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Hematologic and molecular response with dasatinib as second-line treatment in chronic myeloid leukemia (CML) with treatment failure

Juan Enrique Santos-Macías, Enrique Baez de la Fuente and Arnoldo Salas-Delgado*
Department of Hematology, UMAE No 25, Monterrey, N.L., Mexico

Abstract

Background: *Chronic myeloid leukemia is a myeloproliferative disease characterized by the Philadelphia chromosome and with this, the chimeric protein BCR-ABL. The first-line treatment is imatinib, a tyrosine kinase inhibitor, that has showed good results, but with a significant percentage of treatment failure. This failure has led to second-generation tyrosine kinase inhibitors as second-line treatment such as dasatinib.* **Objectives:** *The objective of the study was to evaluate the efficacy of dasatinib as second-line treatment.* **Material and methods***: Observational, longitudinal, and retrospective study. Patients with diagnosis of chronic myeloid leukemia that presented failure to first-line treatment were included in the present study; the hematologic response was evaluated at 3, 6, and 12 months, and molecular response at 12 months of follow-up after dasatinib treatment was started.* **Results:** *Of a total of 14 patients that were included in the study, a response in the white cell count of 84.6% with a mean response at 4.7 months of follow-up was observed; also 84.6% platelet response with a mean response at 4.7 months of follow-up. Molecular response was also evaluated at a 12-month follow-up, achieving a 50% response with a mean response at 11.08 months of follow-up. A survival rate of 80% at a 12-month follow-up was observed.* **Conclusions***: The use of dasatinib as a second-line treatment is effective in achieving a sustained hematologic response of 84.6% and a molecular response in 50%, also finding a hematologic response without achieving a total molecular response.* (Gac Med Mex. 2016;152:299-303)

Corresponding author: *Juan Enrique Santos-Macías, dr.jesantosm@gmail.com*

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disease that was first described in 1845. Clinical presentation is characterized by fatigue, weight loss, abdominal fullness, bleeding, purpura, splenomegaly, leukocytosis and thrombocytosis; in up to 50% of cases it is discovered as an incidental finding[1,2]. It is the first disease where a molecular rearrangement resulting from a genomic fusion and a chimeric protein was recognized, the fusion of the *BCR* and *ABL1* gene, yielding a chimeric mRNA and a protein with a t (9:22) in CML[3].

The determination of the pathophysiology of the disease enabled the design of specific drugs; initially, interferon alpha, which achieved 5-20% complete cytogenetic response in early chronic phases but with

Correspondence:
*Juan Enrique Santos-Macías
Av. Lincoln y Gonzalitos, S7N
Col. Morelos
CP 64180, Monterrey, N.L., México
E-mail: dr.jesantosm@gmail.com

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high toxicity and decreased efficacy that was directly proportional to the duration of the chronic phase. Subsequently, imatinib, the first synthetic competitive tyrosine kinase inhibitor, designed to inhibit the fusion protein *BCR-ABL*, was developed, and has become the cornerstone in the treatment of CML[4,5,6]. Five-year survival is estimated at up to 76%, with this drug being considered the first line of treatment for this type of patients[7,8]. However, resistance or intolerance to imatinib, defined as hematologic, cytogenetic or molecular treatment failure and presence of side effects after administration of the drug, respectively, have been observed, especially in patients at advanced stages of the disease[9,10].

According to the 2009 European Leukemia Net, in case of failure to achieve a favorable response to first-line therapy, treatment adjustment should be considered, since failure, rather than suboptimal response, has demonstrated a direct effect on survival[11], with lower survival rates being found, as well as shorter disease-free survival and a reduced likelihood of reaching a major cytogenetic response, and in case of achieving it, higher probability of losing it[12].

Dasatinib is an orally administered multi-kinase inhibitor, including *BCR-ABL*. It is not structurally related to imatinib, but it is 325 times more potent[4,13,14]. Improved disease-free evolution and cytogenetic response in patients with failure to imatinib therapy are described in the literature[15,16], with a complete hematologic response of up to 90% at the chronic phase of the disease and up to 33% at the accelerated phase[4]. Cervera et al., as well as Quintar-Cardama, report better response in patients considered to be intolerant to imatinib than in resistant patients, without being able to demonstrate cross-resistance between imatinib and dasatinib[17,18]. It is important to highlight that in our country there is scarce information documenting the effectiveness of dasatinib as second-line treatment, and for this reason, the purpose of this study was to document the effectiveness of dasatinib as second-line therapy in patients who have shown failure to first-line treatment with a tyrosine kinase inhibitor, by assessing hematologic and molecular response.

Material and methods

After approval by the Local Committee of Research and Ethics in Health Research of the Unit, an observational, longitudinal, retrolective cohort study was conducted in the population of the hematology department of a tertiary care hospital in the northeastern region of the country.

Patients of the adult hematology department who failed to initial treatment with imatinib and received second-line treatment with dasatinib within a period encompassed from April 2009 to June 2013 were included in the present study. Patients in whom treatment failure could not be demonstrated or who were on first line treatment with dasatinib were excluded.

To assess dasatinib efficacy as second-line drug, blood count determinations were made at baseline and at 3, 6 and 12 months in order to evaluate the hematologic response. Determination of *BCR-ABL* mutation status was also performed 12 months after the treatment was started in order to assess the molecular response to the treatment. With the obtained values, central tendency and dispersion measures were used, such as the mean, median, mode, standard deviation and proportions. Fisher's exact test was used to compare proportions between groups and the Mann Whitney U-test was used for quantitative variables. In the comparison of groups and hypothesis contrast, the chi-square test was used for qualitative variables and Student's t-test for quantitative variables, with the data analysis being made aided by the SSPS software, v. 15 in Spanish language.

Results

One hundred and seventy-seven CML-diagnosed patients were studied, out of whom 14 subjects with failure to first-line treatment with imatinib who started dasatinib as second-line drug were included in the study; 5 (35.7%) were males and 9 (64.3%) were females, with an average age of 43.07 (30-63) years.

The hematological response was assessed using the leukocyte and platelet count values as reference, based on a measurement prior to the start of dasatinib as second-line drug. Follow-up was made at 3, 6 and 12 months.

A decline in the leukocyte count, also with platelet count decrease, was observed during the follow-up. In the baseline measurement, mean leukocytes were reported at 33,046.76 (3,080-122,000), and platelets at 312,850.84 (1,249-672,000), in comparison with the third month measurement, where a mean leukocyte count of 46,315.83 (3,280-394,000) and a mean platelet count of 293,125.00 (76,100-567,000) were obtained. In the measurement performed at the sixth month, both the leukocyte and the platelet count show a clear drop, with mean leukocytes at 6,242.62 (3,600-12,600) and platelets at 225,687.50 (149,000-343,000); however, in the measurement carried out at the twelfth

Table 1. Baseline leukocyte and platelet counts and 3, 6 and 12 months after the start of dasatinib treatment

	Leukocytes					Platelets				
Month	Mean		SD	f	p	Mean		SD	f	p
0	33.04	(3.08-122.00)	38.59			312.85	(1.24-672.00	249.18		
3	46.31	(3.28-394.00)	112.71			293.12	(761.00-567.00)	126.37		
				0.916	0.443				0.584	0.630
6	6.24	(3.60-12.60)	3.04			225.68	(149.00-343.00)	59.01		
12	6.62	(3.84-9.25)	1.58			250.13	(150.70-351.00)	75.37		

Leukocyte and platelet means comparison with baseline measurements at 3, 6 and 12 months and p-values.

month, we observed an increase in both leukocytes and platelet total counts, with mean leukocytes at 6,622.00 (3,846-9,250) and platelets at 250,137.50 (150,700-351,000), all without statistically significant difference because the intra-group range was wide; nevertheless, there was a progressive mean decrease until month 12 of follow-up (Table 1).

To assess the molecular response, the standardization index (SI) was used as reference. Twelve months after the start of the treatment with dasatinib, an average value of 9.51% (p = 0.039), with a standard deviation of 14,059 and a 95% confidence interval of 0.57823-18.44393 were reported.

Based on the values of leukocyte and platelet counts, 11 patients (84.6%) showed hematological response and 2 (15.3%) had no response. With regard to molecular response, 6 (50%) had one and 6 (50%) did not.

During the 12-month follow-up of the patients included in the study, a mean leukocyte response was found 4.76 (3.06-6.47) months after having started the treatment with dasatinib; remarkably, half the patients had a response approximately at the third month of treatment (Fig. 1). With regard to the platelet response, a mean of 4.769 (3.06-6.47) months was found, with a response in 50% of patients also at the third month (Fig. 2).

As for the molecular response in the group of studied patients, a mean was found at 11.083 (9.75-12.40) months, with a response in 20% of the patients by the eight month (Fig. 3).

Of the total of patients included in this study, there were 2 deaths recorded at an average of 8.5 (5.56-11.44) months. A 50% survival was documented in the study population at the seventh month.

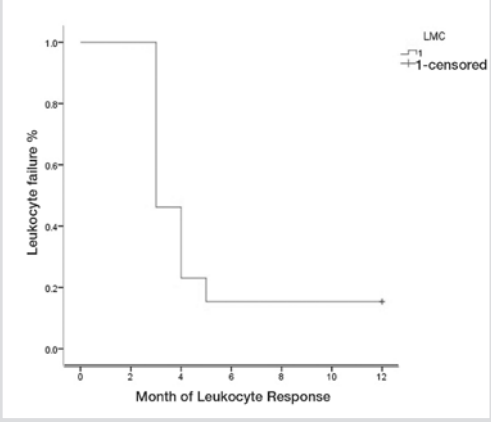

Figure 1. *Percentage of patients with treatment failure and their leukocyte response after the start of dasatinib. Leukocyte response at 12 months of follow-up.*

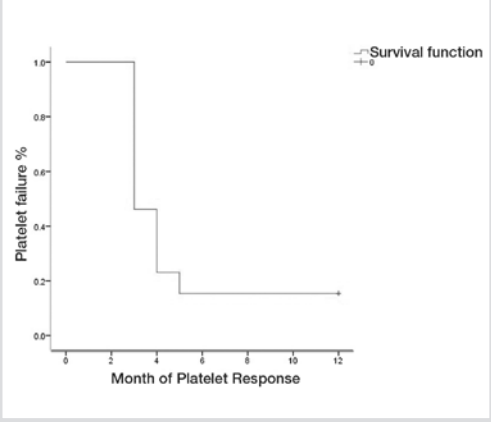

Figure 2. *Platelet response percentage at 12 months of treatment with dasatinib in 14 patients with treatment failure. Patients diagnosed with chronic myeloid leukemia with treatment failure and their response 12 months after the start of dasatinib.*

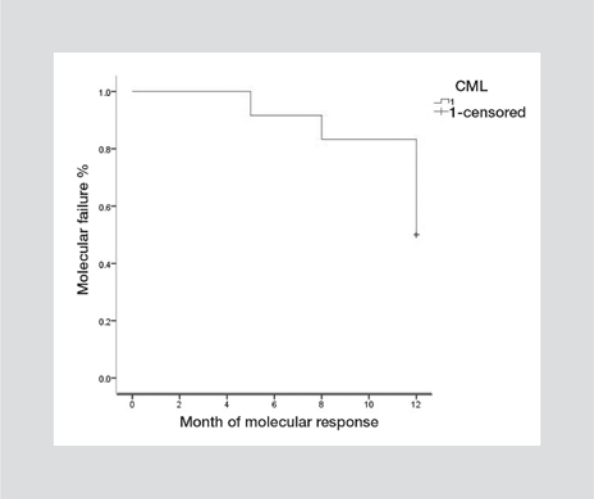

Figure 3. *Percentage of patients at molecular failure and their response to second-line treatment with dasatinib. Patients diagnosed with chronic myeloid leukemia with molecular failure and their response 12 months after second-line treatment with dasatinib was started.*

Discussion

Currently, failure to treatment with imatinib represents a problem with a high impact, since there are a reduced number of second-line treatment options. Tested in the year 2006 as second-line tyrosine kinase inhibitor, dasatinib has been considered a drug by means of which favorable results are obtained.

In the present study, leukocyte and platelet counts were followed-up in patients with CML, regardless of the clinical stage at the moment second-line therapy was started, over a period of 12 months, and a determination of *BCR-ABL* mutation status was made at 12 months, with the purpose to assess the efficacy of dasatinib as second-line agent in the treatment of patients who had failed to first-line treatment with imatinib.

With regard to the hematologic response, in a study carried out by Cortez et al., a response of 32% was obtained at six months of follow-up with average response by the second month[19]. In the studied group, a hematologic response was reported in 50% of the patients at the third month, with an average response at 4.7 months, with a response of 84% at 12 months of follow-up, and the same percentage for leukocyte and platelet counts; with an additional gradual decrease being observed in platelet and leukocyte counts at the third and sixth months until the twelfth month of follow-up, where total count elevation was recorded, without this being considered a criterion for treatment failure; however, this modification in the values should be taken with caution, since it could be indicative of treatment failure or hematologic failure. Therefore, in subsequent studies it will be important to consider obtaining blood counts earlier, with the purpose to assess if the hematological response occurs in a shorter period of time than in this study, where the first cutoff point to assess it was three months after treatment with dasatinib as second-line drug was started; additionally, in cases where there is leukocyte counts elevation, dose adjustment of the drug should be even considered in order to prevent or avoid hematologic failure.

As for dastinib efficacy as second-line drug, the study by Kantarjian et al. shows a molecular response in 64% of patients with intolerance or resistance 24 months after the treatment was started[20]. In the group of studied patients, molecular response was documented in 50% in a 12-month follow-up of treatment with dasatinib; however, since the cutoff point of this study was at 12 months, it will be necessary to consider 18 and 24-month follow-up assessing sustained molecular response or loss of it.

Boquimpani et al. documented that patients who showed a molecular response since the sixth month of treatment achieved a higher molecular response than those who displayed it later, which translated into longer disease-free survival[21] and suggests that it would be important not only to carry out an early measurement as described by Boquimpani, but also to prolong the follow-up to 18 and 24 months for the group not yet showing molecular response, in order to assess if the percentage of response at 24 months coincides with or is even higher than the one described.

In this study, it was possible to assess the evolution and response of CML-diagnosed patients who failed to respond to the drug that is still considered first-line in this unit, with hematologic response being found in 84% of the study population; however, noteworthy, although among the patients included in the study only in 50% was there a molecular response documented, in none of them was there disease relapse reported during the follow-up; therefore, we concluded that it is advisable to start an early follow-up at 6 months and to continue it up to 18-24 months after the start of the second-line treatment in order to assess for molecular response in those patients who failed to show it earlier.

The use of dasatinib as second-line drug in patients who have shown resistance or intolerance to imatinib is adequate, since, as documented in the present study, a favorable response is achieved with an early hematologic response and 12 months after treatment initiation, as well as a major molecular response.

Conclusions

Currently, there are limited options available for second-line treatment of CML. Dasatinib showed significant effectiveness for patients who have shown treatment failure, with a hematologic response documented in 84.6%, mean response at 4.7 months and a molecular response in 50% with a mean response at 11.08 months; in addition, there was a sustained hematologic response in those patients who failed to achieve a molecular response.

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