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Overall survival of chronic myeloid leukemia patients treated with related donor hematopoietic stem cell transplant or imatinib

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ABSTRACT

Objective. To determine the overall survival (OS) of Ph[1] positive chronic myeloid leukemia (CML) patients treated with allogeneic hematopoietic stem cell transplant (AHSCT) vs. imatinib. Material and methods. We retrospectively included CML patients treated with related donor myeolablative and non-myeloablative AHSCT, between 1992 and 2009. Another group consisted of a patient cohort treated with imatinib between 2001 and 2009. The main variable was the persistence of hematologic remission. Results. The AHSCT/imatinib groups included 36/46 patients, average age was 36/46, patients in chronic phase 34/44 and in blastic phase, 2/2. The number of myeloablative/non-myeloablative transplants was 28/8. Imatinib was administered at a dose of 400 to 800 mg/day (median 500 mg). The following events developed in both groups: death 14/3, hematological progression 4/5, 17/41 are alive and in hematological remission (p = 0.00009). The OS probability is 0.42 and 0.76 at 100 months (p = 0.0001). The decrease in absolute risk is 42%. The OS after 17 years remains unmodified in the AHSCT group after the first 6 years. Conclusion. OS at 100 months is superior with imatinib than with AHSCT (p = 0.0001).

Key words. Chronic myeloid leukemia. Allogeneic hematopoietic stem cell transplant. Bone marrow transplant. Imatinib.

Supervivencia global en pacientes con leucemia crónica mieloide, tratados con trasplante de células progenitoras hematopoyéticas de donador relacionado o con imatinib

RESUMEN

Objetivo. Conocer la supervivencia global (SG) en pacientes con leucemia crónica mieloide Ph[1] positivo (LCM), tratados con trasplante alogénico de células progenitoras hematopoyéticas (TACPH) y de quienes recibieron imatinib. Material y métodos. Se incluyeron de manera retrospectiva a enfermos con LCM que recibieron TACPH (mieloablativo y no-mieloablativo) de donador relacionado entre 1992 a 2009. Otro grupo fue una cohorte de pacientes tratados con imatinib entre 2001 a 2009. La variable principal fue la persistencia de remisión hematológica. Resultados. Los grupos de TACPH/imatinib fueron de 36/46 pacientes. La edad promedio de 36/46 años; en fase crónica 34/44; en fase blástica 2/2. La cantidad de trasplantes mieloablativos/no-mieloablativos fue de 28/8. El imatinib se usó en dosis de 400 a 800 mg/día (media 500 mg). Los eventos en ambos grupos: defunciones 14/3; progresión hematológica 4/5; vivos y en remisión hematológica continua 17/41 (p = 0.00009). La probabilidad de SG fue de 0.42 y 0.76 a 100 meses (p = 0.0001). La reducción de riesgo absoluto fue de 42%. La SG a 17 años no se modificó en el grupo con TACPH después de los seis años iniciales. Conclusión. La SG a 100 meses, fue superior con imatinib que con TACPH (p = 0.0001).

Palabras clave. Leucemia mieloide crónica. Trasplante alogénico de células hematopoyéticas progenitoras. Trasplante de médula ósea. Imatinib.

INTRODUCTION

The initial descriptions of cases suggesting chronic myeloid leukemia (CML) appeared in the XIXth century (Velpeau, Donné, Bennet, Creigie and Virchow).[1] In 1865, arsenicals prescribed as Fowler's liqueur, radiation therapy in 1913 and busulphan in 1953 were used as therapeutic modalities.[2] They ac-

tually were more useful in improving the patient's quality of life than in prolonging it. Hydroxyurea was more helpful in that sense. The characteristic cytogenetic abnormality[3] initially known as the Philadelphia chromosome (Ph^1), was described in 1960; it was later analyzed and defined as a t(9;22)(q34;q11) translocation leading to the formation of an abnormal gene, BCR-ABL and hence, an abnormal tyrosine-kinase (TK).

The longest survivals were achieved with allogeneic hematopoietic stem cell transplants (AHSCT). In 1988, data was published[4] suggesting that interferon alpha could induce hematological remission with an associated decrease or even disappearance of the Ph^1 chromosome. The link between the chromosome's disappearance and an extended survival free of progression into advanced phases, led to the use of interferon as routine therapy if AHSCT was not an option. Its use defined a therapeutic strategic modality that would never be abandoned: in order to obtain prolonged survival it was necessary to control the cytogenetic abnormality.

Our understanding of TK's role, a product of the BCR-ABL gene, in CML pathogenesis allowed the discovery of factors that inhibit its activity and interrupt the signals controlling proliferation of leukemic cells; they are known as tyrosine-kinase inhibitors (TKI). Imatinib mesylate proved to have high biochemical activity and specificity, acceptable pharmacokinetics and a tolerable toxicity profile.[5,6]

Treatment with imatinib and other TKI has become routine and led to changes in the general management of CML patients. Our goals are now different since therapeutic options have changed. This new savoir-faire is reflected in the publication of new guidelines that simplify this approach.[7,8] It is now acceptable to initiate therapy with imatinib and choose other options (AHSCT or other TKI) in case of treatment failure, a sub-optimal response or loss of response, including the appearance of mutations. The evaluated response variables are hematologic, cytogenetic and molecular. Molecular monitoring with real-time polymerase chain reaction (RT-PCR) should be emphasized. Full knowledge of the molecular response's magnitude is necessary because in spite of a complete cytogenetic response, the amount of remaining transcripts precludes the hypothetical eradication of leukemic cells.[9] This goal however, is difficult to achieve since with current technology, a maximum molecular response is accepted with transcript numbers of 0.0001 and perhaps less.[9]

There are currently no solid reports of possible cures with imatinib if the molecular response is complete and sustained. Evidence suggests that in this case, imatinib should be administered indefinitely. Cytogenetic and molecular remissions are undoubtedly of prognostic significance and lead to hematological remissions in the long-term, but TKI administration must be maintained. On the other hand, an incomplete response suggests the need to switch TKI or proceed to an AHSCT if possible. This last option appears to currently be the only curative approach to CML.

In our hospital, as in most of our country's hospitals, we do not have routine access to RT-PCR; hence, molecular follow-up is occasional. We rely on imatinib and AHSCT as therapy and recently, nilotinib and dasatinib have been added to the arsenal.

Once hematologic remission with imatinib has been achieved and has directly affected the patient's quality of life, we considered it pertinent to determine its duration, regardless of the cytogenetic and molecular response.

OBJECTIVE

The prime objective of this study is to determine overall survival (OS) without progression into an accelerated or blastic phase in CML patients treated with imatinib or AHSCT.

MATERIAL AND METHODS

This is a retrospective, comparative, and longitudinal study. Data were obtained by reviewing patient clinical charts. Patients with Ph^1 CML were included regardless of their age and gender, in chronic, accelerated or blastic phases. Ph^1 was determined by karyotype or non-quantitative polymerase chain reaction (PCR). Patients unable to be treated with imatinib or a transplant were excluded. All subjects signed a consent form agreeing to undergo the offered therapeutic option. Patients refusing to continue treatment or with an incomplete chart were excluded from the study.

From 1992 through 2009, one group underwent AHSCT. All grafts were obtained from a live related donor. Histocompatibility was determined by PCR; conditioning was myeloablative or non-myeloablative. The maximum accepted age for myeloablation was 45. Conditioning was performed with busulphan 1 mg/kg every 6 hrs (16 doses) and cyclophosphamide, 120 mg/kg IV, divided in two doses. The maximum accepted age for non-myeloablative therapy was 65; conditioning was achieved with busulphan, 10 mg/m^2 PO, divided over a three-day period and

fludarabine 150 mg/m^2 IV, divided over a five-day period. Another group was treated with imatinib.

Hematologic response monitoring was conducted every two months. Cytogenetic response monitoring was conducted every three months by PCR and karyotype. A cytogenetic response was dependent on the absence of Ph[1] in the karyotype (in 20 or more metaphases) and a negative PCR.

Definition of terms

- Accelerated Phase.
  - Blasts, 10 to 19% in blood or bone marrow.
  - Basophils in blood, ≥ 20%.
  - Persistent thrombocytopenia < 100 x 10^9/L (unrelated to treatment).
  - Thrombocytosis > 1,000 x 10^9/L unresponsive to treatment.
  - Splenomegaly and progressive leukocytosis, unresponsive to treatment.
  - Cytogenetic evidence of clonal expansion.

- Blastic phase.
  - Blasts, > 19% in blood or bone marrow.
  - Extra-medullary blast infiltration.
  - Large blast accumulations in bone marrow biopsy.

- Hematologic remission: normal platelets < 450 x 10^9/L; leukocytes < 10 x 10^9/L without immature granulocytes and < 5% basophils; no splenomegaly.

Statistical analysis

Fisher's exact test was used when applying χ^2. Comparison between averages was established by ANOVA or Kruskal-Wallis' test with a significance level of $p < 0.05$. PFS was calculated with Kaplan's method.

RESULTS

The number of patients studied was 82. The AHSCT group included 36 patients and the imatinib group included 46. Relevant initial data at diagnosis are shown in table 1. Findings are comparable in both groups. The largest spleens measured 20 and 30 cm; the largest livers, 10 and 15 cm.

Average age in the AHSCT group was 30 and included 20 males and 16 females. The number of months to transplant from diagnosis was 14 (median) and ranged from 2 to 58 months. Two patients were transplanted during blastic phase and the rest were in chronic phase. Treatment before the procedure was based on chemotherapy (busulphan, hydroxyurea or cytarabine) in 33 patients; 30 also received interferon and 5 received imatinib, with no cytogenetic response. There were 28/8 myeloablative/non-myeloablative trans-

Table 1. Base values at diagnosis (p = NS).

Variable	Imatinib	AHSCT
Fem/Male	23/23	16/20
Median age (range)	46 (15-72)	36 (5-56)
Splenomegaly (n)	35	29
Liver (n)	11	17
Leukocytes (x 10^9/L)	192 (20-650)	250 (28-509)
Blasts (%)	3.6 (0-90)	3 (0-14)
Platelets (x 10^9/L)	497 (75-1,650)	450 (79-1,000)

Table 2. Results of treatment with imatinib (IMA) and allogeneic stem cell transplant (AHSCT).

Variable	IMA	AHSCT	P
In hematologic remission*	41	17	0.00009
In cytogenetic remission	28	17	0.001
Failure	2	0	0.31
Progression	3	5	0.10
Deaths	3	14	0.0009

* Decrease in absolute risk = 42%. Odds ratio = 0.11.

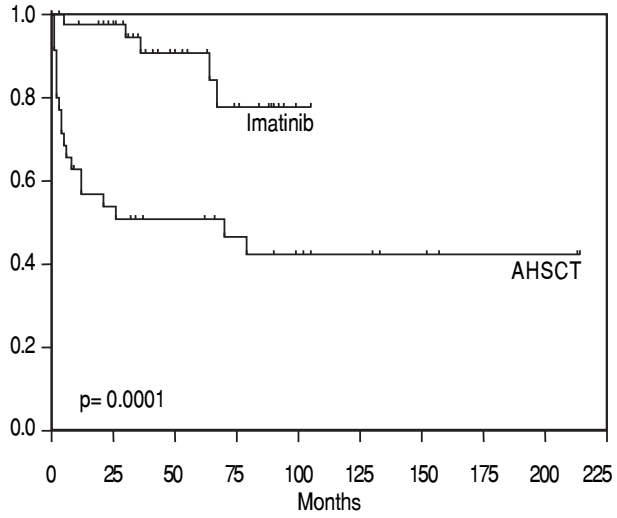

Figure 1. *Probability of overall survival if in hematologic remission.*

plants, all obtained from related donors. Stem cells were obtained from bone marrow or peripheral blood (14/22).

Patients treated with imatinib included 23 males and 23 females. The drug was begun within one month of diagnosis in 36 cases. The other 10 patients were treated within 4 months (median) but ranged from 1 to 83 months. This delay was due to lack of imatinib availability. Pre-transplant therapy was also chemotherapy-based (busulphan, hydroxyurea or cytarabine) in 34 cases; interferon was added in 14 patients. Upon imatinib administration, 44 subjects were in chronic phase and 2 were in blastic phase. The administered dose was 400 to 800 mg/day (median 500 mg).

AHSCT patients' course was as follows: the transplant was performed on day 18 (range: 10 to 28); 29 had fever and neutropenia; 19 developed acute graft *vs.* host disease; the chronic variety developed in 6; there were 2 cases of veno-occlusive disease and 2 other cases did not engraft. There were no differences in the frequency of remissions or deaths in patients that underwent a non-myeloablative transplant ($p = 0.57$).

The following events developed in patients treated with imatinib: hematological remission was achieved in 44 patients and complete cytogenetic remission was demonstrated in 28. The disease progressed in 5 patients, one into an accelerated phase and four into a blastic phase; none went into cytogenetic remission.

Results analysis (Table 2) shows a larger number of patients alive and in hematological remission after treatment with imatinib ($p = 0.00009$), a 42% decrease in absolute risk and an odds ratio of 0.11. The number of deaths is 4 times higher in the AHSCT group ($p = 0.0009$). Among transplanted patients remaining in hematological remission, there is a higher proportion of associated cytogenetic remissions ($p = 0.001$).

OS at 100 months (Figure 1) favors the group on imatinib ($p = 0.0001$). After 6 years, transplanted patients have shown no disease progression. After 17 years since this program's inception, patients show an OS probability, free of disease progression and in cytogenetic remission, of 0.43.

DISCUSSION

The patients herewith presented are comparable in terms of their clinical characteristics at diagnosis. In all cases, routine drugs at the time such as interferon with or without cytarabine were used before imatinib or transplant. Said treatment induced no remissions. In both groups, most patients were in a chronic phase when transplanted or beginning imatinib therapy. Statistical results strongly favor the group on imatinib after an 8 year follow-up. Several transplanted patients have been followed for up to 17 years. Although OS is superior with imatinib, some facts should be emphasized. After the first 6 years of follow-up of transplanted patients, no progression has been detected and all are in cytogenetic remission. This suggests superior efficacy of AHSCT. However, a high mortality (39% in our study) is a major drawback. Perhaps, non-myeloablative transplants may decrease complications and still remain effective, but in our small number of patients, this was not the case. Our results in terms of myeloablative AHSCT do not differ greatly from other studies. A Mexican publication[10] reported an OS of 55% and a mortality of 31% after a three year follow-up of 45 CML patients. Although their OS is superior to ours, follow-up was only for 3 years.

A panel of the American Society of Hematology[8] concluded that if patients are transplanted during the chronic phase of the disease, progression-free survival (PFS) is approximately 50% after 5 years. In 2005, the results of a study of 102 transplanted patients in one center and followed for 15 years, were published;[11] their OS was 53% with a relapse rate of 8% and a mortality of 46%. The curve tended to plateau approximately after 10 years. The results of the EBMT[12] published in 2006, and that included 13 416 CML patients transplanted in 592 centers between 1980 and 2003, showed an OS probability of 34% and a mortality of 41% (in those transplanted before

1990) that decreased to 30% after that year. This is apparently the largest cohort followed for the longest period of time that has been reported. With results obtained from over 500 centers, this report confirms the effectiveness of transplants that according to their data, clearly benefits over a third of the patients in spite of a still significant mortality.

Non-myeloablative AHSCT has decreased morbidity and mortality. The Latin-American group, LACOHG, published results[13] 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%. A few years before, the results obtained by a German group[14] on CML patients in chronic, accelerated and blastic phases were reported. Overall survival was superior in patients in chronic phase (55% at 25 months) and relapses were most common in advanced stages ($p = 0.01$). An EBMT[15] multi-center study included 186 patients in chronic, accelerated and blastic phases. Overall survival and progression-free survival at three years were 58 and 37%; mortality at two years was 23%. As in the previous study,[14] results worsen in advanced stages. According to European guidelines,[8] low-intensity transplants are recommended for some patients, particularly the elderly; but its long-term impact remains unknown.

A recent Mexican publication[16] on non-myeloablative transplants shed interesting results: 50 patients treated with imatinib and 22 patients treated with non-myeloablative transplant were compared. After a 6 year follow-up, OS were 84 and 77%, respectively ($p = NS$). Transplant-associated mortality was 18%. Although these morbidity and mortality rates persist, this transplant modality may become the preferred option as opposed to allogeneic myeloablative transplant.

Our results on patients treated with imatinib do not differ significantly from those reported by others. The drug's effectiveness is well established. Since the IRIS study, it has proven superior to interferon and cytarabine combinations. PFS is 97%.[8] Patient tolerance and quality of life is also superior when compared to interferon.[17] Long-term responses depend on various factors such a timing of drug initiation, initial prognostic markers,[18] dosage, treatment adherence, tolerance, response (hematologic, cytogenetic and molecular) and development of mutations. In a recent study[19] of 454 patients followed for 6 months, PFS was 61%, overall survival was 76% and complete molecular remission was 57%. A prospective, comparative study on 476 patients[20] followed for one year, compared imatinib doses, 400 mg *vs.* 800 mg/day; its purpose was to determine the frequency of molecular remission, resulting in 40% with 400 mg and 46% with 800 mg ($p = 0.34$).

Upon administering imatinib, it is essential to establish a clear initial diagnosis as well as a strict hematologic, cytogenetic and molecular follow-up[7,8,21,22] as determined in current guidelines. Its prognostic implications and indications for eventual therapeutic modifications to other TKI or AHSCT are well-known. Chilean and Colombian guidelines follow the same principles.[23,24] In light of the results herewith presented, we share the same point of view.

There are cost-analysis studies comparing transplants *vs.* imatinib. A recent systematic review[25] compared both treatment options. In the case of transplants (allogeneic, non-related donor), the frequency and duration of remission (hematologic and cytogenetic) and the mortality associated to the procedure were evaluated. Frequency and duration of remission (hematologic, cytogenetic and molecular) and toxicity were evaluated in cases treated with imatinib. Medical and laboratory expenses, hospitalization, drugs, blood products and other variables are analyzed. They concluded that in two years, the probability of PFS was 0.44 with a transplant and 0.91 with the use of imatinib. These calculations are applicable in the United States. These cost results cannot, of course, be extrapolated to our country where supplies are highly priced but salaries are low.

CONCLUSION

PFS at 100 months is superior with imatinib than with AHSCT ($p = 0.00009$). The difference is determined by the high mortality associated to the transplant procedure. After 6 years, no disease progression and persistent cytogenetic remission has been established in patients surviving the transplant.

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