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The changing profile of Ph-positive chronic myeloid leukemia at presentation: possible impact of earlier diagnosis on survival

FRANCISCO CERVANTES, JUAN-CARLOS HERNÁNDEZ-BOLUDA, ANA FERRER, JOAN CID, EMILIO MONTSERRAT
Hematology Department, Hospital Clínic, Institut d'Investigacions Biomèdiques (IDIBAPS), University of Barcelona, Spain

ABSTRACT

Background and Objective. **Although there are indications that the profile of chronic myeloid leukemia (CML) at presentation has changed in recent years, information is scarce. The objective of the present study was to ascertain whether the initial features of CML have changed over time, as well as the possible impact on survival.**

Design and Methods. **The initial features of 167 patients diagnosed with chronic phase Ph-positive CML from 1972 to 1985 were compared with those of 174 such patients diagnosed at the same institution from 1985 to 1998. The survival of the two groups was also compared.**

Results. **CML patients diagnosed since 1985 were significantly older at presentation (mean age 47+17 vs 43+17 years, p = 0.04), were more often asymptomatic (36% vs 19%, p = 0.0003), less often had constitutional symptoms (30% vs 45%, p = 0.004), less frequently had splenomegaly (59% vs 75%, p = 0.0008) and hepatomegaly (35% vs 49%, p = 0.01), had less marked leukocytosis (mean WBC count $139\pm124\times10^9$/L vs $179\pm132\times10^9$/L, p = 0.007), with 30% of them showing an initial WBC count below 50×10^9/L (vs 19%, p = 0.02), and showed less marrow blast cell infiltration (p = 0.0003). No significant differences were observed in the distribution by Sokal's risk groups. Median survival of patients diagnosed since 1985 was 5.33 years (95% CI: 4.3-6.36), vs 4.06 years (95% CI: 3.28-4.84) for patients diagnosed before (p= 0.07). Finally, patients asymptomatic at diagnosis had a longer survival (median survival 5.7 years, 95% CI: 4.5-6.9, vs 4.1 years, 95% CI: 3.4-4.7, p= 0.03).**

Interpretation and Conclusions. **A substantial proportion of CML patients are currently diagnosed early in the course of the disease. The effect of earlier diagnosis on survival prolongation in such patients should be taken into account.**

Key words: chronic myeloid leukemia, presenting features, natural history, survival

Correspondence: Francisco Cervantes, MD, Hematology Department, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain. Phone/fax: international +34-93-2275428.

The classical description of the clinicohematologic picture of chronic myeloid leukemia (CML) at presentation included the presence of constitutional symptoms, splenomegaly with its derived symptoms and marked leukocytosis in the vast majority of patients.[1] There are, however, some indications that, due to the increasing practice of routine laboratory studies, CML is currently diagnosed at earlier stages, therefore in many cases displaying a less florid clinicohematologic picture. Indeed, it has recently been pointed out that an increasing proportion of CML patients are asymptomatic, have no palpable spleen and show moderate leukocytosis at disease presentation. The information available on the subject, however, is scarce, and based on data from a single institution.[2,3]

The primary aim of the present study was to compare the initial characteristics of two groups of patients diagnosed with Ph-positive (or bcr/abl-positive) CML in a single institution during two different time periods, in order to ascertain whether the clinicohematologic profile of CML at presentation has changed over the years.

Design and Methods

Patients

Between 1972 and 1998, 357 patients were diagnosed as having Ph-positive (or bcr/abl-positive) CML at the Hematology Department of the Hospital Clínic of Barcelona. Sixteen patients fulfilled criteria of blast crisis[4] at CML diagnosis and were excluded from the analysis, which was therefore restricted to the 341 patients with the disease diagnosed in the chronic phase.

Treatment

The patients' treatment varied over the years, reflecting the progresses in CML therapy that have occurred in the last two decades. Thus, the vast majority of patients (140 out of 167) diagnosed prior to 1985 were given busulfan as primary treatment for the chronic phase of CML, with 10 patients also receiving intensive combination therapy (vincristine, prednisone, 6-thioguanine and Ara-C) within the first year, and 12 being submitted to splenectomy. In

their turn, patients diagnosed since 1985 were treated with hydroxyurea (70 patients), busulfan (11 patients) or both (30 cases), α-interferon (46 cases) or allogeneic hemopoietic progenitor cell transplantation (25 patients). Treatment of the BC consisted of oral 6-mercaptopurine and transfusional supportive therapy in most patients with non-lymphoid BC, whereas patients with lymphoid BC received chemotherapy regimens including vincristine and prednisone.[4]

Parameters evaluated

For each patient the main clinical, hematologic, and biochemical data at diagnosis were recorded: age, gender, the presence of constitutional symptoms (fever, night sweats, weight loss), splenomegaly-derived symptoms or other symptoms, time lapse between first symptoms and CML diagnosis, spleen and liver size, hemoglobin concentration (Hb), platelet count, WBC count with its differential, bone marrow blast cell percentage, and the serum levels of LDH and uric acid. In addition, Sokal's score was calculated for each patient.[5]

Statistical analysis

The patients' characteristics according to diagnostic period (before of since 1985) were compared by means of the Students' t-test and the chi square test with Yates' correction. Actuarial survival curves were plotted by the method of Kaplan and Meier,[6] and compared by the log-rank test.[7]

Results

Out of the 341 patients with chronic phase Ph-positive CML who are the subject of the present study, 167 were diagnosed prior to 1985 and 174 thereafter. Table 1 summarizes the patients' main clinical features at disease presentation according to diagnostic period. As can be seen, patients diagnosed since 1985 were significantly older, were more frequently asymptomatic, complained less often of constitutional symptoms, and less frequently displayed splenomegaly and hepatomegaly at CML presentation. In contrast, no significant differences were observed between the two groups with regard to either the time lapse from first symptoms to disease diagnosis or the distribution by Sokal's risk groups. Table 2 shows the main hematologic and serum biochemical parameters of the two groups at diagnosis. As can be observed, the only significant differences were a lower leukocyte count in patients diagnosed since 1985 (with more than a half of the patients showing an initial WBC count below 100×10^9/L, and 30% of them a WBC count below 50×10^9/L), and a lower proportion of blast cells in the bone marrow aspirate.

Median survival of the overall series was 4.6 years (95% CI: 4.06-5.14). Figure 1 depicts the actuarial survival curves of the patients separated according to diagnostic period. With 135 patients having died at the time of the analysis, median survival of the group of patients diagnosed prior to 1985 was 4.06

Table 1. Main clinical features at presentation in 341 patients with chronic phase Ph-positive CML according to diagnostic period.

Feature	*Before 1985 (n=167)*	*Since 1985 (n=174)*	*p value*
Age, mean (SD)*	43 (17)	47 (17)	0.04
Sex (M/F)	83/84	91/83	NS
Absence of symptoms	19%	36%	0.0003
Constitutional symptoms	45%	30%	0.004
Lapse symptoms-diagnosis, [mean (SD)]°	4.7 (7.9)	3.6 (6.3)	NS
Splenomegaly	75%	59%	0.0008
Hepatomegaly	49%	35%	0.01
Sokal's risk group:			
Low risk	38%	34%	NS
Intermediate risk	28%	37%	NS
High risk	34%	29%	NS

**years; °months; NS: not significant.*

Table 2. Main hematologic and serum biochemical parameters at presentation in 341 patients with chronic phase Ph-positive CML according to diagnostic period.

Feature	*Before 1985 (n=167)*	*Since 1985 (n=174)*	*p value*
Hb, g/L*	120 (25)	115 (23)	NS
WBC $\times10^9$/L*	179 (132)	139 (124)	0.007
$< 100\times10^9$/L	36%	52%	0.004
$< 50\times10^9$/L	19%	30%	0.02
% blood basophils*	4.6 (3.1)	5.1 (3.2)	NS
% blood blasts*	2.2 (2.8)	1.8 (2.2)	NS
Platelets $\times10^9$/L*	443 (270)	513 (526)	NS
$\geq 400\times10^9$/L	45%	47%	NS
$\geq 700\times10^9$/L	15%	18%	NS
% marrow blasts*	3.5 (3.3)	2.1 (2.9)	0.0003
Serum LDH, IU/L*	1238 (796)	1221 (616)	NS
Serum uric acid, mg/dL*	6.4 (2)	6.1 (2.3)	NS

**mean (SD); NS: not significant.*

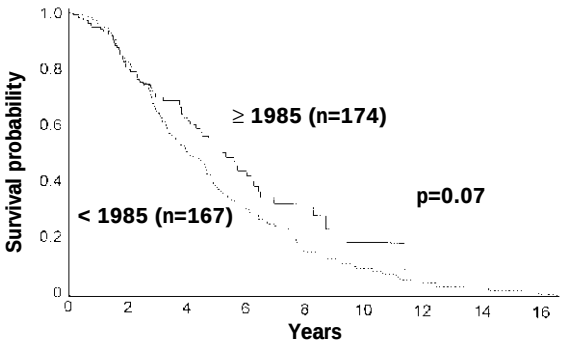

Figure 1. Actuarial survival curves of chronic phase Ph-positive CML patients diagnosed prior to 1985 and afterwards.

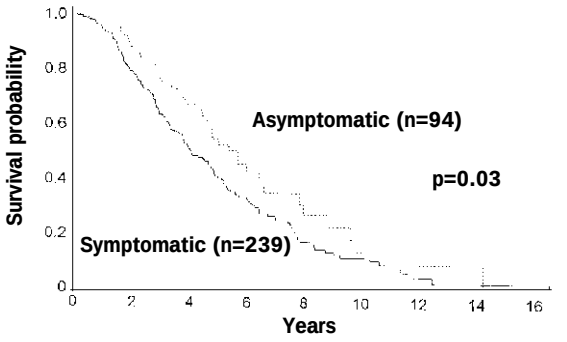

Figure 2. Actuarial survival curves of chronic phase Ph-positive CML patients according to the presence or absence of symptoms at diagnosis (n = 333).

years (95% CI: 3.28-4.84). In its turn, with 65 deaths having been registered in patients diagnosed since 1985, the projected median survival for this group was 5.33 years (95% CI: 4.3-6.36). Although a trend for statistical significance was observed (p= 0.07), the difference between the survival of the two groups was not significant. Finally, comparison of the survival of patients with and without symptoms at disease diagnosis in the overall series yielded a significant difference in favor of asymptomatic patients (median survival 5.7 years, 95% CI: 4.5-6.9, versus 4.1 years, 95% CI: 3.4-4.7, for symptomatic patients, p= 0.03, Figure 2).

Discussion

As a result of the widespread use of routine blood testing, the clinicohematologic profile of the chronic myeloproliferative disorders at presentation has changed over time. This is especially true for essential thrombocythemia, a disease currently diagnosed mostly in asymptomatic patients,[8] and to a lesser degree for myelofibrosis with myeloid metaplasia, in which an increasing proportion of patients show a less florid clinical picture at presentation in recent years.[9] With regard to CML, although there have been some indirect indications that the initial clinicohematologic profile of the disease at presentation is changing, the available information on this specific subject is scarce and based on the analysis of patients from a single institution.[2,3]

In the above context, we undertook the present study, in which the presenting features of two groups of patients with standard CML (i.e., Ph-positive or *bcr/abl*-positive and in the chronic phase) from a single center, diagnosed during different time periods, were compared. Most of the differences found in the present analysis support the notion that CML is currently diagnosed earlier. Thus, almost 40% of the patients diagnosed since 1985 had no symptoms at the time of diagnosis, as compared to less than 20% of the patients diagnosed before. The former figure is roughly similar to the one recently registered by the Houston group, and contrasts with the vast majority of symptomatic patients reported in older CML series.[1] The lower frequency of initial symptoms observed in the more recently diagnosed patients was due to a lower occurrence of constitutional symptoms (which indicate a hypermetabolic state) and also to a lower frequency of symptoms derived from excessive spleen enlargement. The above two findings constitute an indirect reflection of the existence of a lower tumor burden in more recently diagnosed patients, a fact in keeping with the lower rate of splenomegaly and hepatomegaly registered in such patients. In this context, the 41% of patients with no palpable spleen at CML diagnosis observed in the more recent diagnosis group is especially noteworthy, since it is in sharp contrast with the 10% or less registered in older CML series.[1] The lower leukocyte counts in such patients constitute additional evidence in favor of the trend towards lower tumor burden at presentation of CML in recent years. Thus, more than a half of the patients from the second diagnostic period had an initial leukocyte count below 100×10^9/L, and in almost a third of them it was lower than 50×10^9/L. Moreover, the lower proportion of marrow blasts in the patients more recently diagnosed would be another indicator or less advanced disease in such cases.

The lack of significant difference observed in the present study between the two diagnostic periods with regard to the patients' distribution by Sokal's risk groups could argue against the above considerations. However, to explain such a discrepancy, it must be taken into account that no significant differences were observed between the two groups in two of the parameters (namely, platelet count and blood blast percentage) included in Sokal's formula. Concerning the remaining two factors (age and spleen size), the unfavorable prognostic weight of

older age of patients more recently diagnosed would be neutralized by the presence of a smaller spleen in such cases.

Median survival of patients diagnosed since 1985 exceeded that of patients diagnosed before by more than one year. Although the difference between the two groups did not reach statistical significance, this was probably due to the low proportion of deaths registered in the more recently diagnosed patients. The above survival advantage for the more recently diagnosed patients must be ascribed in part to changes in the therapy of CML since the mid eighties, such as the substitution of busulfan by hydroxyurea as conventional therapy for the disease,[10] and the use of α-interferon.[11-14] However, taking into account the longer survival of asymptomatic patients observed in the present study and the higher proportion of such patients in recent years, it should be considered whether survival prolongation might be an effect of earlier diagnosis.

Contributions and Acknowledgments

FCR was responsible for clinical assessment of the patients, conception of the study and writing of the paper. JC-HB was responsible for data-handling and statistical analysis. AF and JC helped in data collection and follow-up updating. EM gave some ideas for the study and participated in writing the paper. The order in which the names of the authors appear is based on the importance of their contributions, with EM being the head of the Department.

Disclosures

Conflict of interest: none.

Redundant publications: no overlapping with previous papers.

Manuscript processing

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References

1. Spiers ASD. The clinical features of chronic granulocytic leukaemia. Clin Haematol 1977; 6:77-95.
2. Cortés J, Kantarjian HM, Giralt S, Talpaz M. Natural history and staging of chronic myelogenous leukaemia. Bailliére Clin Haematol 1997; 10:277-90.
3. Kantarjian HM, Giles FG, O'Brien SM, Talpaz M. Clinical course and therapy of chronic myelogenous leukemia with interferon-alpha and chemotherapy. Hematol Oncol Clin N 1998; 12:31-80.
4. Cervantes F, Villamor N, Esteve J, et al. "Lymphoid" blast crisis of chronic myeloid leukaemia is associated with distinct clinicohaematological features. Br J Haematol 1998; 100:123-8.
5. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984; 63:789-99.
6. Kaplan G, Meier P. Nonparametric estimation for incomplete observations. J Am Stat Ass 1958; 53:457-80.
7. Peto R, Pike MC. Conservation of the approximation E(O-E2)/E in the logrank test for survival data on tumor incidence data. Biometrics 1973; 29:579-84.
8. Pearson TC. Primary thrombocythaemia: diagnosis and management. Br J Haematol 1991; 78:145-8.
9. Cervantes F, Pereira A, Esteve J, Cobo F, Rozman C, Montserrat E. The changing profile of idiopathic myelofibrosis: a comparison of the presenting features of patients diagnosed in two different decades. Eur J Haematol 1998; 60:101-5.
10. Hehlmann H, Heimpel J, Hasford J, et al. Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: Prolongation of survival by hydroxyurea. Blood 1993; 82:398-407.
11. Italian Cooperative Study Group on Chronic Myeloid Leukemia. Interferon-α-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. N Engl J Med 1994; 330:820-5.
12. Kantarjian HM, Smith TL, O'Brien S, et al. Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-α therapy. Ann Intern Med 1995; 122:254-61.
13. Carella AM, Frassoni F, Melo J, et al. New insights in biology and current therapeutic options for patients with chronic myelogenous leukemia. Haematologica 1997; 82:478-95.
14. Zuffa E, Bandini G, Bonini A, et al. Prior treatment with alpha-interferon does not adversely affect the outcome of allogeneic BMT in chronic phase chronic myeloid leukemia. Haematologica 1998; 83:231-6.