Original Article

Chronic Myeloid Leukaemia in Advanced Phase: An Analytical Evaluation

Sehar Khaliq[1]

[1,] Assistant Professor, Pathology,
Fauji Foundation Hospital, Rawalpindi

Author`s Contribution
[1] *Conception of study*
[1] *Experimentation/Study conduction*
[1] *Analysis/Interpretation/Discussion*
[1] *Manuscript Writing*
[1] *Critical Review*
[1] *Facilitation and Material analysis*

Corresponding Author
Dr. Sehar Khaliq
Assistant Professor, Pathology,
Fauji Foundation Hospital, Rawalpindi
Email: seharkhalique@yahoo.com

Article info.
Received: 30/11/2019
Accepted: 20/12/2019

Cite this Article: *Khaliq, S. (2019). Chronic Myeloid Leukaemia in Advanced Phase: An Analytical Evaluation. Journal of Rawalpindi Medical College, 23(4), 241-245.*

Conflict of Interest: *Nil*
Funding Source: *Nil*

Access Online:

https://journalrmc.com/index.php/JRMC/article/view/1308

Abstract

Objective: To evaluate the clinical and morphological features in advanced phase chronic myeloid leukaemia.
Methods: This descriptive observational study was conducted at the Pathology Unit of Fauji Foundation Hospital, Rawalpindi from June 2012 till June 2016. Diagnosed patients of chronic myeloid leukaemia in the accelerated and blast phase of the disease were included in the study. History was taken, physical examination, complete blood counts, peripheral blood film examination, and bone marrow biopsy was done.
Results: The mean age in the advanced phase was 47 years. The female to male ratio was 5:1. 19 patients were in blast phase; 14(74%) in myeloid transformation, 4(21%) patients in lymphoblastic transformation and 1(05%) patient transformed into acute biphenotypic leukaemia showing both lymphoid and myeloid markers. Forty-six patients were in the accelerated phase.
Conclusion: There is usually not a single criterion for the transition into accelerated phase but certain variables coexist at the same time.
Keywords: Chronic myeloid leukaemia, advanced phase, blast phase, WHO classification.

Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder. The underlying pathology is a transcript formed by the fusion of the BCR- ABL1 gene that is present in the Philadelphia chromosome.[1] The Philadelphia chromosome is formed by the reciprocal translocation between chromosomes 9 and 22. This balanced chromosomal translocation causes the fusion of the Abelson oncogene (ABL) from chromosome 9q34 with the breakpoint cluster region (BCR) on chromosome 22q11.2, *t*(9;22)(q34;q11.2) and results in the formation of BCR-ABL1 fusion gene, this gene then translates into Bcr-Abl oncoprotein which has a molecular weight of 210 kD. It has an increased tyrosine kinase activity which not only results in leukemic cell growth but it also contributes to the clonal evolution of the disease.[1]

The fusion of transcript BCR-ABL translates into a Bcr-Abl oncoprotein. This oncoprotein most frequently has a molecular weight of 210 kD (p. 210) and displays increased tyrosine kinase activity which causes growth factor independence and leukemic cell growth in

hematopoietic cell lines, contributes also to the clonal evolution of the disease and leads to its evolution toward acute leukemia, results in an increase in the activity of the enzyme tyrosine kinase which leads to increase proliferation of myeloid cells.[2] The course of CML is either biphasic or triphasic. In patients who are untreated, it includes an initial chronic phase, an accelerated phase, and a blast phase.[3] The management of patients in the advance phase becomes challenging as compared to chronic phase especially if there is a new cytogenetic clonal evolution or there is a development of some resistant mutation.[5]

WHO criteria for accelerated phase (AP): [4]

1. Persistent or increasing WBC count of more than 10,000/µL and/or persistent or increasing splenomegaly unresponsive to therapy.
2. Persistent thrombocytosis with a platelet count of more than 1,000 × 10^3/µl, uncontrolled by therapy.
3. Persistent thrombocytopenia with a platelet count of less than 100 × 10^3/µl, unrelated to therapy.
4. Evidence of cytogenetic evolution occurring after the initial diagnostic karyotype
5. 20% or more basophils in the peripheral blood.
6. 10% to 19% myeloblasts in the blood or bone marrow.

WHO criteria for blast phase (BP): [4]

1. Blasts equal to or greater than 20% of the peripheral blood leukocytes or of the nucleated cells of the bone marrow.
2. An extramedullary proliferation of blasts.

The data reported in patients showed a majority of patients (96.8%) in the chronic phase while few patients were in accelerated and blast phases (2.2%) and (0.9%) respectively. Imatinib is a drug that selectively inhibits tyrosine kinase activity and it is the drug of choice in patients with chronic myeloid leukaemia.[6] It has been observed that life expectancy of patients in the chronic phase of the disease can be comparable to general healthy population however accelerated and blast phase of the disease still represents a challenge especially after failing to respond to tyrosine kinase inhibitors.[6]

Material and Methods

This descriptive study was conducted at the Pathology Unit of Fauji Foundation Hospital, Rawalpindi from June 2012 till June 2016. Only those patients who were in the advance phase of the disease (AP and BP) were included in this study. Patients who were in the chronic phase were excluded.

A thorough history was taken and a detailed physical examination was done in all patients. A complete blood picture was performed on automated hematology analyzer Sysmex 1800i. Peripheral blood film was stained with Leishman stain and bone marrow aspiration was done using Salah bone marrow aspiration needle and trephine biopsy using a trephine biopsy needle and stained with Leishman stain. Cytochemistry for bone marrow aspiration slides was done using Sudan Black B, chloroacetate esterase, acid phosphatase, and alpha naphthyl acetate esterase stains. Hematoxylin & eosin staining was done on trephine biopsy slides and were needed for Gomori reticulin stain for presence and grading of fibrosis. Reporting of the peripheral film was done by a fourth-year hematology resident and bone marrow aspiration and trephine biopsy reporting were done by consultant hematologist/histopathologist. The Immunophenotype of selected cases was sent to the Armed Forces Institute of Pathology, Rawalpindi. WHO 2008 criteria were used to categorize the patients in AP and BP. Informed written consent was taken from the patient and permission was sought from the hospital ethical committee. The data were analyzed through SPSS for windows version 11. The numerical data i.e. age is reported as mean ± S.D. The categorical data i.e. gender and different phases of the disease were expressed as frequencies (percentages).

Result

The mean age of patients in the advanced phase was 47 years. The female to male ratio was 5:1. A total of 65 patients were in advance phase out of which 19 patients were in the blast phase while 46 patients were in the accelerated phase as shown in Figure-I.

In Table I Marrow fibrosis in the accelerated phase was seen in 15 patients of chronic myeloid leukaemia. The fibrosis was between grades 1-3 according to WHO defined 4-point scoring system.[4]

The diagnosis of AML and ALL were based on bone marrow aspirate examination followed by cytochemistry with myeloperoxidase stain, Sudan black- B stain, alpha naphthyl acetate esterase, chloroacetate esterase, and periodic acid Schiff stain. The patient with biphenotypic leukaemia had a hypercellular marrow comprising of more than 90% heterogeneous blast cells**.** On immunophenotyping

theses, blasts showed dual expression of CD33 and CD 19, CD34, iCD22, TdT, and MPO.

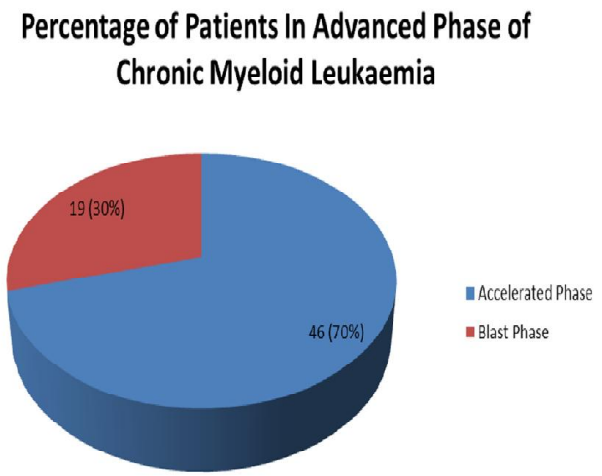

FIGURE-I: A total of 65 patients were in the advance phase. 19 patients in the accelerated phase and 46 patients were in the blast phase.

Table-I showing clinical and laboratory features in the accelerated phase of chronic myeloid leukaemia.

CLINICAL FEATURES	*FREQUENCY (%)*
Blast between 10-19%	10(21%)
Increased Blasts + thrombocytosis	04(08%)
Increased Blasts + Increasing Splenomegaly	04(08%)
Increased Blasts + Increasing WBCs	05(10%)
Increased Blasts +Thrombocytosis + Increased Basophils	03(06%)
Thrombocytopenia +Increasing Splenomegaly	02(04%)
Thrombocytosis +Increasing WBCS	02(04%)
Thrombocytosis + increasing splenomegaly	04 (08%)
Increased Basophils only	02(06%)
Thrombocytosis only	03(06%)
Increased Basophils+ Increased Blasts +Increasing splenomegaly+Thrombocytosis	04(08%)
Increasing Splenomegaly+Increased WBC	03(06%)

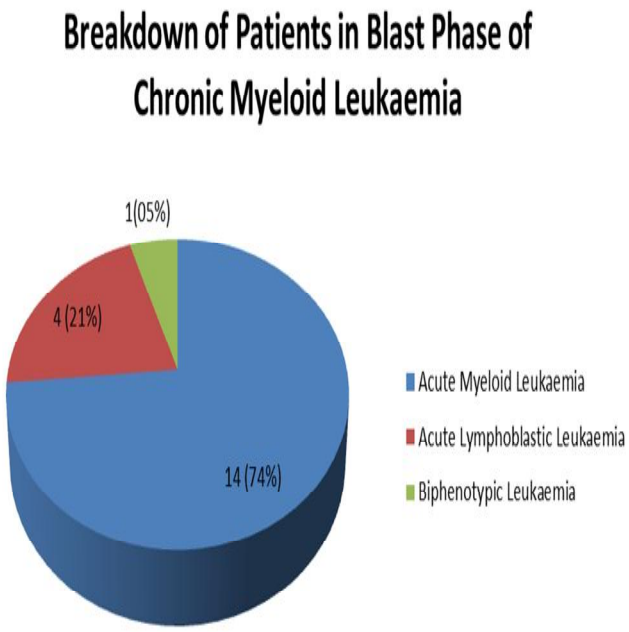

Figure-II: Distribution of blast phase of the disease: 14 patients transformed into acute myeloid leukaemia, 4 patients into acute lymphoblastic leukaemia and 1 patient into biphenotypic leukaemia.

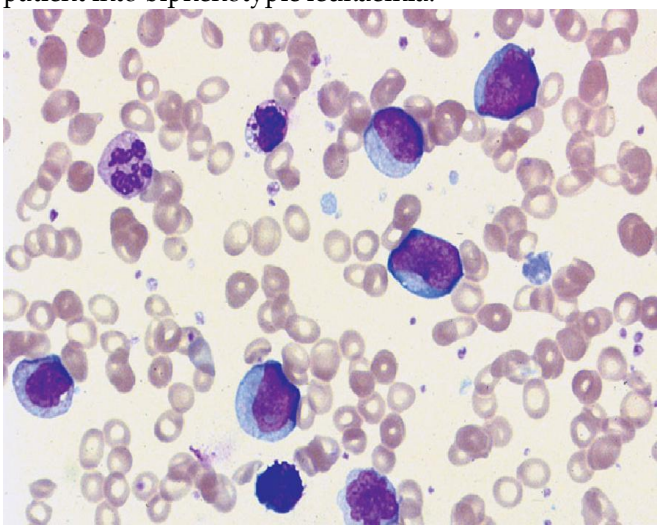

Figure-III: Chronic Myeloid Leukaemia in Accelerated Phase showing an increased number of blast cells.

Discussion

The annual incidence of CML is 1.6 per 100,000 population. The median age of onset of chronic myeloid leukaemia is 53 years.[7] The mean age of onset of CML in our study was 47 years. In a local study, the mean age was found to be 37 years, the younger age group was due to the inclusion of patients in both the chronic and advanced phases while our study

included patients in advanced phase only.[8] The reason being chronic myeloid leukaemia presents at a younger age in this part of the world compared to Western countries.[9,10] The local series results are consistent with a younger age where the mean age of presentation of this disease was found to be 34-37 years.[11]

CML in its advanced stage comprises an accelerated phase (AP) which is followed by a more aggressive phase which is the blast phase (BP). However, it has been observed that some of the patients do not go through the accelerated stage of this disease and they directly progress to the blast phase. [12,13]Our study showed a total of 65 patients were in advance phase out of which 46 (70%) patients were in accelerated phase, 19 (30%) patients were found to be in a more aggressive blast phase. In a study done locally, 35 (77.8%) patients were found to be in chronic phase, while 7 (15.5%) patients were in accelerated phase and 3 (6.7%) patients were in the blast phase of the disease .[8] In a local study that included 275 patients of CML, the percentage of patients in different stages of the disease were CP (87.3%), AP (8.1%) and BP (4.7%).[14]

In a study done on CML in France the frequency of CP, AP and BP were found to be 96.8%, 2.2%, and 0.9% respectively.[9] In comparison to having included patients in all three phases of the disease our data, there is a difference in the number of patients in various phases of the disease the reason for the difference in statistics is these studies and not just the advance phase**.** The accelerated phase of CML is characterized either by the deterioration of the hematologic parameters or there could be worsening of the physical condition of the patient. There is not a single criterion but a number of criteria to define CML-AP.[15,16,17] In our study patients who were in the accelerated phase of the disease did not have a single criterion but had multiple features of accelerated phase.[16]

According to WHO in blast phase of chronic myeloid leukaemia 70% transform into acute myeloid leukaemia, 20% transform into acute lymphoblastic leukaemia, the rest transform into biphenotypic/bilineage leukaemia.[4]

In, an international study was done, the majority of patients in the blast phase transformed into acute myeloid leukaemia. 25% of the patients transformed into acute lymphoblastic leukaemia (pre-B).[18] Rarely transformation into acute lymphoblastic leukaemia (T-type) has also been identified.[19,20]

In another study, about 70% of patients in acute transformation had blasts classifiable as myeloid leukaemia with myeloblastic or myelomonocytic type predominance.[21] CML may transform into acute lymphoblastic leukaemia in approximately 30 % of patients. The lymphoid cells generally express terminal deoxynucleotide transferase (TDT). The above study conforms to our study as the breakdown of cases into AML, ALL and bilineage/biphenotypic leukaemia showed nearly the same statistics.

Only one case was of biphenotypic leukaemia which showed both myeloid and lymphoid differentiation which corresponded to an international study that had also shown lymphoid and myeloid differentiation.[22] The limitation in our study was the lack of cytogenetic studies as cytogenetic evolution is one of the criteria of accelerated phase due to lack of the availability of this facility.[21,22]

Conclusion

There is usually not a single criterion for the transition into accelerated phase but certain variables coexist at the same time. In the blast phase, myeloid transformation is most common followed by lymphoid and then mixed-lineage transformation.

Reference

1. Vardiman JW. Chronic Myelogenous Leukemia, BCR-ABL1+. AJCP 2009 132:250-260.
2. Hoffbrand AV, Moss PAH, Petit J E. Essential Haematology 5thedn. Oxford. Blackwell Publishing Ltd; 2006.
3. Fehniger TA, Welch JS, Pluard TJ. Chronic myeloid leukemia. In: Govindan R, Arquette MA (eds). The Washington Manual of Oncology. Philadelphia. Lippincott Williams and Wilkins ;p 320
4. Vardiman JW. Chronic myelogenous leukaemia, BCR-ABL1 positive. WHO classification of tumours of haematopoietic and lymphoid tissues. 2008:32-7.
5. Brian JD, Stephanie JL. Chronic myelogenous leukemia. In: DeVita VT, Hellman S, Rosenberg SA (eds). Cancer: Principles and practice of oncology. 7th ed. Philadelphia: Lippincott William and Wilkins; 2005.p.2121.leukemia.
6. Hehlmann R, Hochhaus A, Baccarani M. European Leukemia Net. Chronic myeloid leukemia. Lancet 2007; 28:342-50
7. Perrotti D, Jamieson C, Goldman J, Skorski T. Chronic myeloid leukemia: mechanisms of blastic transformation. The Journal of clinical investigation. 2010 Jul 1;120(7):2254-64.
8. Ahmed R, Naqi N, Hussain I, Khattak BK, Nadeem M, Iqbal J. Presentating phases of chronic myeloid leukaemia. J Coll Physicians Surg Pak. 2009 Aug 1;19(8):469-72.
9. Tardieu S, Brun-Strang C, Berthaud P, Michallet M, Guilhot F, Rousselot P, et al. Management of chronic myeloid leukemia in France: a multicentered cross-sectional study on 538 patients. Pharmacoepidemiology and drug safety. 2005 Aug;14(8):545-53.
10. Cortes JE, Richard TS, Hagop K. Chronic myelogenous leukemia. In: Padzur R, Coia LR, Hoskins WJ, Wagman LD

(eds). Cancer Management: a multidisciplinary approach. 10th ed. Lawrence: CMPMedica; 2007.p.789
11. Khalid A, Zahid M, Rehman A, Ahmed ZU, Qazi S, Aziz Z. Clinicoepidemiological features of adult leukemias in Pakistan. JOURNAL-PAKISTAN MEDICAL ASSOCIATION. 1997 Apr;47:119-21.
12. Rosenthal S, Canellos GP, Whang-Peng J, Gralnick HR. Blast crisis of chronic granulocytic leukemia: Morphologic variants and therapeutic implications. The American journal of medicine. 1977 Oct 1;63(4):542-7.
13. Atallah E, Talpaz M, O'brien S, Rios MB, Guo JQ, Arlinghaus R, et al. Chronic myelogenous leukemia in T cell lymphoid blastic phase achieving durable complete cytogenetic and molecular remission with imatinib mesylate (STI571; Gleevec) therapy. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2002 Jun 1;94(11):2996-9.
14. Aziz Z, Iqbal J, Akram M, Saeed S. Treatment of chronic myeloid leukemia in the imatinib era: a perspective from a developing country. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2007 Mar 15;109(6):1138-45.
15. Cortes JE, Talpaz M, O'Brien S, Faderl S, Garcia-Manero G, Ferrajoli A, et al.Staging of chronic myeloid leukemia in the imatinib era: an evaluation of the World Health Organization proposal. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2006 Mar 15;106(6):1306-15.
16. Falkenburg JF, Wafelman AR, Joosten P, Smit WM, van Bergen CA, Bongaerts R, et al. Complete remission of accelerated phase chronic myeloid leukemia by treatment with leukemia-reactive cytotoxic T lymphocytes. Blood. 1999 Aug 15;94(4):1201-8.
17. Kantarjian HM, Talpaz M, Giles F, O'Brien S, Cortes J. New insights into the pathophysiology of chronic myeloid leukemia and imatinib resistance. Annals of internal medicine. 2006 Dec 19;145(12):913-23.
18. Perrotti D, Jamieson C, Goldman J, Skorski T. Chronic myeloid leukemia: mechanisms of blastic transformation. The Journal of clinical investigation. 2010 Jul 1;120(7):2254-64.
19. Bertazzoni U, Brusamolino E, Isernia P, Scovassi AI, Torsello S, Lazzarino M,et al. Prognostic significance of terminal transferase and adenosine deaminase in acute and chronic myeloid leukemia. Blood. 1982 Sep 1;60(3):685-92..
20. Chen X, Rutledge JC, Wu D, Fang M, Opheim KE, Xu M. Chronic myelogenous leukemia presenting in blast phase with nodal, bilineal myeloid sarcoma and T-lymphoblastic lymphoma in a child. Pediatric and Developmental Pathology. 2013 Mar;16(2):91-6.
21. Mitelman F. The cytogenetic scenario of chronic myeloid leukemia. Leuk Lymphoma. 1993;11(suppl 1)11–15.
22. Melo JV, Barnes DJ. Chronic myeloid leukaemia as a model of disease evolution in human cancer. Nat Rev Cancer. 2007; 7:441–453.