Original Study

Prognostic Factors, Response to Treatment, and Survival in Patients With Chronic Myeloid Leukemia in Blast Phase: A Single-Institution Survey

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Abstract

We retrospectively analyzed data from 51 patients with chronic myeloid leukemia in blast phase (BP) at a single institution. Disease characteristics and prognostic factors are described. Lymphoid BP and use of tyrosine kinase inhibitors were independent prognostic factors for response. Age, hemoglobin level, and chromosomal aberrations were identified as prognostic factors for overall survival.

Introduction: Data from 51 patients (23 women) with chronic myeloid leukemia (CML) in blast phase (BP) were analyzed in order to identify prognostic factors for complete hematologic response (CHR) and survival. **Patients and Methods:** Forty-four patients experienced disease progression from chronic or accelerated phase, and 7 cases presented as CML-BP. Thirteen patients (25.5%) had extramedullary involvement at diagnosis, and 71% were myeloid BP. Clonal evolution was identified in 53% of the cases, and the abnormalities most frequently observed were isochromosome (17q), double Philadelphia chromosome, and trisomy 8. Forty-five patients received treatment: 60% chemotherapy (CT) alone and 40% CT plus tyrosine kinase inhibitors (TKI) or TKI alone; 42% of them experienced CHR. **Results:** Median overall survival (OS) in patients whose disease responded to treatment was 7 months (95% confidence interval, 1.7-6.2 months), with a median disease-free survival of 5 months (95% confidence interval, 2.8-5.8 months). One out of 3 patients who underwent hematopoietic stem-cell transplantation remains alive. Multivariate analysis revealed that lymphoid BP and TKI therapy had a statistically significant positive impact as prognostic factors for CHR. In the multivariate analysis, age $>$ 60 years, hemoglobin $<$ 10 g/dL, and complex karyotype were statistically significant negative prognostic factors for OS. There was no statistical significant difference in OS between patients who received only CT (1988-2002) with those treated with CT plus TKI (2003-2013). **Conclusion:** This is the first study in Mexico to report prognostic factors associated with CHR and OS in patients with CML-BP.

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with an annual incidence of 1 or 2 cases per 100,000 adults.[1,2] The hallmark of the disease is a balanced translocation involving chromosome 9 and chromosome 22, known as the Philadelphia chromosome (Ph).[3] The resulting oncoprotein, termed BCR-ABL, promotes growth and replication driving leukemogenesis.[2,4-8]

At diagnosis, approximately 90% of CML patients present in chronic phase. As the disease progresses, it may follow a biphasic or triphasic course evolving through an accelerated phase and/or blast phase (BP), in which hematopoietic differentiation has become arrested and immature blasts accumulate in the bone marrow (BM) and spill into the peripheral blood.[8-10]

The mechanisms for progression to BP are varied and not entirely understood. These include differentiation arrest, genomic

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instability, telomere shortening, alterations in apoptotic signals, and loss of tumor-suppressor functions, which leads to clonal evolution.[8] This is evidenced as nonrandom additional cytogenetic aberrations (ACA)[11-13] and molecular alterations including mutations in the BCR-ABL tyrosine kinase domain, *p53, RUNX1,* and *IKZF1,* among others.[11,14,15]

CML-BP is highly refractory to treatment. Multiple induction CT regimens have been evaluated with response rates of approximately 30%.[16-20] Among those with response, median overall survival (OS) is approximately 3.5 to 19 months.[16] Introduction of tyrosine kinase inhibitors (TKI) to the treatment of CML in chronic phase has greatly improved outcomes.[21] In previously untreated CML-BP patients, complete hematologic and cytogenetic responses (CyR) are achieved with imatinib alone in about 50% and 15%, respectively, with a 12-month OS of approximately 20% to 30%.[22-25] Hematologic response rates for second-generation TKI range between 55% and 65%, and CyR are observed in 40% to 55% of cases. Despite this, responses are short, with median OS between 5.3 and 11.8 months.[16,26,27] Allogeneic hematopoietic stem-cell transplantation (HSCT) is recommended in patients who experience complete hematologic response (CHR). However, the long-term survival rate is low—nearly 20%.[28,29]

Studies depicting CML-BP characteristics are scant,[30-34] and to our knowledge there are no previous reports regarding the clinical characteristics and outcome of this entity in the Mexican population. Thus, the aim of this study was to retrospectively analyze our experience in patients with CML-BP and describe their clinical, cytogenetic, and immunophenotypic characteristics as well as their prognostic features and outcomes.

Patients and Methods

We retrospectively analyzed the characteristics of 51 patients with CML-BP diagnosed and treated at our institution between 1988 and 2013. All patients fulfilled World Health Organization 2008 criteria for CML-BP.[1] Patients were evaluated with complete blood counts, BM aspiration and biopsy, blast immunophenotyping by flow cytometry, and conventional cytogenetics. Fluorescence in-situ hybridization (FISH) analysis started in 1999.

CHR was defined as an absolute neutrophil count $\geq 1 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, $\leq 5\%$ marrow blasts with absence of blasts in peripheral blood and no evidence of extramedullary disease, lasting for at least 4 weeks.[35] Relapse was defined as reappearance of blasts in peripheral blood or $\geq 5\%$ of blasts in BM or extramedullary disease in those patients who previously had experienced CHR. Patients who died within 4 weeks from the beginning of therapy were considered as early deaths.

CyR in patients who received TKI were determined by the percentage of Ph-positive cells in at least 20 analyzable BM metaphases. Depending on the percentage of Ph-positive cells, CyR was classified, according to the European LeukemiaNet recommendations,[36] as complete (0), partial (1%-35%), major (0%-35%), minor (36%-65%), minimal (66%-95%), or none (96%-100%). The presence of ACA in Ph-positive clones at diagnosis was reported following the International System for Human Cytogenetic Nomenclature (ISCN) 2009.[11-13]

OS was calculated from the date of CML-BP diagnosis to the date of death from any cause or loss during follow-up. Disease-free survival (DFS) was calculated from the date of documented CHR to the date of relapse.

Numerical variables were described in terms of mean ± standard deviation or median and range; categorical variables were described in frequencies and proportions. In order to compare categorical or

Table 1 Characteristics of Patients With CML in BP

Characteristic	Variable	Value
Gender, n (%)	Male	28 (54.9)
	Female	23 (45.1)
CML phase at initial diagnosis, n (%)	Chronic	35 (68.6)
	Accelerated	9 (17.6)
	Blast	7 (13.7)
Treatment previous to progression, n (%)	Total	44 (86.3)
	Busulfan	15 (29.4)
	Imatinib	12 (23.5)
	Hydroxyurea	10 (22.7)
	Interferon-α	7 (13.7)
Complete hematologic response to previous treatment, n (%)	Total	31 (60.8)
	Other therapies	22 (43.1)
	Treated with TKI	9 (17.7)
Cytogenetic response in TKI-treated cases, n (%)	Total	12 (23.5)
	Complete CyR	3 (25)
	Partial CyR	3 (25)
	Minor CyR	3 (25)
	No response	2 (16.7)
	Not available	1 (8.3)
Blast cell lineage, n (%)	Myeloid	36 (70.6)
	Lymphoid	12 (23.5)
	Mixed phenotype	3 (5.9)
Extramedullary disease, n (%)	Total	13 (25.5)
	Central nervous system	6 (46.1)
	Skin	3 (23.1)
	Bones	2 (15.4)
	Ganglion	1 (7.7)
	Intestinal	1 (7.7)
Available karyotype at BP diagnosis		36 (70.5)
Complex karyotype, n (%)		8 (22.2)
ACA, n (%)	Total	19 (53)
	Major route ACAs	12 (63)
	Other ACAs	7 (37)
Hemoglobin count, g/dL, median (range)		8.8 (4.4-15.2)
WBC count, $\times 10^9$/L, median (range)		36 (1.9-648)
Platelet count $\times 10^9$/L, median (range)		68 (6-1060)
Treatment, n (%)	CT	27 (52.9)
	CT + TKI	16 (31.4)
	TKI alone	2 (3.92)
	Supportive care	6 (11.7)

Abbreviations: ACA = additional cytogenetic alterations; BP = blast phase; CML = chronic myeloid leukemia; CT = chemotherapy; CyR = cytogenetic response; TKI = tyrosine kinase inhibitors; WBC = white blood cell count.