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Treatment of Ph1-positive chronic myelogenous leukemia in children: comparison between allogeneic bone marrow transplantation and conventional chemotherapy

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Abstract

Background and Objective. **To compare the estimated survival and disease-free survival between children with Ph1-positive chronic myeloid leukemia treated with allogeneic bone marrow transplantation or conventional chemotherapy.**

Design and Methods. **In this retrospective study we compared the results obtained in a group of 14 children who received allogeneic bone marrow transplantation (BMT) between 1983 and 1993, and another group of 27 children treated with busulfan, hydroxyurea or α-interferon during the same time period. Patients were transplanted at a median of 7 months from diagnosis and all except one were in their first chronic phase. Conditioning consisted in total body irradiation and cyclophosphamide in 12 cases, and busulfan was added in two.**

Results. **Of the 14 patients treated with BMT, two died of transplant-related complications and two relapsed 18 and 48 months after the BMT. Ten children remain alive and disease free at a median follow up of 60 months. The probability of DFS at 5 years is 70%. Of the 27 patients treated with chemotherapy, 22 have died at a median of 36 months from diagnosis. The probability of survival at 5 years is 5% versus 83% for the BMT group (p = 0.001).**

Interpretation and Conclusions. **Allogeneic BMT is a safe and very effective treatment for Ph-positive CML in children. Patients who have an HLA-identical sibling donor must receive a transplant as soon as possible after being diagnosed.**

Key words: chronic myeloid leukemia, children, bone marrow transplantation, chemotherapy

Ph1-positive chronic myelogenous leukemia (CML) is a disease rarely seen in children and accounts for only 3-5% of childhood leukemias.[1] Chemotherapy fails to prolong significantly the chronic phase or to increase the overall survival in children[2] as well as in adults. Interferons are being widely used in adults,[3] but there is no information about their benefit and safety in pediatric patients. Experience acquired in many centers during the last decade shows that allogeneic bone marrow transplantation (BMT) can cure patients with CML.[4] Patients < 20 years of age have a lower transplant-related mortality and a better event-free survival.[5,6] Few studies have focused on treatment of Ph1-positive CML in children and, those that do, refer to a small number of patients.[7,8]

In this retrospective study, we compared the results achieved by BMT and conventional therapy in children treated at Spanish pediatric centers during the same time period.

Materials and Methods

All patients in the study were registered in the Spanish National Registry of Pediatric Tumors (RNTI). The RNTI is a hospital-based registry which includes data on diagnosis, treatment and follow-up.[9]

The BMT group comprised 14 patients with Ph1-positive CML transplanted between January 1983 and August 1993 at four Spanish pediatric centers. There were 7 boys and 7 girls with a median age at transplant of 7 years (range 4-15 years). BMT was carried out in their first chronic phase in 13 patients and in the blastic phase in one. The median time from diagnosis to transplant was 7 months (range 5-72 months). Before BMT patients were treated with busulfan or hydroxyurea. In 13 cases the donor was an HLA-identical sibling. The patient transplanted in the blastic phase received the marrow of an HLA-nonidentical mother. The conditioning regimens combined fractionated twice daily total-body irradiation (12-13.5 Gy) with cyclophosphamide at the dose of 120 mg/kg in 12 patients. In two children, busulfan at a dose of 12 mg/kg was added to TBI and cyclophosphamide. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin A and methotrexate in 12 patients, T-cell depletion in the one receiving the haploidentical marrow and ATG and prednisone in one. Disease-free survival (DFS) was defined as a

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Table 1. Initial patient characteristics.

	BMT (n = 14)	*Conventional therapy (n = 27)*
WBC count ($\times 10^9$/L) median (range)	25.1 (10-170)	26 (15-165)
Hb (g/dL) median (range)	13.5 (10-14)	13 (9-13.5)
Platelet count ($\times 10^9$/L) median (range)	530 (90-755)	490 (115-850)
Circulating basophils (%) median (range)	4.3 (1-22)	3 (2-17)
Marrow basophils (%) median (range)	1 (0-31)	1.5 (0.5-27)
Splenomegaly*	4	8

**defined as ≥ 2 cm below costal margin.*

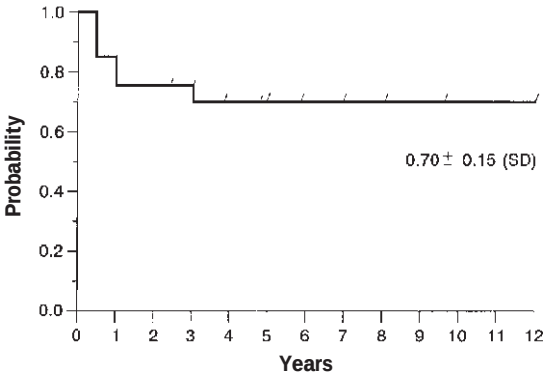

Figure 1. Probability of disease-free survival (DFS) after BMT for the group of patients treated by BMT; tick marks indicate patients in continuous complete remission (CCR). N = 14; 10 in CCR.

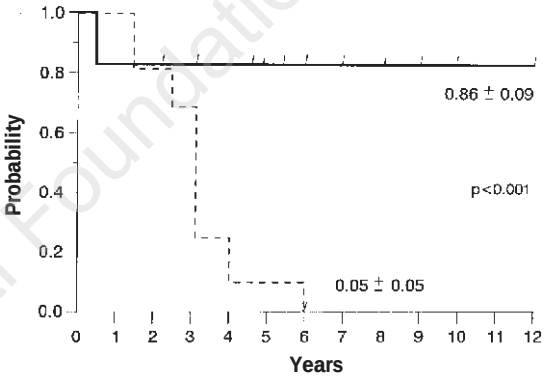

Figure 2. Probability of survival after diagnosis in the group of BMT versus non-BMT patients from the time of diagnosis. The difference is highly significant.

status both hematologically and cytogenetically [PCR for the translocation (t9:22)] negative for the presence of disease. The conventional therapy-treated group comprised 27 patients with Phl-positive CML registered in the RNTI during the same period, January 1983-August 1993, in a stable chronic phase. There were 15 girls and 12 boys with a median age at diagnosis of 11 years (range 3-14 years): all lacked an HLA-identical related donor. Patients were treated with either busulfan or hydroxyurea at conventional doses, except the 4 patients diagnosed after 1991, who received α-interferon (α-IFN).

The initial characteristics of the patients at the time of diagnosis were similar in the BMT group and the group treated with conventional therapy (Table 1).

Overall survival was calculated from diagnosis for BMT and non-BMT patients. In the group of transplanted children, disease-free survival (DFS) was calculated from the date of BMT. Results were analyzed using the Kaplan and Meier method. Differences between the BMT and non-BMT groups were assessed with the Mantel-Cox log-rank test.

Results

In the group of children who received BMT all except one engrafted. The follow-up ranged from 30 to 150 months. Ten patients are alive and disease-free at a median follow-up of 60 months. The probability of DFS at 5 years is 70% (SE 0.13)(Figure 1). Two children relapsed 18 and 48 months after BMT and received a second allogeneic graft from the same donors. They remain alive and disease-free 48 and 30 months after the second BMT. Two patients have died: the child transplanted in the blastic phase from an HLA-identical mother did not achieve engraftment. One patient died of acute GVHD grade IV, two months after BMT. There was no acute GVHD among the surviving patients, although two of them developed chronic GVHD with lung involvement.

Of the 27 patients treated with conventional chemotherapy, 22 died during blast crisis between 12 and 72 months after diagnosis (median survival 36 months). Five are alive in their first chronic phase. None of the patients who received α-interferon survived. The probability of survival at 5 years is 5% (S.E. 0.05). The survival of transplanted (85%, S.E. 0.09) and non- transplanted children is compared in Figure 2. The difference between the two groups is highly significant ($p = 0.001$).

Discussion

The results of our series of exclusively pediatric patients confirm the widely accepted hypothesis that BMT is the only cure for CML, with a probability of DFS of 70%, versus a DFS of 5% in the group of

patients treated with conventional chemotherapy, as previously reported by other authors.[1,2,10,11] Klingebiel *et al.* reported a DFS of 61% for 14 children transplanted in the first or second chronic phase.[7] Gamis *et al*.[8] obtained a DFS of 78% in a study of 11 children transplanted in the chronic or blastic phase.

The interval between the diagnosis of CML and BMT influences ultimate survival. When performed within the first 12 to 18 months after diagnosis, independent of disease phase, BMT confers a better chance of DFS.[4,10,12] The median interval to BMT was 7 months in our patients and 8 months and 17 months in the Gamis and Klingebiel studies, respectively.[7,8] Even with unrelated donors, a relatively good outcome can be expected. In 11 children transplanted by Gamis *et al.*[8] in the chronic or blastic phase with marrow from unrelated HLA-identical donors, the estimated DFS was 45%.[8] However, acute GVHD was more prevalent and persistent than in transplanted patients with related donors.

There is wide experience in the treatment of CML Ph1 with α-IFN in adults. Cytogenetic and hematologic complete response rates in the range of 40% to 80% have been reported,[6] but it remains to be determined whether this treatment modality produces a better overall survival of patients than conventional therapy. On the other hand, it has been reported that prolonged pretransplant α-IFN administration is associated with a higher risk of transplant-related mortality, more delay and graft failure, and a lower survival.[13] Moreover, as children with CML Ph1 in first chronic phase are initially all candidates for an allogeneic BMT, it would be wise to avoid the use of α-IFN as frontline cytoreductive therapy.

For adult patients relapsing after a BMT from an HLA-identical sibling, many investigators are studying the use of donor peripheral blood leukocyte infusions and in some cases complete cytogenetic and hematologic remissions have been achieved.[14] Schwinger *et al.* have reported on two children treated with this procedure.[15] The published literature supports the use of second transplants in pediatric patients in relapse at least 6 months after the first BMT.[16,17] Two of our children who relapsed more than 1 year after their first BMT received a second graft from the same donors using a busulfan alone conditioning regimen,[17] and remain alive, in good condition and disease-free 48 and 30 months later.[18]

It has been recently emphasized in this journal that, in view of the increasing therapeutic options available, treatment of CML patients needs to be individualized.[19,20] As far as children are concerned, we conclude that children with CML who have a related HLA-identical donor must receive a BMT as soon as possible after being diagnosed.

Appendix

Patients treated by conventional therapy: list of participating centers and physicians.

Badalona: Hospital German Trias, G. Javier.
Barcelona: Hospital San Pablo, J. Cubells.
Hospital Valle de Hebrón, J.J. Ortega.
Hospital San Juan de Dios, J. Estella.
Madrid: Hospital Gregorio Marañón, M. Ramos.
Hospital Niño Jesús, T. Contra.
Hospital Ramón y Cajal, A. Muñoz.
Hospital 12 de Octubre, J. López.
Palma de Mallorca: Hospital San Dureta, J.P. Payarols.
Pamplona: Hospital Virgen del Camino, J. Molina.
San Sebastian: Hospital Virgen de Aránzazu, J. Guerrero.
Santiago: Hospital General de Galicia, J.M. Couselo.
Toledo: Hospital Virgen de la Salud, M. Velasco.
Valencia: Hospital Clínico, R.F. Delgado.

Contributions and Acknowledgments

AM designed the study and co-ordinated the collaboration among the other authors. EB, JJO and LM collected the clinical and analytical data. CR, TO and MSM were responsible for the data handling. MAD made the statistical analyses and prepared the bibliography. AM wrote the manuscript, which was reviewed by EB and JJO before it was submitted to the rest of the authors for their approval.

The order of appearance of the names was based on the importance of each individual contribution, as previously established and accepted by all the authors.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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