

Twenty Years of Unrelated Donor Bone Marrow Transplantation for Pediatric Acute Leukemia Facilitated by the National Marrow Donor Program

Margaret L. MacMillan,¹ Stella M. Davies,² Gene O. Nelson,³ Pintip Chitphakdithai,³ Dennis L. Confer,³ Roberta J. King,³ Nancy A. Kernan⁴

¹Division of Pediatric Hematology, Oncology, and Blood and Marrow Transplantation, University of Minnesota Blood and Marrow Transplant Program, Minneapolis, Minnesota; ²Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; ³National Marrow Donor Program, Minneapolis, Minnesota; and ⁴Memorial Sloan-Kettering Cancer Center, New York, New York

Correspondence and reprint requests: Margaret L. MacMillan, MD, University of Minnesota, Department of Pediatrics, 420 Delaware Street, Southeast, MMC 484, Minneapolis, MN 55455 (e-mail: macmi002@umn.edu).

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ABSTRACT

The National Marrow Donor Program (NMDP) has facilitated unrelated donor hematopoietic cell transplants for more than 20 years. In this time period, there have been many changes in clinical practice, including improvements in HLA typing and supportive care, and changes in the source of stem cells. Availability of banked unrelated donor cord blood (incorporated into the NMDP registry in 2000) as a source of stem cells has become an important option for children with leukemia, offering the advantages of immediate availability for children with high-risk disease, the need for a lesser degree of HLA match, and expanding access for those with infrequent HLA haplotypes. Overall survival (OS) in children with acute leukemia transplanted with unrelated donor bone marrow (BM) is markedly better in more recent years, largely attributable to less treatment-related mortality (TRM). Within this cohort, 2-year survival was markedly better for patients with acute lymphoblastic leukemia (ALL) in first complete response (CR1) (74%) versus second complete response (CR2) (62%) or more advanced disease (33%). Similar findings are observed with patients with AML, suggesting earlier referral to bone marrow transplant (BMT) is optimal for survival. Notably, this improvement over time was not observed in unmodified peripheral blood stem cell (PBSC) recipients, suggesting unmodified PBSC may not be the optimal stem cell source for children.

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KEY WORDS

National Marrow Donor Program • NMDP • Unrelated donor • Bone marrow transplantation • Pediatric acute leukemia

INTRODUCTION

The National Marrow Donor Program (NMDP) has facilitated unrelated donor hematopoietic cell transplantation (HCT) in pediatric patients since 1987. With the NMDP celebrating its 20th anniversary, it is an ideal time to reflect on the outcome of HCT facilitated through this program in treating children with acute leukemia, evaluate what has been learned, and what we surmise the future holds.

Acute leukemia is the most prevalent type of cancer in children, and the most frequent indication for unre-

lated donor HCT. Despite major advances in chemotherapy for acute leukemia, HCT remains the best therapeutic option for a subset of patients with high-risk disease at presentation, as well as for the majority of patients who relapse. This review will focus on the outcomes of HCT facilitated by the NMDP over the past 20 years for pediatric patients with acute leukemia.

Data Collection

The study population included 1494 children <18 years of age who received an unrelated donor bone

marrow transplant (BMT) following myeloablative therapy for treatment of acute leukemia since the inception of the NMDP in 1987 through March of 2006, at 1 of 102 transplant centers. Data from this cohort were collected on standard NMDP forms, and included only patients for whom informed consent was obtained. Four hundred one patients were omitted from the study because of consent issues.

These data were grouped into 4 time periods (1987-1995, 1996-1998, 1999-2002, and 2003-2006) chosen as approximately equal in length (3-4 years) with similar numbers of patients. A longer early period (1987-1995) was chosen to have enough cases for analysis.

Statistical Analysis and Definitions

Probabilities of survival were calculated using the Kaplan-Meier method. Probabilities of treatment-related mortality (TRM) and relapse were calculated using the cumulative incidence method. Chi-square tests were used for pointwise rate comparisons. TRM is defined as death without relapse. Relapse was treated as a competing risk. Relapse and TRM were censored at the occurrence of a second transplant.

Disease stage at conditioning was classified into 3 categories: first complete remission (CR1), second complete remission (CR2), or advanced (relapse, primary induction failure, and third or greater complete remission (CR3)). Myeloablative conditioning regimens included 1 of the following: total body irradiation (TBI) dose >500 cGy as a single fraction, TBI dose >800 cGy regardless of the number of fractions, melphalan (Mel) dose >150 mg/m², busulfan dose ≥ 9.5 mg/kg, any combination of Mel and Bu, or any combination of cyclophosphamide (Cy), Etoposide (VP-16), and TBI. Based on the best available typing data at the time of analysis, HLA matching was classified into 3 categories (well-matched, partially matched, and mismatched) according to a recently developed algorithm that considers level of HLA typing resolutions and matching at HLA-A, -B, -C, and -DRB1 loci [1]. Well-matched cases had either no identified HLA mismatches and informative data at 4 loci or allele matching at HLA-A, -B, and -DRB1. Partially matched pairs had a defined, single locus mismatch and/or missing HLA data. Mismatched cases had ≥ 2 allele or antigen mismatches.

RESULTS

The annual number of pediatric transplants in all diseases performed through the NMDP has steadily increased over 20 years as shown in Figure 1. The source of unrelated donor stem cells has changed from solely bone marrow (BM), to include peripheral blood stem cells (PBSC) in 1995, and umbilical cord blood (UCB) in 2000 (Figure 1). The proportion of

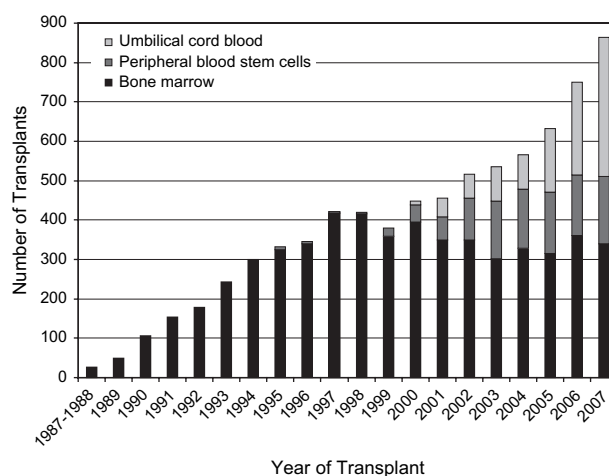


Figure 1. Number of pediatric transplants facilitated by the NMDP, by year and stem cell source.

transplants from UCB has increased briskly since 2000, when the NMDP first included cord blood units (CBUs) in standard search algorithms, and UCB transplants now represent 1/3 of all transplants for children with acute leukemia. The use of PBSC has increased in the last 8 years, but to a lesser extent than in adult practice, with a plateau in utilization in the last 4 years. The lesser enthusiasm for PBSC in pediatric compared with adult practice likely reflects published data indicating higher rates of graft-versus-host disease (GVHD) and lower survival in children receiving unmodified PBSC from both related and unrelated donors [2].

In our study population 1494 children with acute leukemia have received unrelated donor BM transplants facilitated through the NMDP. Patient and transplant characteristics for these BM recipients are shown in Table 1.

Survival

UCB and PBSC utilization has only been substantial in the last 5 years. Therefore, in this report we focused on patients who received an unrelated donor BM transplant. We selected to focus on patients with acute leukemia, because our goal was to examine changes in transplant outcomes over the 20 years that the NMDP has facilitated unrelated donor transplantation, and the analysis required a sufficient number of patients with specific diagnoses to have been treated in each range of years. Encouragingly, survival has improved over time, with most of the improvement occurring since 2003 (Figure 2). Patients transplanted from 2003 to 2006 ($n = 308$) had the best survival at 2 years at 58% (95% confidence interval [CI] 52%-64%). In contrast, 2-year survival was 44% (95% CI 39%-49%) for 404 patients transplanted in 1999 to 2002, 42% (95% CI 37%-47%) for 360 patients transplanted

Table 1. Patient and Transplant Characteristics

| Characteristic | 1987-1995 | | 1996-1998 | | 1999-2002 | | 2003-2006 | |
|--|--------------|---------------------|--------------|---------------------|-------------|--------------------|-------------|-------------------|
| | N | % | N | % | N | % | N | % |
| Number of recipients | 422 | | 360 | | 404 | | 308 | |
| Follow-up time among survivors | | | | | | | | |
| Median months (range) | 146.8 | (42.5-216.7) | 108.0 | (10.5-135.4) | 72.0 | (3.4-100.9) | 25.3 | (3.1-51.4) |
| Recipient race | | | | | | | | |
| Caucasian | 368 | 87 | 295 | 82 | 289 | 72 | 201 | 65 |
| Other | 54 | 13 | 65 | 18 | 115 | 28 | 104 | 34 |
| Disease stage at conditioning | | | | | | | | |
| ALL Total | 317 | 75 | 218 | 61 | 245 | 61 | 195 | 63 |
| ALL CR1 | 54 | 13 | 54 | 15 | 59 | 15 | 42 | 14 |
| ALL CR2 | 143 | 34 | 103 | 29 | 116 | 29 | 107 | 35 |
| ALL Advanced | 120 | 28 | 61 | 17 | 70 | 17 | 46 | 15 |
| AML Total | 105 | 25 | 142 | 39 | 159 | 39 | 113 | 37 |
| AML CR1 | 19 | 5 | 36 | 10 | 39 | 10 | 35 | 11 |
| AML CR2 | 33 | 8 | 45 | 13 | 70 | 17 | 46 | 15 |
| AML Advanced | 53 | 13 | 61 | 17 | 50 | 12 | 32 | 10 |
| Performance score at conditioning | | | | | | | | |
| 90 to 100 | 331 | 78 | 275 | 76 | 320 | 79 | 236 | 77 |
| 10 to 80 | 91 | 22 | 84 | 23 | 59 | 15 | 22 | 7 |
| Time from diagnosis to transplant | | | | | | | | |
| Median months (range) | 21.9 | (0-161) | 15.7 | (1-166) | 17.7 | (0-153) | 16.8 | (1-125) |
| < 6 months | 55 | 13 | 79 | 22 | 95 | 24 | 72 | 23 |
| 6 to 12 months | 93 | 22 | 69 | 19 | 59 | 15 | 51 | 17 |
| 12 to 24 months | 76 | 18 | 79 | 22 | 97 | 24 | 69 | 22 |
| ≥ 24 months | 198 | 47 | 133 | 37 | 151 | 38 | 116 | 38 |
| HLA match CIBMTR definition | | | | | | | | |
| Well-matched | 79 | 19 | 72 | 20 | 138 | 34 | 180 | 58 |
| Partially matched | 138 | 33 | 163 | 45 | 156 | 39 | 91 | 30 |
| Mismatched | 205 | 49 | 125 | 35 | 110 | 27 | 37 | 12 |

ALL indicates acute lymphoblastic leukemia, AML, acute myelogenous leukemia; CR1, CR2, first and second complete remission.

in 1996 to 1998, and only 35% (95% CI 31%-40%) for 422 patients transplanted in 1987 to 1995 ($P < .001$).

Similar improvements in survival in patients transplanted more recently are observed when examining a subset of patients who underwent unrelated donor BMT for acute leukemia in CR1 as shown in Figure 3A, or CR2 as shown in Figure 3B.

The recent improvement in survival after unrelated donor BMT for patients with acute leukemia is because of a decrease in treatment-related mortality (TRM), which has dramatically declined over the last 20 years (Figure 4). The cumulative incidence of TRM at 1 year after BMT for acute leukemia in CR1 and CR2 was 40% (95% CI 34%-46%) for patients transplanted in 1987 to 1995, 28% (95% CI 23%-34%) for the 1996 to 1998 cohort, 28% (95% CI 23%-33%) for the 1999 to 2002 cohort, and only 15% (95% CI 11%-20%) for the recent 2003 to 2006 cohort ($P < .001$).

Methods for HLA testing have improved over the last 20 years, with a higher proportion of more recent transplant recipients having a known HLA well-matched donor than in the past (Table 1). For recipients of well-matched donors, the probability of 2-year survival is better for more recently transplanted patients (Figure 5A). Notably, the survival advantage

in the 2003 to 2006 cohort is substantially greater compared to earlier transplant recipients for those who received recipients of the HLA mismatched donor transplants (Figure 5B).

For patients with acute leukemia transplanted with unrelated donor BMT in 2003 to 2006, survival is superior for patients in CR1 than CR2, and significantly worse for those in third or greater CR or relapse. As shown in Figure 6 and Table 2, the probability of

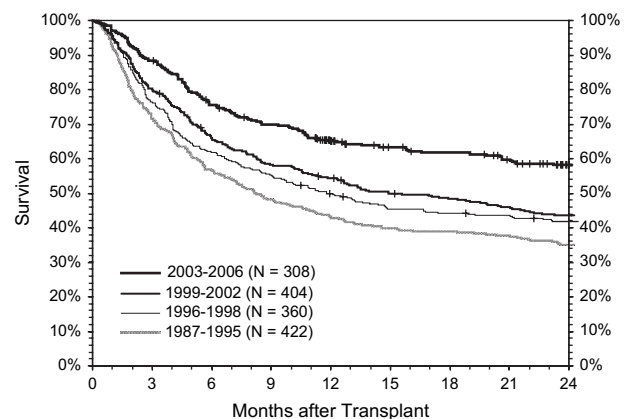


Figure 2. Probability of survival after unrelated donor for children with acute leukemia, by transplant period. P -value at 2 years $< .001$.

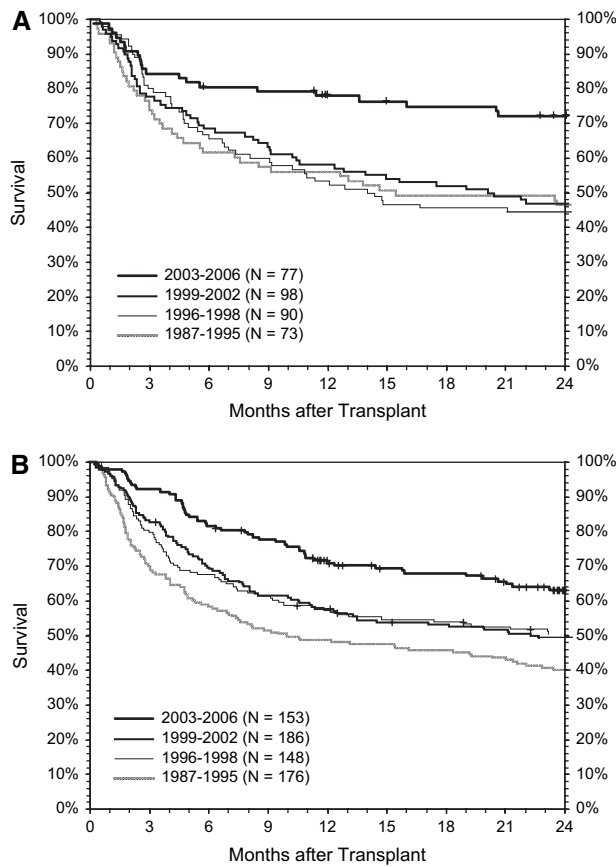


Figure 3. (A) Probability of survival after unrelated donor BMT for children with acute leukemia in first complete remission (CR1) at time of transplant, by transplant period. *P*-value at 2 years <.001. (B) Probability of survival after unrelated donor BMT for children with acute leukemia in second complete remission (CR2) at time of transplant, by transplant period. *P*-value at 2 years = .001.

survival at 2 years after unrelated donor BMT for patients with acute lymphoblastic leukemia (ALL) was significantly better for children in CR1 (74% [95% CI 60%-86%]), versus CR2 (62% [95% CI

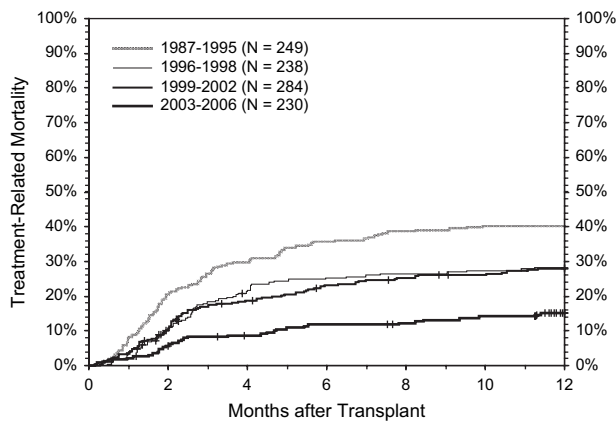


Figure 4. Cumulative incidence of TRM in children with acute leukemia in CR1 or CR2 at the time of BMT, by transplant period. *P*-value <.001.

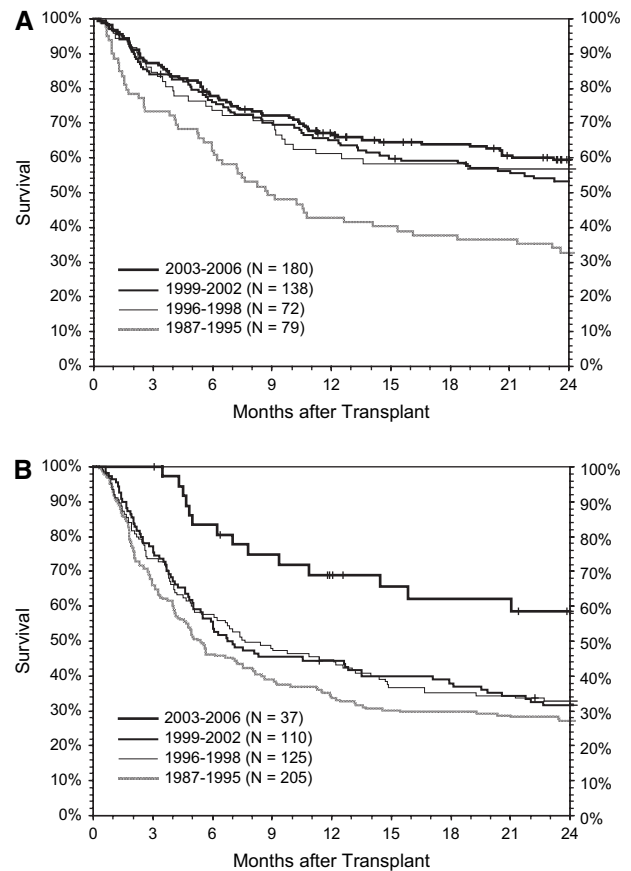


Figure 5. (A) Probability of survival after HLA well-matched unrelated donor BMT for children with acute leukemia, by transplant period. *P*-value at 2 years <.001. (B) Probability of survival after HLA mismatched unrelated donor BMT for children with acute leukemia, by transplant period. *P*-value at 2 years = .008.

52%-71%) or in third or greater CR or relapse at the time of BMT (33% [95% CI 20%-48%], *P* < 0.001). Similarly, the probability of 2-year survival for patients with acute myelogenous leukemia (AML)

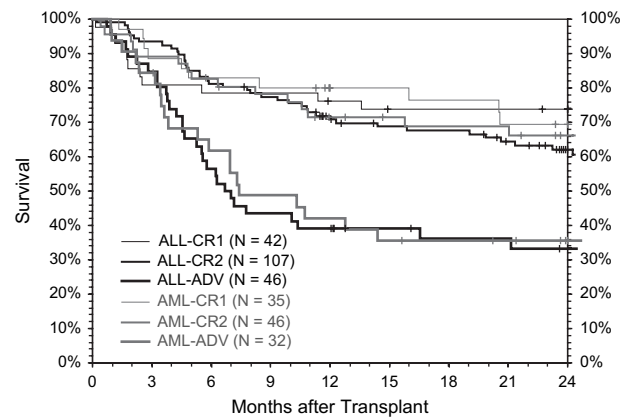


Figure 6. Probability of survival after unrelated donor BMT in 2003 to 2006 for children with acute leukemia, by disease state at time of transplant. *P*-value at 2 years <.001 for ALL, =.007 for AML.

Table 2. *Survival by Disease*

| | Year of HCT | Number of Cases | Survival at 1 year (95% CI) | Survival at 2 years (95% CI) |
|--------------------------------|-------------|-----------------|-----------------------------|------------------------------|
| ALL CR1 | 1987-1995 | 54 | 52% (39-65) | 48% (35-61) |
| | 1996-1998 | 54 | 63% (50-75) | 54% (40-67) |
| | 1999-2002 | 59 | 59% (47-71) | 54% (42-67) |
| | 2003-2006 | 42 | 76% (62-88) | 74% (60-86) |
| ALL CR2 | 1987-1995 | 143 | 48% (40-56) | 43% (35-51) |
| | 1996-1998 | 103 | 51% (42-61) | 44% (35-54) |
| | 1999-2002 | 116 | 57% (48-66) | 50% (41-59) |
| | 2003-2006 | 107 | 71% (62-79) | 62% (52-71) |
| ALL > CR2 or relapse | 1987-1995 | 120 | 32% (24-40) | 23% (16-31) |
| | 1996-1998 | 61 | 46% (34-58) | 34% (22-46) |
| | 1999-2002 | 69 | 45% (33-57) | 25% (15-35) |
| | 2003-2006 | 46 | 39% (26-53) | 33% (20-48) |
| AML CR1 survival | 1987-1995 | 19 | 68% (46-87) | 42% (21-64) |
| | 1996-1998 | 36 | 39% (24-55) | 31% (17-46) |
| | 1999-2002 | 39 | 56% (41-71) | 36% (22-51) |
| | 2003-2006 | 35 | 80% (65-91) | 69% (53-84) |
| AML CR2 survival | 1987-1995 | 33 | 52% (35-68) | 30% (16-47) |
| | 1996-1998 | 45 | 71% (57-83) | 64% (50-78) |
| | 1999-2002 | 70 | 59% (47-70) | 48% (37-60) |
| | 2003-2006 | 46 | 71% (58-84) | 66% (52-79) |
| AML > CR2 or relapse | 1987-1995 | 53 | 34% (22-47) | 28% (17-41) |
| | 1996-1998 | 61 | 31% (20-43) | 25% (15-36) |
| | 1999-2002 | 49 | 44% (31-58) | 40% (27-54) |
| | 2003-2006 | 32 | 42% (26-60) | 36% (20-53) |

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CR1, CR2, first and second complete remission.

was significantly better for those patients in CR1 at the time of BMT (69% [95% CI 53%-84%]) or CR2 (66% [95% CI 52%-79%]) compared to patients in third or greater CR or relapse (36% [95% CI 20%-53%], $P = 0.007$).

In contrast to the improved survival observed in unrelated donor BMT recipients over time, there has been no improvement in survival after transplantation with unrelated donor unmodified PBSC over time, although the period of observation has been short. Probability of survival at 2 years after PBSC transplant was 40% (95% CI 26-54) for 43 patients who received a PBSC transplant from 1999 to 2002 compared to 46% (95% CI 37%-54%) for the 141 patients who received a PBSC transplant from 2003 to 2006 ($P = .48$).

The NMDP has been facilitating transplants using unrelated donor UCB for a short time period so it is not possible to examine survival over time with this stem cell source.

DISCUSSION

Unrelated donor HCT is well established as effective therapy for children with high-risk leukemia [3-8]. The NMDP has facilitated unrelated donor HCT for pediatric patients with acute leukemia since 1986. This report demonstrates significant improvements in survival over a 20-year period, particularly since 2003.

Changes in chemotherapy regimens that have occurred in parallel with changes in transplantation approaches impact which children are referred for

transplantation. Intensification of post-induction chemotherapy and the use of risk-adapted chemotherapy have improved outcomes for children with ALL considerably. Similarly, intensified therapy and better supportive care have improved outcomes for children with AML. The advances in upfront chemotherapy likely means that currently treated children who relapse and are referred for transplantation in CR2 have more aggressive leukemia than children referred 20 years ago.

Improved strategies to identify patients with very high-risk disease, such as those with Philadelphia chromosome-positive ALL, have led to early referral of these children for transplantation in CR1. As patients transplanted in CR1 fare particularly well following an unrelated donor BMT, these children now have the opportunity to survive long term, whereas in the past they continued on chemotherapy, suffered early relapse, and frequently died without achieving CR2 and potentially benefiting from transplantation. The U.S. Children's Oncology Group is investigating the role of unrelated donor transplant for the highest risk subsets of children with leukemia (monosomy 7, induction failure, early relapse) utilizing improved strategy for donor selection (studies of KIR match and mismatch): these strategies may further increase the number of children likely to benefit from transplantation.

Although we have focused on children with acute leukemia in this report, it is important to note that similar improvements in survival have been noted in children with non-malignant disorders including

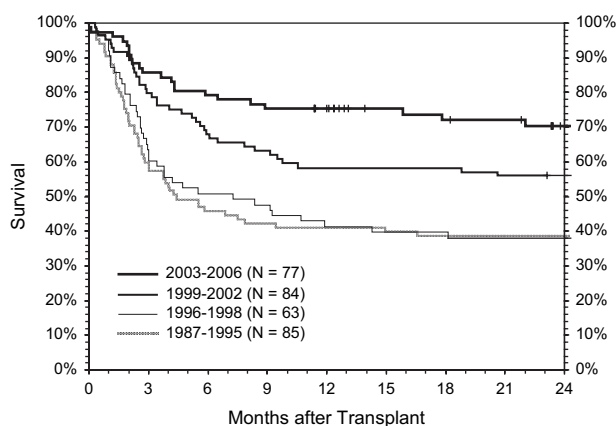


Figure 7. Probability of survival after unrelated donor BMT for children with SAA by transplant period. Dataset includes additional recipients with non-myeloablative conditioning regimens. Pointwise P -value at 2 years $<.001$.

severe aplastic anemia (SAA) (Figure 7) and congenital disorders of immune deficiency and metabolic disorders [9].

A series of enhancements to the NMDP search algorithm, including addition of high-resolution matching, enhanced graphical interfaces, and the introduction of HapLogic™, have improved the ability to identify optimal unrelated volunteer donors and CBUs. A significant number of children in whom HLA mismatches, or mismatch at HLA-C, would have been overlooked by serologic typing may have had their match grade improved by these strategies, contributing to the notable reduction in TRM [10-12].

The selection of donors for BM donation based on more stringent HLA typing has not contributed to a decrease in number of transplantation procedures performed for pediatric patients with acute leukemia, as results following HLA partially matched and mismatched transplants have also improved over time, and the utilization of UCB with less stringent HLA matching requirements has expanded the pool of available donors.

In well-established transplant centers, patients who receive a well-matched unrelated donor HCT have similar outcomes as HLA-identical sibling HCT recipients [13-17]. Our data lends further support for referral of children with high-risk acute leukemia in CR1, or any acute leukemia in CR2-3, for unrelated donor HCT similar to that for HLA-identical sibling donor transplants. Delaying referral for an unrelated donor transplant increases the risk for TRM and relapse, resulting in poor survival.

We observed a change in the stem cell source over time, particularly with the recent growth of the use of UCB. In contrast, the use of PBSC has not increased in recent years. This may be due in part to less experience in the HLA-matched sibling donor setting for pediatric patients secondary to small donor size. More

importantly, the limited utilization of this stem cell source may be because of recent reports suggesting poorer outcomes after PBSC compared to BM transplantation in children [18]. Our data suggest that in contrast to BM recipients, no improvement in survival after unmodified PBSC transplants has been observed in children. Whether T cell-depleted (CD34 depleted) PBSCs will improve outcomes for children with leukemia remains to be explored. Reported data has shown similar outcomes in unrelated donor UCB and BM recipients [16,19,20]. An ongoing national randomized study comparing outcomes using single or double cord blood grafts for transplantation may importantly change clinical practice in this area in the next 5 years.

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