

Long-Term Outcomes of Tyrosine Kinase Inhibitors Treatment for Chronic Myeloid Leukemia

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Abstract

Introduction: Chronic myeloid leukemia Ph⁺ (CML) is a myeloproliferative neoplasm that originates in a pluripotent and abnormal bone marrow cell, consistently associated with the BCR-ABL fusion gene, 1 located on the Ph chromosome, represents 15% of all leukemias. Treatment has evolved along with the disease using alkylators, antimetabolites, immunomodulators, and tyrosine kinase inhibitors (TKI), that have significantly improved patient survival, including ponatinib, effective for the T315I mutation.

Objective: To know the overall survival and progression-free survival of TKIs (imatinib, nilotinib and dasatinib) in patients with Ph⁺ CML treated at the CMN Hematology Service "20 de Noviembre" ISSSTE, in a long-term follow-up.

Patients and Methods: Over 15 years with Ph⁺ CML from 1999 to 2016 not treated with ITQ and without contraindication to receive them. Those who rejected this treatment were not included. Those who died due to some comorbidity not related to CML, those who switched to progenitor hematopoietic stem cell transplantation, those who refused to continue receiving TKIs or when treatment was suspended for administrative reasons (loss of right to institutional insurance).

Results: A total of 82 patients were analyzed. In 37% of the patients, the initial treatment was chemotherapy. Patients who achieved molecular remission had a mean of 5 months before starting TKIs. Imatinib was only used in the first line (n=65), nilotinib was the majority in the second line (n=18) and dasatinib was the only one indicated in the third line (n=8). Molecular remission was profound in 26 patients and greater in 24%. No remission was achieved in four patients. The PFS, recorded from the start of any TKIs, was likely 0.83 to 156 months of follow-up. The OS was 0.92 to 191 months.

Conclusions: Imatinib was used in our hospital in 2001. Until then, it was treated with hydroxyurea, busulfan, or cytarabine + IFN. The patients who started receiving TKIs during the first two months, after diagnosis, had OS as well as those who were delayed more than this time. The depth of remission was related to the time at which TKIs administration was started and only reached remission in those who started it within the first six months. We found no significant difference between the three TKIs. Failure to respond was the most frequent condition. The months elapsed waiting for a response was greater than 6 months, which is prolonged, particularly in the case of the passage from first to second line. This delay, in our cases, is related to the lack of second-generation TKIs. More than half had molecular remission, major or profound, with one or more of the inhibitors employed. However, the SG is not affected by the existence of cytogenetic or molecular remission.

Keywords: Chronic myeloid leukemia; Tyrosine kinase inhibitors; Molecular remission; Cytogenetic remission; Chronical phase; Accelerated phase; Blastic phase

Background

Ph⁺ Chronic myeloid leukemia Ph⁺ (CML) is a myeloproliferative neoplasm originating in a pluripotent and abnormal bone marrow cell, and consistently associated with the fusion gene BCR-ABL, 1 gene located in Ph chromosome. It is characterized by an increase in the proliferation of myeloid elements in all stages of maturation.

Generally, it manifests itself with anemia, splenomegaly, leukocytosis, and increase in granulocytes in different stages of maturation, basophilia and thrombocytosis [1]. Since the time that

treatment only included chemotherapy (busulfan, hydroxyurea, and cytarabine) with or without interferon (IFN) predictive factors of its evolution were sought, when the disease appeared, and soon, prognostic scales became orchestrated, one of which, widely used, is Sokal's [2]. It is still taken as a reference, even in the era of tyrosine kinase inhibitors (TKI).

The addition of IFN to CML treatment, in addition to prolonging the progression-free survival (PFS), included the knowledge that it was necessary to obtain cytogenetic remissions to obtain prolonged responses [3,4]. This tactic has become definitive in the disease's therapeutic strategy, now with TKI.

Since the last century, the transplant of hematopoietic progenitor cells (HPC) has been recognized as the only existing curative

treatment. However, the difficulty in finding a compatible donor, the age of the receptor, the high morbidity and mortality, and the negative consequences in quality of life is serious drawbacks to this procedure. The transplant's effectiveness is 50% over 5 years, according to a European Leukemia Net panel, if the transplant is carried out during the disease's chronic phase [5].

Understanding of the role of abnormal tyrosine kinase, as a product of the BCR-ABL alteration, in the CML pathogenesis, enabled the discovery of compounds that inhibit its activity and interrupt the signals that induce the proliferation of leukemic cells; they are known as TKI [6]. Imatinib mesylate, first in clinical use, exhibited high biochemical activity, and highly specific, with acceptable pharmacokinetic characteristics, and a tolerable toxicity profile [7]. In prospective, multicenter and international studies [8], it was compared with the combination cytarabine + IFN, the most effective up to then; hematological remissions (95%) and cytogenetic remissions (55%) were clearly favorable to TKI. This advantage, in favor of imatinib, has been confirmed in many other studies [9-11]. Additionally, the adverse effects have been consistently less than with other treatments.

Other TKIs have been found, recognized as second generation. Nilotinib, with a better bond to the hybrid BCR/ABL is 20 times more potent [12] and effective and dasatinib is considered to be 320 times more potent than imatinib because it binds to several sites of BCR/ABL [13,14]. Frequently, if one fails, it is followed by another. Currently, TKIs will be considered the regular treatment for CML. Featured among other new inhibitors is ponatinib, with efficacy for the T3151 mutation, resistant to other TKIs [15].

Cytogenetic analysis is the basic study of the vigilance of the response to TKIs and its permanence. It is also necessary to have a count of the number of BCR/ABL transcripts through PCR molecular study [16].

The purpose of this study is to learn the efficacy of TKIs (imatinib, nilotinib, and dasatinib) in patients with Ph+ CML treated at Centro Medico Nacional ISSSTE (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado [Government Worker Social Security and Services Institute]) "20 de Noviembre" Hematology Department, in long-term follow-up. Many of them started treatment with chemotherapy and IFN, before 2001, when there was no inhibitor yet. Our hospital is concentrated, and before the appearance of TKIs, the demand for patients with CML was high. Subsequently, the majority of these patients are treated at general or regional hospitals, whereby the request for care has decreased.

Patients and Methods

Patients with Chronic Myeloid Leukemia (CML) were included; they were treated at ISSSTE "20 de Noviembre," Hospital Center Hematology Department from 1999 to 2016. Inclusion criteria: over 15 years old with CML (Ph+) not treated with TKI and without contraindications to receive them. Those who rejected this treatment were not included. The following patients were eliminated: those who died from a comorbidity unrelated to CML, those who underwent a transplant of hematopoietic progenitor cells (HPC), those who refused to continue receiving TKIs, or when treatment was suspended for administrative reasons (loss of the right to institutional insurance).

TKIs, in the Department, were available beginning in 2001 (imatinib); two years later, nilotinib and dasatinib were added. Patients who received the conventional treatment were included, up to then,

and they were given TKIs. The conventional therapy included: busulfan, hydroxyurea, cytarabine, and IFN.

Some patients received hydroxyurea, to induce hematological remission, for one to two months, before starting TKI.

The following variables were studied: age and sex; diagnosis dates, and TKI start dates; initial symptoms; liver and spleen size; existence of granulocytic sarcomas; hematic biometry and bone marrow; lactate dehydrogenase (LDH); Sokal index; evolutionary phase (chronic, accelerated or blastic) upon starting TKI; other cytogenetic findings. Initial treatment was assigned and its duration without TKI; use of TKIs in first, second, or third line; remission reached (hematological, cytogenetic, or molecular); duration of remission, final destination and follow-up. Variables with prognostic implications were sought

Only complete cytogenetic remission and greater or deep molecular remission were considered.

The central objectives of this study are overall survival (OS) and progression-free survival (PFS) which include the initial failures and the transfer to the accelerated or blastic phases.

Definition of Terms

Chronic phase

Existence of the disease in the absence of one of the manifestations indicated in the accelerated or blastic phases.

Accelerated phase

Any of the following, with treatment

- Persistent or progressive leukocytosis ($>10 \times 10^9/L$)
- Blasts: in blood or bone marrow, 10%-19%
- Basophils: in blood, $>19\%$
- Persistent thrombocytopenia $<100 \times 10^9/L$
- Persistent thrombocytosis $>1,000 \times 10^9/L$
- Progressive splenomegaly and leukocytosis, refractory to treatment.
- Cytogenetic evidence of clonal evolution

Blastic phase

Any of the following

- Blasts: in blood or bone marrow, $>19\%$
- Blasts in extramedullary infiltration(s)
- Blasts: large accumulations in bone marrow biopsy

Hematological remission

All of the following

- Leucocytes $>10 \times 10^9/L$. Without immature forms: Basophils $<5\%$.
- Platelets $<450 \times 10^9/L$. WBC $<10 \times 10^9/L$
- Non-palpable spleen

Cytogenetic remission

- Complete Ph+, 0
- Partial: Ph+, 1% to 35%
- Lesser Ph+, 36 to 65%

- Minimum: Ph+, 66% to 95%
- Null: Ph+, more than 95%

Molecular remission

Determined with the test on the polymerase chain reaction with reverse transcriptase for BCR-ABL1 (PCR)

- Deep: <0.01% of BCR-ABL
- Greater: <0.1 % of BCR-ABL

Statistical Analysis

Statistical program SPSS version 20.0 for Windows was used. Descriptive analysis was performed with measures of central tendency and dispersion, absolute measures and percentages according to the type of variable. Comparisons were assessed using non-parametric (numerical variables) Wilcoxon or Kruskal-Wallis tests; the nominal variables were evaluated with χ^2 . The association tests, for numerical variables, were non-parametric (Kruskal-Wallis) and χ^2 for the nominal ones. The Kaplan Meier method was used for overall and progression-free survival. Statistical significance was considered at $p < 0.05$. Confidence intervals are given to 95%.

Results

82 patients were treated. The main clinical and hematic data are found in (Table 1). Males prevailed. Only 13 patients had a fever, less than 38.5°C. Weight loss was found in 30 individuals, of up to 12 kg. Average LDH was 761 μ /dL with limits of 196 μ /dL to 2,869 μ /dL. One case debuted with granulocytic sarcoma in the gluteal region. In the basal molecular study, 2 cases of T3151 were found.

Data	Result
Gender (M/F)	39/43
Age in years, mean (Limits)	44 (16-83)
Splenomegaly n= (Limits cm)	54 (2-30)
Hepatomegaly n= (Limits cm)	26 (2-19)
Hematocrit %, mean (Limits)	35 (11-52)
Leukocytes $\times 10^9/L$, mean (Limits)	170(21-650)
Blasts %, mean (Limits)	3 (0-90)
Platelets $\times 10^9/L$, mean (Limits)	511(75-1,900)
Sokaln=(Low/Intermediate/High)	27/29/26
Phase(Chronic/accelerated/basic)	75/2/5

Table 1: Initial clinical and hematic data.

In 30 (37%) patients, the initial treatment was chemotherapy (CT): busulfan: (n=2), hydroxyurea (n=16), and cytarabine + IFN (n=12). Under this regimen, patients waited 3 to 85 months (mean=23) before starting a TKI. Out of these, those who attained molecular remission had an mean of 5 months (7 to 9) before starting TKI. In patients without TKI for a longer time, the responses were only cytogenetic or hematological. When they started them, they were in the chronic phase (n=25), accelerated (n=2), or blastic (n=3).

The TKIs used in the first, second, and third line are found in Table 2. Thirty-one patients went from first to second line and 8 to third. Imatinib was only used in first line (n=65). Nilotinib was the majority in the second line (n=18). And dasatinib was the only one indicated in the third line (n=8). Nilotinib was indicated at 600 mg/day; dasatinib at 100 mg/day. Imatinib doses were variable with an mean of 500 mg and limits from 300 mg-800 mg/day. In 29 patients, the imatinib indicated as an initial treatment was changed to a second-line TKI after an mean of 38 months (26 to 49 months). Nilotinib and dasatinib, indicated in first line, were only changed on one occasion, each one, at 9 and 10 months. The events that justified the change of inhibitor are found in Table 3.

The most frequent one was the lack of cytogenetic remission or its loss. The adverse effects of imatinib were diarrhea (30%), cytopenias (20%), edema (60%) and myalgias 20%; of dasatinib, jaundice (associated with ingestion of paracetamol) and pleural effusion, in three cases, steroid-controlled, diuretic and supportive measures, in one patient there was pleural and pericardial effusion requiring drainage and endopleural probe that resolved with adjustment of dose of dasatinib. It was only on one occasion that it was necessary to change the inhibitor, imatinib to nilotinib, due to persistent diarrhea.

The frequency of the different types of maximum remission obtained is found in Table 4. The months in which it was reached are also recorded, with 95% confidence intervals.

In four patients, no remission whatsoever was achieved; two of them died in 5 and 6 months, and the rest abandoned the treatment. Molecular remission was profound in 26 patients and major in 24. In 5 cases, this could not be evaluated due to insufficient treatment time with TKI (<6 months). The maximum remissions reached, with the different inhibitors, are found in Table 5.

Inhibitor	1st Line	2nd Line	3RD Line
Imatinib	65	0	0
Nilotinib	11	18	0
Dasatinib	6	13	8

Table 2: Tyrosine kinase inhibitors used in first, second, and third, lines.

Event	At 2nd Line	At 3rd Line
Without Hematological Remission	3	2
Without Cytogenetic Remission	13	3
Without Molecular Remission:	3	2
Loss of Cytogenetic Remission	3	1
Loss of Molecular Remission	7	0
Blastic Phase Progression	1	2
Toxicity	1	0

Table 3: Events that caused the change of inhibitor.

The final destination Table 5 includes 58 patients in chronic phase, and without any event. The PFS, recorded at the commencement of any TKI yielded a probability of 0.83 at 156 months of follow-up. It is

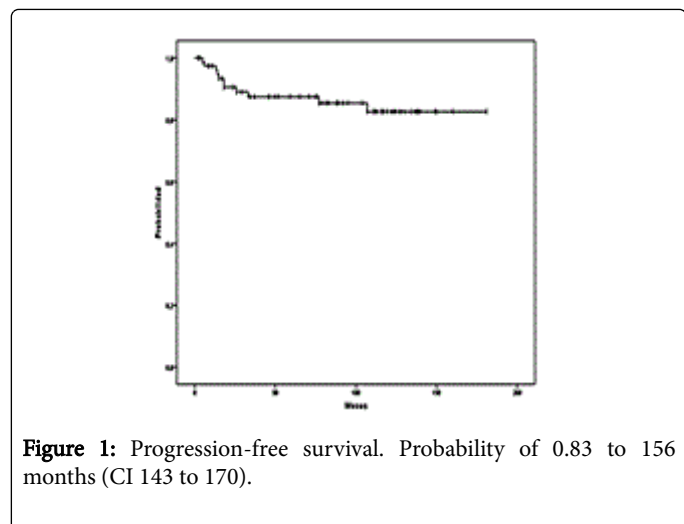
found in Figure 1. The OS, surveyed upon admission to treatment with QR, IFN or TKIs went from 0.92 to 191 months of follow-up, Figure 2.

Remission	N=	Months	CI at 95%
None	4	-	
Hematological	14	1.2	0.97 a 1.46
Cytogenetic	14	8.6	6.2 a 11.1
Molecular	50	16.5	12.9 a 20.2

Table 4: Maximum remission reached and months lapsed since commencement of the first TKI recorded at mean and confidence interval.

Destination	N=	%
Follow-up	58	70.7
Deaths	5	6.1
Eliminated	19	23.2
Abandoned	10	12.2
Comorbidities	5	6.2
HPC	4	5

Table 5: Final destination HPC Transplant of hematopoietic progenitor cells.

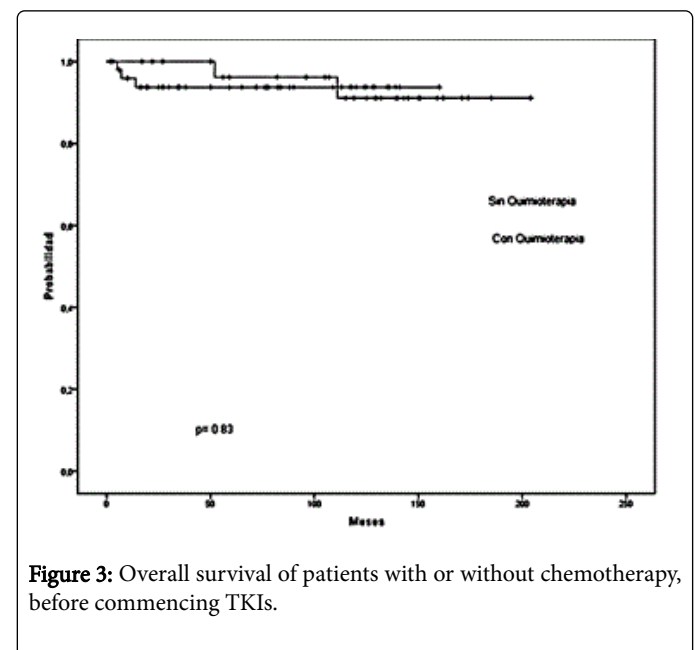
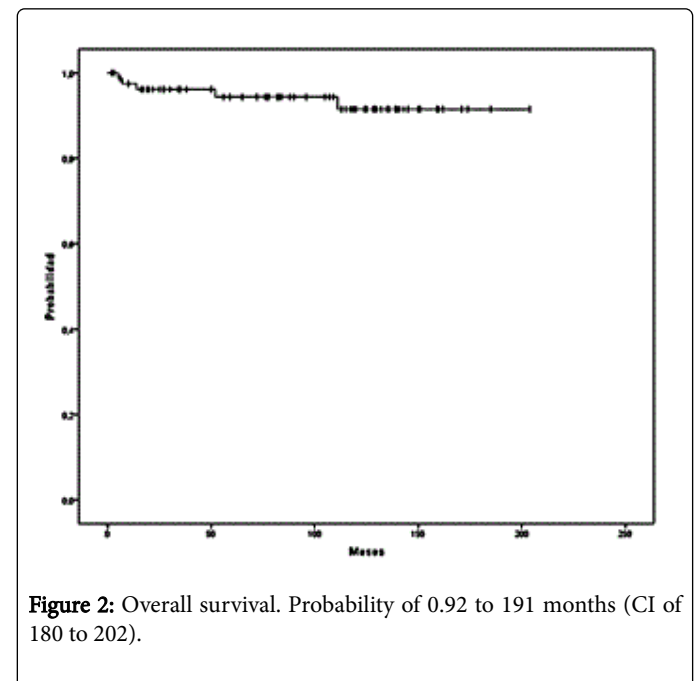


The OS of patients with or without CT and IFN, for more than two months after the diagnosis is found in Figure 3.

Nineteen (23%) patients who include four who moved on to HPC were eliminated. The remaining patients (18%) left, for personal or administrative reasons, or died from comorbidities.

Data with prognostic influence in the PFS were sought. In the multivariate analysis they had a negative prognostic value: patients in the blastic phase at its beginning had fewer favorable initial responses ($p=0.0001$); those who originally had to receive CT, with or without interferon, before starting a TKI had a greater frequency of progression to the blastic phase ($p=0.04$); the exclusively hematological response

was related to greater progression frequency (0.0001); no difference was found ($p=0.14$) in the progression frequency among those who reached cytogenetic or molecular remissions. The Sokal scale did not have a prognostic influence either ($p=0.49$).



Two patients had T3151. Dasatinib was indicated for both. Neither reached cytogenetic remission, and they are in the blastic phase at 15 and 18 months.

The variables with negative prognostic influence, with the multivariate analysis, in OS, were: the existence of initial fever ($p=0.02$); blastic or accelerated phase, in its debut ($p=0.001$); first solely hematological remission ($p=0.0001$); No difference in the efficacy of

the different TKIs was found regarding the frequency of maximum remissions reached ($p=0.07$).

Discussion

The age and gender of the population studied is not very different than the one reported by the WHO, although the mean of 44 years, in our study, is less than the 50 to 60 age limit stated by this organization in 2008 [17]. For the primary objectives of this revision, the lower age of our population does not seem to have an impact.

The first TKI available in Mexico was imatinib. It has been usable at our hospital since 2001. Until then, they were treated with hydrea, busulfan, or cytarabine + IFN. The first patients included were being managed with CT or IFN; some were admitted to the treatment with imatinib in the accelerated or blastic phase. These patients had an adverse prognosis and poor OS. Those who arrived at the chronic phase have had a OS comparable to the rest of the population. The profoundness of the remission was related to the time at which administration of TKI began, and only those who started it in the first six months reached molecular remission.

The patients who began receiving the TKI in the course of the first two months, since diagnosis, had a OS equal to those who delayed more than this time. In this study, there is no influence, in the OS, taking as an indicator the delay in administration of the inhibitors.

The sequential indication of the three available TKIs, in our universe, do not differ from the ones suggested in different spheres [18,19]. The causes for changes to second or third line were the lack of response and in only one case, toxicity. The prevalence of imatinib in the first line is not due to preference of imatinib, but rather its unique initial availability.

In this analysis, we do not find a significant difference between the three TKIs. The comparison, however, is biased because most of the initial patients received imatinib, and already in the second line, they were treated with nilotinib or dasatinib. In prospective studies, however, greater efficacy has been shown with nilotinib or dasatinib [8,19]. The practice of using TKIs sequentially, in relation to the response to the first or second line, has become more widespread, and is frequently recommended [18,19]. In our case, the lack of response was the most frequent condition. More than 6 months lapsed waiting for a suitable response. This is lengthy, particularly in the case of the transition from first to second line. This delay, in our cases, is related to the lack of second generation TKIs.

The efficacy of imatinib, in terms of PFS, was demonstrated in the IRIS study: at 18 months, the PFS was maintained at 97%; in the update to 5 years of follow-up, it was at 93% [20,21]. Recently, the last update shows a OS of 83%, at 11 years of follow-up M[22]. Second-line inhibitors, dasatinib and nilotinib, have proven comparable efficacy in terms of PFS and OS [23]. The results reported here, at more than 16 years of follow-up, do not veer from those proven in other studies, including those reported in a Mexican experience [24].

Cytogenic remissions, and particularly, the molecular remission, are determining factors of PFS and OS. In our cases, more than half had molecular remission, major or profound, with one or more of the inhibitors employed. These figures coincide with those of other reports [25,26]. However, the OS is not affected by the existence of cytogenetic or molecular remission.

The efficacy of nilotinib or dasatinib, after failure or toxicity to imatinib, as they were used in this study, has not shown substantial differences, although in some studies, there is a reduced advantage in efficacy and cost in favor of nilotinib [27].

Almost one-fourth of the patients were eliminated. Out of those, only four, this transitioned to HPC, which they did for medical reasons. The remaining patients died from a comorbidity or abandoned the study due to personal or administrative reasons. The high number of discarded patients, for reasons other than efficacy of the TKIs, affected the OS. Even so, it is greater than 80% at more than 16 years.

Since 2010, studies in which the TKI has been effectively suspended have appeared. One of the first, in patients with continuous molecular remission (levels not detectable from the transcript), who received imatinib (for more than two years), showed, over the course of the first 12 months, after the effective suspension, sustained molecular remission at 41% of the cases [28]. Those who relapsed entered a second molecular remission, after having restarted imatinib. These patients, who did not relapse, have been monitored during the 9 to 95 following months. At 60 months, the molecular relapse is 38%; in all, the recovery from molecular remission has been obtained with imatinib [29]. There are several similar experiences, with comparable results. In some, IFN alpha 2a has been employed in maintenance, after TKI was suspended, with results that seem to discreetly improve the ones obtained in the free IFN results [30]. This increase in efficacy must be associated with the disadvantage of the adverse effects of this protein and the consequent decrease in quality of life. The elective suspension has also been orchestrated with second generation TKIs (nilotinib and dasatinib), with results similar to those of imatinib [31]. After interrupting the TKI, it is necessary to frequently monitor PCR every three months (first year) and every six months afterward, until loss of response. It is possible that the frequency of the determinations is exaggerated and may be reduced [32].

Until now, there are several results of the prospective studies that leave behind several lessons: the patients with profound and sustained molecular remission are candidates of elective suspension; approximately 40% of them will be in remission at the end of one year of withdrawal from the TKI; those who relapse respond to the resumption of the inhibitor [33]. The elective suspension strategy continues to be experimental, and its use must be protocolized. Its current implications, in the clinical context, show indisputable financial benefits in view of the high cost of TKIs.

Before the introduction of TKIs, the prognostic data had an evident impact. The Sokal scale was necessary at that time to decide the therapeutic strategy. Currently, however, this scale only has prognostic value in patients who are taken to elective suspension of the TKI [29]. This scale had no prognostic relevance in our study. In the multivariate analysis, we find negative prognostic influence, in relation to the PFS and the OS, in more patients with progression in patients with fever, at their debut; more cases of resistance in those who received TKIs in the blastic phase; greater progress at the blastic phase in those who began receiving TKIs after being treated with CT/IFN; the lack of cytogenetic remission was associated with early progression; patients with the mutation T3151 had a clearly negative prognosis, without response to any TKI. This finding has been reported for several years [34,35].

Conclusions

The delay of the TKIs, after six months, in which they were treated with CT or IFN, is related to the impossibility of obtaining molecular remission. This delay, on the other hand, does not influence the duration of the OS. The use of TKIs is very efficacious in terms of OS and PFS, even if they are administered after the use of CT with or without IFN if they are in the chronic phase.

The sequential use of imatinib, nilotinib, and dasatinib is useful to obtain and maintain PFS and OS above 80% and 90%, at more than 16 years of follow-up, in the cases studied here, in spite of including patients with CT and IFN before the TKIs.

The patients with the mutation T3151 had a clearly negative prognosis without a response to the second generation TKIs.

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