of CML-BC.

3.1.2.Cytochemistry

LAP could be done only in 13 cases. Eleven out of thirteen patients had low LAP score. All these were in CML-CP. The two cases who had high scores were patients with CML-BC. On Sudan black,

cytoplasm showed black and granular positivity in the cytoplasm of blasts. PAS was occasionally positive. On myeloperoxidase, blasts cytoplasm showed brown and granular positivity.

3.1.3.Bone Marrow Biopsy

Bone Marrow Biopsy was studied in 33 cases. Cellularity and Myelopoesis was increased in all the cases of CML-CP, CML-AP & CML- BC cases. Erythropoiesis was decreased in 96% cases of CML-CP and 100% of CML-AP & CML-BC cases. Megakaryopoiesis was increased in 80% of CML-CP, 66% and 50% cases of CML-AP and CML-BC respectively. It was decreased in 50% cases of CML-BC. Fibrosis was graded according to Wickramasinghe to 4 categories: Grade I, II, III and IV.

Grade I was found in 25% of CML-CP cases. Grade II was found in 25% and 33% of CML-CP AND CML-AP cases respectively. Grade III was found in 50% of CML-CP, 66% of CML-AP and 100 % of CML-BC patients.

Two patients of CML-CP which progressed two blast crisis had Grade III fibrosis at presentation while one case which progressed to CML-AP had Grade –II fibrosis.

4.Discussion:

Consistent pre-treatment poor prognostic factors for survival include the presence of splenomegaly, hepatomegaly, older age, leukocytosis, increased blast counts and expansion of paratrabecular seams of myeloblasts [10], increased basophil counts, thrombocytopenia, or thrombocytosis and cytogenetic clonal evolution [11]. According to the study done by Gomez et al in 242 patients LAP is very important for further prognostication of CML cases. According to study done by sokal et al in 242 patients, LAP was one of the prognostic factors for survival [18]. He observed that 5 patients had increased values of LAP. Their survival was significantly worse than that of 110 patients with normal or decreased scores. In the present study LAP was done in 13 patients out of whom 11 showed low scores. Patients who presented with blast crisis denovo had high LAP scores, during follow up, these patients died.

Based on cytochemistry both cases of blast crisis were typed to be myeloid blast crisis. According to study done by Knowles [1], myeloid blast phase was common than lymphoid blast phase. Roman et al [19], in his study mentioned that lymphoid blast phase constitute about only 20-30 % of cases. Dekmezian R Kantarjian et al [16] stated in his study of 138 patients that grade –III reticulin fibrosis was strongly associated with poor prognostic features of disease including splenomegaly, anaemia, increased marrow and peripheral blood blasts. In the present study two patients who had grade-III fibrosis progressed to blast crisis and one patient who progressed to accelerated phase had grade-II fibrosis.

Follow-up of 46 cases:

Follow-up of 46 cases:

1 Two patients who progressed to blast crisis had haemoglobin less than 7 gm% at presentation. Significant anaemia early in the disease could be recognized as an ominous sign as mentioned in literature [20].

2 The one patient who progressed to blast crisis and the other who developed accelerated phase during the course of study had thrombocytopenia at presentation. According to Theogides thrombocytopenia was well accepted as an ominous prognostic sign [20].

3 All the patients who progressed to higher grade leukaemia had spleen size > 10 cm at presentation. Walters et al in his study of 303 patients found that patients who had spleen size > 10 cm at presentation had poor prognosis than the patients having < 10 cm of spleen [21].

4 The 2 patients who progressed to blast crisis had grade III fibrosis. The one patient who progressed to accelerated phase had grade II fibrosis. The presence of gradeIII reticulin fibrosis was often associated with refractory disease and imminent blast crisis which was well mentioned in literature[15].

5 In the present study. 29% CML-G patients progressed to blast crisis and 4% of CML-GM progressed to accelerated phase. Burkhard et al in his study mentioned that CML-G patients had poor prognosis [22].

6 In the present study two patients who presented in blast crisis de novo had spleen size >10 cm, hepatomegaly, thrombocytopenia with a platelet count, 80000/cu mm and 65000/ cu mm respectively. Peripheral blasts ranging from 20-91 %, 13% of basophilia in one of the patients and had high LAP scores (145-160). These two patients had died on follow up. Peripheral blasts more than 5% in patients had 38% mortality during the first 2 years as compared to only 12% mortality in patients who had blast percentage less than 5%.

The survival was significantly worse in patients who had high LAP scores as compared to patients who had normal or decreased LAP.

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