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The treatment of chronic myeloid leukemia: A single-center, 20-year experience

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ABSTRACT

Background: Treatment of chronic myeloid leukemia (CML) Ph + has changed rapidly from chemotherapy to the use of inhibitors of tyrosine kinase, with progressively better results in terms of overall survival.

Objective: To analyze the results obtained with different types of treatment in patients with CML in the Hematology Department of Centro Médico Nacional 20 de Noviembre, Mexico City.

Material and method: An observational, longitudinal, retrospective, descriptive and comparative study was done with patients treated from 1990 to 2010, CML *of novo*, older than 15 years, both sexes. The clinical records were reviewed. Treatments were grouped into chemotherapy, busulfan or hydrea (CT), interferon (IFN), haematopoietic stem cell transplantation (HSCT), and inhibitors of tyrosine kinase (TKI).

Results: 206 patients were included and were submitted to: CT = 66, IFN = 42, HSCT = 35 (of them 8 were non-myeloablative), ITQ = 63. The greater likelihood of overall survival was achieved with ITQs and HSCT: 0.92 to 200 months and 0.52 to 250 months, respectively (p = 0.0001). Progression to phase accelerated or blastic were 4 and 2 (p = NS). Mortality was 9.5% and 48% (p = 0.001). The probability of overall survival with IFN or CT was less than 100 months.

Conclusion: TKIs are the best therapeutic option for Ph + CML. Without being curative, they allow long survivals with a commonly acceptable toxicity. The second option is HSCT which, although not universally applicable, is curative, with the inconvenience of a high morbidity-mortality. These findings are similar to the reported in other centers.

Key words: chronic myeloid leukemia, treatment, survival.

Tratamiento de la leucemia mieloide crónica: 20 años de experiencia en una sola institución

RESUMEN

Antecedentes: el tratamiento de la leucemia mieloide crónica Ph+ ha cambiado rápidamente de la quimioterapia, en el siglo pasado, a la actual administración de inhibidores de la tirosina cinasa. Los resultados han mejorado en términos de supervivencia global.

Objetivo: analizar los resultados obtenidos con diferentes tipos de tratamiento en pacientes con leucemia mieloide crónica Ph+, atendi-

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dos en el Servicio de Hematología del Centro Médico Nacional 20 de Noviembre, ISSSTE, en la Ciudad de México.

Material y método: estudio observacional, longitudinal, retrospectivo, descriptivo y comparativo de pacientes atendidos de 1990 hasta 2010, con leucemia mieloide crónica Ph+ *de novo*, mayores de 15 años, de cualquier sexo. Se revisaron los expedientes clínicos. Los tratamientos se agruparon en quimioterapia, busulfán o hidroxiurea, interferón (IFN); trasplante de células progenitoras hematopoyéticas e inhibidores de la tirosina cinasa: imatinib, nilotinib o dasatinib.

Resultados: se incluyeron 206 pacientes que recibieron los siguientes tratamientos: quimioterapia (n = 66), interferón (n = 42), trasplante de células progenitoras hematopoyéticas (n = 35, de ellos, ocho fueron no mieloablativos) e inhibidores de la tirosina cinasa (n = 63). La mayor probabilidad de supervivencia global se alcanzó con inhibidores de la tirosina cinasa y trasplante de células progenitoras hematopoyéticas, 0.92 a 200 meses y 0.52 a 250 meses (p = 0.0001). La progresión a fase acelerada o blástica fue 4 y 2 (p = NS). La mortalidad fue de 9.5 y 48% (p = 0.001). La probabilidad de supervivencia con interferón o quimioterapia fue menor de 100 meses.

Conclusión: los inhibidores de la tirosina cinasa son la mejor opción terapéutica contra la leucemia mieloide crónica Ph+. Sin ser curativos, permiten largas supervivencias con toxicidad comúnmente aceptable. La segunda opción es el trasplante de células progenitoras hematopoyéticas que, aunque no es universalmente aplicable, es curativo, con el inconveniente de causar morbilidad y mortalidad altas. Estos resultados son similares a los reportados en otros centros.

Palabras clave: leucemia mieloide crónica, tratamiento, supervivencia.

BACKGROUND

Ph+ chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm that originates in multipotent abnormal cells in the bone marrow and consistently associated with the fusion gene BCR-ABL 1, located in the Ph chromosome. It is characterized by increased proliferation of myeloid cells at all stages of maturation. It generally presents with anemia, splenomegaly, leukocytosis, increased granulocytes at different stages of maturation, basophilia, and thrombocytosis.[1,2]

It is a condition where reciprocal translocation t(9;22)(q34;q11.2) exists, commonly called Ph chromosome. Occasionally, in 5 to 10% of events, the abnormality is not observed in the karyotype but, by means of FISH or real-time PCR techniques, the existence of the fusion gene BCR-ABL 1 is established. In its natural history, three phases are identified: chronic, accelerated, and blastic, which is usually is the terminal stage.

Since 1865 arsenic products, prescribed as Fowler's solution, followed by radiotherapy, in 1913, busulfan in 1953, and hydroxyurea were used as therapeutic agents.[2] In fact, they were more useful to improve life quality rather than to extend it. However, the last two were the routine therapeutic management up to the end of the past century.[3,4] In randomized studies, hydroxyurea showed superiority in the duration of survival

compared to busulfan (58 *vs* 45 months).[5] Lower toxicity was an additional advantage for hydroxyurea. Since not all patients responded in the same manner to treatment, searching factors which would predict the duration of survival became more used: the Sokal score has been one of the most commonly used[6] and it is still useful even in the age of tyrosine kinase inhibitors (TKIs).

In 1987 the results[7] showing that interferon alpha (IFN) obtained hematologic remissions with decreased or disappearing Ph[1] chromosome presence, were published. The relationship between the disappearance of this chromosome and the increase of progression-free survival to advanced stages explains that, in the following years, interferon, frequently combined with cytarabine,[8] became the routine therapy when allogeneic hematopoietic stem cell transplantation (HSCT) was not possible. In patients who achieved complete cytogenetic remissions, survival could reach 10 years.[9] This therapeutic strategy would not be abandoned again: to obtain prolonged survivals it is necessary to control cytogenetic abnormality. A serious inconvenience of IFN was toxicity, which frequently caused dose discontinuation or reduction. In 1993 a study reported that patients received only 60% of the ideal dose to reduce adverse effects and achieve adherence.[10] Since 1990, IFN was frequently associated with low cytarabine doses. This was an alternative which leads to a survival of up to 70% at 5 years, but once again, toxicity limited its use.[4]

Hematopoietic stem cell transplant has been recognized as the only curative therapy for chronic myeloid leukaemia. Cells have been obtained from related, and unrelated donors, as well as from umbilical cord, and both myeloablative as well as non-myeloablative, also known as reduced-intensity, conditioning regimens have been used prior to the transplant. Excellent relapse-free survivals have been achieved, but with a low overall survival due to the increased mortality associated with the procedure. In 2006 a panel of the European LeukemiaNet[11] concluded that, if transplant is performed during the chronic phase of CML, progression-free survival at 5 years was approximately 50%. Compatible donor availability, co-morbidities, and the patient's age are some limits which constantly affect the possibility of the use of HSCT.

Understanding the role of abnormal BCR/ABL tyrosine kinase activity in the pathogenesis of CML, allowed finding compounds that inhibit its activity and interrupt those signals which control leukemic cell proliferation; they are known as tyrosine kinase inhibitors (TKIs). Imatinib mesylate showed a highly specific and high biochemical activity, with acceptable pharmacokinetic characteristics and a tolerable toxicity profile.[12,13] Several prospective, multicenter, and international studies[14,15] have compared it to IFN plus cytarabine. Both initial hematologic remission (95.3% and 55%) and major cytogenetic remission have been higher with imatinib (85% and 22%). This advantage has been confirmed in many other studies. In addition, adverse effects have been lower. However, up to a third of patients discontinue treatment due to intolerance, lack or loss of response.[16]

Other TKIs usually referred to as "second line" are now available. Nilotinib with a better binding to hybrid BCR/ABL results 20 times more potent and effective[17] and dasatinib is considered 320 times more potent than imatinib for binding to several sites of BCR/ABL, and has been suggested that it has activity against leukemic stem cells.[18,19]

Currently, TKIs are considered routine therapy for CML, although it is common to start with imatinib and move patients to second line TKIs in cases of loss of response, progression, or intolerance.[20]

Cytogenetic analysis is the backbone monitoring response to TKIs. Disappearance of Ph+ guarantees response and establishes the prognostic

patterns. A study with a higher precision and accuracy is real-time PCR measurement of the amount of transcripts of BCR/ABL.[21,22]

The purpose of this study is to compare the overall survival (OS) of patients with Ph+ CML with the different therapies which have been used in the Hematology Department of Mexico City's Centro Medico Nacional 20 de Noviembre, during the last twenty years.

MATERIAL AND METHOD

An observational, longitudinal, retrospective, and comparative study was done including patients attended to Hematology Department of CMN 20 de Noviembre, Mexico City, between 1990 and 2011, diagnosed as *de novo* Ph+ chronic myeloid leukemia, older than 15 years of age, both sexes, and who were included in any CML therapeutic program.

Diagnostic criteria was persistent leukocytosis, above 20 x 10^9/L, predominantly with granulocytes in several stages of maturation, increased serum lactate dehydrogenase (LDH), hypercellular bone marrow with abundant granulocytes, and existence of Ph+.

Patients whose clinical histories were incomplete or not available were not included and patients who discontinued treatment were eliminated.

The list of patients was obtained from the database of the Hematology Department. Data concentration sheets of each patient and their clinical records were reviewed. Additional cytogenetic abnormalities were recorded. Baseline and final phase of the disease were classified for each subject. All the used anti-leukemic therapeutic resources were recorded, including HSCT.

For purposes of the analysis, groups were formed according to therapeutic programs: chemotherapy (CT), IFN, HSCT, and TKIs. The final objective was to compare the overall survival reached with the various therapeutic programs. Numeric variables are expressed as media and real limits; nominals as percentage. Comparisons were performed with χ^2 test. For comparisons of numeric variables, ANOVA was used. Absolute risk and the odds ratio were estimated. Overall survival was measured with Kaplan Meier's method; log-rank was used for comparisons.

Therapeutic programs administered

Chemotherapy (CT): busulfan, 0.25 mg/kg, orally until obtaining a 50% decrease of leukocytes; then dose reduction up to 50% until hematologic remission. It was re-started for relapses. Hydroxyurea, 50 mg/kg, orally, until obtaining a 50% decrease of leukocytes; it was continued according to the previous criterion.

Alfa-interferon (IFN): 5,000,000 IU/day, subcutaneously. It was associated with hydroxyurea according to the above-mentioned dosage.

Hemopoietic stem cell transplant (HSCT): In all cases from a related donor. Myeloablative conditioning done with busulfan and cyclophosphamide, and non-myeloablative (NMA) regimen consisted of busulfan and fludarabine.

Tyrosine kinase inhibitors (**TKI)**: imatinib mesylate, 400 mg to 600 mg daily, orally. Nilotinib, 600 mg daily, orally. Dasatinib, 140 mg daily, orally.

Definitions

Chronic phase. Presence of the disease, in absence of abnormalities observed at accelerated and blast phases.

Accelerated phase. Any of the following: 10% to 15% of blast cells in blood or bone marrow; basophilia 19%; platelets < 100 x 10^9/L or > 1,000

x 10^9/L; splenomegaly or persistent leukocytosis refractory to treatment; cytogenetic evidence of clonal progression.

Blastic phase. Any of the following: blast cells >19% in blood or bone marrow; blast cells in extra-myeloid infiltrations; accumulation of blast cells in bone marrow.

Hematologic remission. Normal complete blood count, basophils < 5%; platelets < 450 x 10^9/L; no palpable spleen.

Cytogenetic remission: major: 1% to 35% Ph+ metaphases. Complete cytogenetic remission (CCR): no Ph+ metaphases.

Molecular remission: major (MMR): with < 0.1% BCR-ABL1. Profound: < 0.01% BCR-ABL1.

RESULTS

We included 206 patients. Ages ranged from 15 to 86 years. The most common clinical data at diagnosis were splenomegaly, hepatomegaly and weight loss. The most frequent visceromegaly was splenomegaly up to 30 cm. The lowest value of hematocrit (Ht) was 11%; leukocytes ranged from 20 x 10^9/L to 980 x 10^9/L. Platelet count was from 12 x 10^9/L to 3,324 x 10^9/L. Ninety-eight patients (47.8%) had initial blast cells in blood, ranging from 1% to 90%. Demographical data are shown on Table 1.

Nine cytogenetic abnormalities different to Ph+ were recorded: one del(7q)(q15), one del(7)(q22), one double Ph+, one hypotriploidia, one inv(17), one t(11;19), two t(13;14) and one 48,XXYY.

Patients with del(7)(q15), double Ph+, XXYY and inv(19) were treated in the CT group; the first three died: two due to leukemic activity, and the remaining due to co-morbidity; another one withdrew from treatment in the chronic phase. Events occurred at 1, 13, 3, and 15 months. Patients with t(13;14), t(11;19), del(7)(q22), and hypotriploidia were managed with IFN; the first three died due to activity; the fourth one withdrew from treatment in the chronic phase; events occurred at 81, 12, 20 and 20 months. The patient with inv(17) received imatinib and died due to activity at 43 months. The second patient with t(13;14) received HSCT and cytogenetic remission which is maintained at +172 months. Patients with chromosomal abnormalities other than Ph+ had non-significant decrease in less overall survival (p= 0.80).

Table 1. Demographical data for complete population

Data	Number (%)	Mean	Limits
Sex (female)	101 (49)	-	-
Age (years)	-	43	15-86
Weight loss (kg)	75 (37)	7	2-22
Hepatomegaly (cm)	84 (41)	4	2-20
Splenomegaly (cm)	146 (71)	11	2-30
Hematocrit (%)	-	34	11-57
Leukocytes (x 10^9/L)	-	198	36-999
Neutrophils (%)	-	82	40-97
Intermediate (%)	-	6	0-55
Blasts (%)	98 (48)	3	0-90
Platelets (X 10^9/L)	-	544	10-3,324

According to the Sokal prognostic score for our complete group, patients were almost equally distributed: low risk in 38%, intermediate in 32%, and high in 30%. In our group, Sokal prognostic score did not show a prognostic influence in any of the four cohorts (p> 0.31).

When the disease was diagnosed, 192 patients were in chronic phase and 14 were in blastic phase; there was no distribution difference among the four groups (p= 0.36).

The type of treatment was related with the time of management: Up to the year 2000, CT, IFN, and HSCT were used. Starting in 2001, TKI

were started. Distribution of patients among the four therapeutic groups was: CT 66, IFN 40, HSCT 35 (from which 8 were NMA), and TKI 64. Patients who entered into HSCT were all in chronic phase.

Twelve patients treated with CT were switched to TKI due to progression to accelerated phase after 7 to 84 months of starting treatment. From the IFN group, another 12 patients were transferred to TKI after 7 to 75 months.

In the TKI cohort 59 patients started with imatinib and 5 with nilotinib. At the date of this analysis 42 continued with imatinib, 13 with dasatinib and 9 with nilotinib. Switching was due to intolerance, lack of cytogenetic remission, or loss of response. Therapeutic results, including remission magnitude, can be found on Table 2.

The disease showed progression to accelerated or blast phase in most of patients who received CT or IFN. Less than 10% occurred in those who received HSCT or TKI (Table 2). Status of patients at this analysis is found in Table 3. Patients appearing as eliminated in the CT or IFN cohorts, correspond to withdrawals or switches to the TKI group.

Table 2. Therapeutic results according to the maximum remission achieved (p = 0.0001) and progression to an advanced phase (p = 0.001)

Result	CT (%)	IFN (%)	HSCT (%)	TIK (%)
Without remission	26	3	0	5
HR	74	98	51	92
CCR	0	2	49	59
MMR	0	0	17	33
Without progression	39*	43*	94	93
AP	17	14	3	2
BP	44	43	3	5

HR: hematologic remission; CCR: complete cytogenetic remission; MMR: major molecular remission; AP: progression to accelerated phase; BP: progression to blastic phase; CT: chemotherapy; IFN: interferon; HSCT: allogeneic hematopoietic stem cell transplant; TIK: tyrosine kinase inhibitors. * switched to HSCT or TKI.

Table 3. Results by therapeutic group (p = 0.0001)

Treatment	N	Alive (%)	Death (%)	Eliminated (%)
Chemotherapy	66	0	58	42
Interferon	42	14	57	29
HSCT	35	44	50	6
TKI	63	84	10	6

HSCT: hematopoietic stem cells transplant; TKI: tyrosine kinase inhibitors.

In the group that received CT or IFN the most common cause of death was leukemic progression (41% and 55%, respectively). In patients receiving HSCT the most common cause of death was graft-*versus*-host disease (GVHD) with 32%. Those treated with TKI died due to activity or comorbidity (5% each). Table 4

The major toxicity in the CT group was grade 1 to 4 cytopenias in 68% of cases. In the IFN group only one patient did not show toxicity; in the remaining fatigue (80%), fever (85%), and myalgias (70%) were predominant toxicities. More than 50% of patients in this group had temporary dose reductions. All patients who received HSCT had one or more of the following toxicities: cytopenia-related infection and bleeding, secondary to the conditioning regimen, immunosuppression and GVHD. Those who received imatinib experienced diarrhea (30%), cytopenias (20%), edema (60%), and myalgias 20%; in 5 cases it

Table 4. Death causes, numbers (p = 0.0001)

Cause	CT	IFN	HSCT	TKI
Activity	27	22	1	4
Toxicity	8	0	3	0
GVHD	0	0	11	0
Comorbidity	3	1	2	3
Total	38	23	17	7

CT: chemotherapy; IFN: interferon; HSCT: hematopoietic stem cell transplant; TKI: tyrosine kinase inhibitors; GVHD: graft-*versus*-host disease.

was necessary to switch to another TKI due to toxicity. No toxicity has been found in those who received nilotinib or dasatinib.

Using the CT and IFN groups as control groups, the absolute risk reduction for patients who received a HSCT is 10% and for those who received TKI is 43.8%. The odds ratio is 0.75 and 0.07, respectively. Kaplan Meier curve is shown on Figure 1.

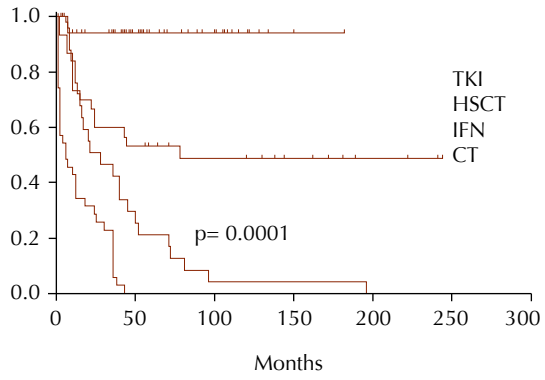

Figure 1. Overall survival per group.
TKI: tyrosine kinase inhibitors; HSCT: hematopoietic stem cell transplant; IFN: interferon; CT: chemotherapy.

DISCUSSION

CML is one of the few neoplastic diseases where the discovery and understanding of its molecular abnormalities has allowed obtaining a very significant impact on the overall survival with a possibility of cure.

Up to the year 2000 the chances of achieving 8-year survival were very slim, except for patients who survived to an allogeneic transplant. Comparable findings are found in a 1997 publication from the MD Anderson.[23]

In our experience, there was little difference in the efficacy between busulfan and/or hydroxyurea. These findings were well known years ago, and the use of hydroxyurea was preferred due to lower toxicity as well as easier dosing. In absence of other therapies, it was considered the standard drug for CML.[24]

Although the first cytogenetic responses were found with the use of interferon, they were seldom complete. In 1996, our group published a comparative study of busulfan *versus* IFN in which the overall survival doubled for IFN patients compared to the busulfan arm, with almost no cases of cytogenetic remissions.[25] Although the magnitude and frequency of cytogenetic remissions with different treatments was a subject of controversies, in a 1999 systematic review[26] results ranged from 0% to 38% and although this was an enormous variability, IFN was clearly the first compound that allowed to clearly correlate the decrease or disappearance of Ph+ chromosome with the duration of survival.

Sokal's[6] well-known prognostic score in the CT era and is still useful, even in the age of TKIs. In our patients, the score's discrimination capacity was not observed, probably due to our small numbers: in the referred study,[6] 813 patients were analyzed.

Cytogenetic abnormalities additional to Ph+ were found in 5% of patients; finding comparable to a recent publication.[27] Although additional cytogenetic abnormalities are deemed of bad prognosis, their exact impact has not been fully determined. The European LeukemiaNet suggests considering them a poor prognosis indicator. In an analysis of 378 *de novo* patients with Ph+ CML, additional abnormalities were found in 5.6%; their OS was lower, although the difference was not significant.[27]

In our patients the efficacy of HSCT was significantly superior when compared to that of CT

and IFN, this finding is similar to other reports.[28] Our patients treated with transplant in chronic phase have follow-up up to 17 years, and only 6 experienced relapse; all of them before six years of the procedure; the remaining maintain cytogenetic remission with 49% being alive after 8 years. Results are consistent with the opinion of a panel of the American Society of Hematology,[29] where it was concluded that, if transplant occurs in chronic phase, progression is approximately 50%. In a Mexican publication[30] an OS of 55% was reported at 3-year follow-up. Stabilization of survival curve after 8 years has been reported in other studies,[31] evidence of the curative possibility of HSCT. Currently the indication of the transplant is relatively well defined: without access to TKI, intolerance or lack of efficacy of these drugs.[32]

In a recent publication of the EBMT,[33] it was found that up to 30% of patients with transplant died as consequence of the procedure, in a series of more than 10,000 events from 592 hospital centers. These results confirm the high morbidity-mortality, particularly in the first one hundred days post-transplant. They represent the high cost of their efficacy. One alternative is to use conditioning regimens that do not eliminate all myeloid tissue cells. Chemotherapy or radiotherapy programs known as programs of reduced intensity (RIR)[34] NMA. These conditioning regimens offer a lower toxicity and morbidity-mortality, but their efficacy is lower to that of myeloablative transplant. In a multicenter report,[35] with 186 patients who received HSCT of reduced intensity an OS of 58% was found at 3 year follow-up; mortality was only 23% at two years. In a recent article, efficacy of RIR and NMA[36] is compared; only in patients older than 60, was an advantage found in receiving RIR. However, The Latin-American group, LACOHG, published results[37] on 25 patients on a low-intensity regimen; all patients were in a chronic phase. The probability of total survival at 830 days was 92% and mortality was 8%.

Our experience clearly shows that TKIs represent the best option for CML patients. Overall survival at 200 months almost doubles that achieved with HSCT. Although only a third of the patients who received TKIs achieved MMR, and nearly 60% reached CCR, less than 10% have progressed. These data are accompanied by a tolerable toxicity and a better life quality, when compared to those who received HSCT.

In our group, most TKI experience was with imatinib. As second-line inhibitors have been available, several patients have been switched to nilotinib or dasatinib.

In several papers results with TKIs are similar to our findings. Since the IRIS study,[14] it has been known that imatinib produces CTG responses of 70% and MMR of 24%, with an OS of 85% at 8 years. Since these results, imatinib became the routine therapy for CML.

Shortly after nilotinib[38] and dasatinib[39] appeared; both with higher potency than imatinib. These so called "second generation TKIs" were initially used after resistance or intolerance to imatinib. In recent years, numerous reports showed the superiority of both to induce quicker and deeper cytogenetic and molecular responses compared with imatinib.[40] Although their use is now common in *de novo* patients, in our study, they were not used in this setting.

We believe that in the near future TKIs will still be considered the backbone of CML management. Their combination with other drugs, such as pegylated interferon and cytarabine, is an option that could offer higher efficacy without an unacceptable increase of toxicity. Surely, third-generation inhibitors may come and the chance that they could eliminate Ph+ stem cells is an event that would allow the cure of this type of leukemia. However, the high cost of the available TKIs is a limitation for use. According

to a recent opinion of 119 experts,[41] the price of these drugs makes it impossible to use in all patients and generates great economic difficulties in governmental health systems.

CONCLUSION

Tyrosine kinase inhibitors are the best therapeutic option for Ph+ CML. Without being curative, they allow long survivals with a commonly tolerable toxicity. The second option is HSCT that, although not universally applicable, is curative, with the inconvenience of a high morbidity-mortality.

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