**Haematology and Blood Transfusion** Vol. 31
Modern Trends in Human Leukemia VII
Edited by Neth, Gallo, Greaves, and Kabisch


# Bone Marrow Transplantation in Leukemia in the Absence of an HLA-Identical Sibling Donor

R. Dopfer [1], G. Ehninger [2], and D. Niethammer [1]

## A. Introduction

Bone marrow transplantation is a potentially curative treatment for patients with leukemia, aplastic anemia, metabolic disorders, and immunodeficiency. One of the main problems of this procedure is the graft-versus-host reaction induced in the recipient by the immune function of the transplanted marrow. In order to minimize the risks of graft rejection and graft-versus-host disease (GVHD), marrow transplantation has in general been limited to patients with HLA-identical sibling donors. The majority of patients, however, will not have such a family member available. To cope with such patients, several alternative approaches have been investigated. One of them is autologous bone marrow transplantation (with or without antileukemic treatment of the marrow); another is transplantation of haploidentical marrow after T-cell depletion by separation with lectins, E rosetting, or monoclonal antibodies. Most experience in this field has been gained in patients with severe combined immunodeficiency. Another alternative for these patients is bone marrow transplantation with the marrow of an unrelated but matched or partially matched donor, or even a mismatched family donor. Only few clinical data are available to assess the latest acceptable limits for HLA incompatibility in human bone marrow transplantations with a mismatched related or unrelated donor. Such transplantations have been performed to explore the limitations of this procedure, mainly in the United Kingdom and the United States. The results of these transplantations are described in this short overview.

## B. Mismatched Unrelated Donors

It is evident that there are major logistic problems in identifying suitable unrelated donors quickly enough and in sufficient numbers to make an impact on the management of leukemia or aplastic anemia. Table 1 describes the probability for a given antigen system that the donor pool will include at least one person phenotypically identical to a random recipient [1]. Values are applied to Caucasian donors and recipients, and are based on haplotype frequency estimates published in *Histocompatibility Testing 1980,* with the exception of HLA-A,B, for which haplotype frequencies from the Terasaki laboratory were used. As one can imagine, the donor pool has to be very large (for some rare haplotypes, over 1 million) to find a suitable donor. However, for selecting donors who are only partially identical, the pool needed is significantly smaller. Experience with matched and mismatched bone marrow transplantations has been gained in several centers. In Tables 2–5, the results from the United Kingdom (Hammersmith and Westminster Hospitals) and the United States (Seattle and Iowa City) are summarized [2–5].

[1] Department of Pediatric Hematology and Oncology, University Children's Hospital, Ruemelinstrasse 21–26, Tuebingen, FRG
[2] Department of Internal Medicine, University of Tuebingen, Otfried-Müller-Strasse 23

**Table 1.** Pool size calculations for the search for HLA-identical bone marrow donors. (After [1])

| Pool Size | A | B | DR | A, B | A, DR | B, DR | A, B, DR |
|---|---|---|---|---|---|---|---|
| 1 | 3.08 | 0.807 | 3.29 | 0.097 | 0.166 | 0.085 | 0.013 |
| 5 | 13.4 | 3.9 | 14.9 | | | | |
| 10 | 23.7 | 7.5 | 27.1 | | | | |
| 20 | 38.1 | 14.1 | 45.6 | 1.86 | 4.0 | 3.6 | |
| 40 | 54.5 | 29.9 | 73.4 | 3.6 | 6.9 | 5.2 | |
| 80 | 70.0 | 40.1 | 86.3 | 6.7 | 11.9 | 8.0 | |
| 500 | 94.8 | 81.9 | 99.3 | 25.9 | 39.3 | 26.3 | |
| 1000 | 97.9 | 90.7 | 99.8 | 37.2 | 53.3 | 37.6 | |
| 5000 | 99.7 | 98.8 | 100.0 | 65.3 | 81.4 | 66.5 | |
| 10000 | | | | 75.5 | 89.2 | 77.3 | 29.1 |
| 50000 | | | | 91.1 | 97.9 | 93.3 | 55.5 |
| 100000 | | | | | | | 66.6 |
| 500000 | | | | | | | 86.4 |

**Table 2.** Seattle experience with BMT from phenotypically identical unrelated donors (After [2])

| BMT with phenotypically identical donors | | | | |
|---|---|---|---|---|
| | n | Survival | GVHD, acute | Causes of death |
| ALL II. rem. | 1 | 711 | 0 | relapse |
| AML I. rem. | 1 | 288+ | II | |
| AA | 3 | 224, 161, 29 | II, II, I | Asp., no graft, bleeding |
| CML-CP | 6 | 61, 101, 47, 31, 56, 40+ | III, IV, III, II, IV, I | CMV, GVHD, VOD, I.P. |
| CML-AP | 1 | 139 | IV | GVHD |
| CML-BC-CP | 1 | 349+ | I | |

**Table 3.** Westminster experience with BMT from unrelated donors. (After [3])

| Age | Disease | HLA | | | | GVHD prophylaxis | Take | GVHD | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | A | B | DR | MLC | | | | |
| 19 | ALL 2. CR | = | = | ND | = | CyA | Early | No | Hemorrhage+15 |
| 18 | ALL 3. CR | = | = | ND | = | CyA | Full | III | +45 |
| 39 | AML 1. CR | = | = | = | = | CyA | Full | Chronic | Well > 1 500 days |
| 9 | ALL 3. CR | = | = | ND | = | T-Dep CyA | Full | II | Aspergillus+55 |
| 4 | ALL 1. CR | = | = | = | = | T-Dep CyA | Full | No | Metabolic+27 |
| 9 | ALL 1. CR | = | = | = | = | T-Dep CyA | Full | No | Aspergillus+27 |
| 22 | PreAML | = | = | = | = | T-Dep CyA | Full, Rej | No | Aspergillus+66 |

**Table 4.** Hammersmith experience with BMT of unrelated donors. (After [4])

| Disease | Engraftment | GVHD | Survival |
|---|---|---|---|
| SAA 8<br>CGL – CP 2<br>CGL – AP 1<br><br>Fanconi 3 | 8/14 | 6/9<br>Grade 3–4 | 4/14 (120–1 599 days) |

SAA, severe aplastic anemia.

**Table 5.** Outcome of BMT with unrelated DR,D-matched donors in Iowa City (After [5])

| Disease | | n | Survival: Continuous and/or > 1 yr. | Causes of Death |
|---|---|---|---|---|
| ANLL | 2nd CR | 3 | 3 | |
| | 3rd CR | 0 | | |
| | 4th CR | 1 | 0 | HSV/CMV |
| | Relap | 7 | 0 | ARDS, Asp., Leg, GVHD/HSV, Mucor, Gm-, Gm-, |
| ALL | 2nd CR | 2 | 0 | Gm-/CDS, GVHD |
| | 3rd CR | 4 | 1 | CMV, Crypto, P. carinii* |
| | Relap | 2 | 0 | Asp., HSV |
| AUL | 2nd CR | 1 | 0 | GVHD/Asp |
| CML | SP | 4 | 1 | GHVD/Gm-, P. carinii* |
| | AP | 9 | 4 | GVHD/HSV, GVHD, Asp., Can., Gm- |
| | BC SP | 2 | 0 | GVHD, Gm- |
| RAEB | | | 1 | |
| SAA | | 4 | 1 | NE/Asp, Asp, NE/VOD |
| Total | | 39 | 11 | |

* TMP-SM allergy

HSV, herpes simplex virus infection; CMV, cytomegalovirus infection; GVHD, graft-versus-host disease; ASP, aspergillus infection; ARDS, acute respiratory distress syndrome; LEG, legionella infection; Gm-, gram-negative sepsis; VOD, veno-occlusive disease; Crypto, cryptococcus infection; Can, candida infection; Ne, engraftment failure.

**Table 6.** Correlation of GVHD with HLA class I match[a]. (From [5])

| | | Grade aGVHD[b] | | | | |
|---|---|---|---|---|---|---|
| | | 0 | I | II | III | IV |
| Number of HLA A & B Matches | 0 | – | – | – | 1 | 1 |
| | 1 | – | 3 | 1 | 1 | – |
| | 2 | – | 3 | 2 | 1 | – |
| | 3 | 2 | 3 | – | 1 | 2 |
| | 4 | 2 | 2 | – | 1 | 1 |
| Totals: | | 4 | +11 | +3 | +5 | +4=27 |

[a] All patients matched at HLA class II antigens. [b] Median time of onset GVHD, day 22 (12–40)

**Table 7.** Clinical status of survivors. (From [5])

| UPN | Age | Disease | Match, HLA A,B[a] | (mos.) | Status | cGVHD[b] | Karnofsky |
|---|---|---|---|---|---|---|---|
| 94 | 18 | CML-AP | 1A, 1B | 28+ | Bronchitis | L | 90 |
| 101 | 39 | CML-AP | 1A | 24+ | Sinusitis, bronchitis | S, L | 90 |
| 108 | 32 | ANLL 2nd CR | 2A | 25+ | Well | – | 100 |
| 127 | 12 | SAA | 1A, 1B | 18+ | | S | 100 |
| 131 | 5 | CML | 1B | 15+ | Bronchitis | S | 80 |
| 150 | 32 | ANLL 1st CR | 1A, 2B | 9+ | | G | 80 |
| 151 | 38 | CML-AP | 1A, 2B | 8.8+ | Bronchitis | S | 90 |
| 159 | 28 | RAEB | 2A, 2B | 6+ | CMV enteritis | – | 90 |

[a] all patients HLA D/DR matched
[b] S = skin, L = Liver, G = gut
RAEB, refractory anemia with excess of blasts.

Because the GVHD prophylaxis, state of disease, and degree of HLA identity vary, comparison of the results is difficult. However, it is possible to draw the conclusion that bone marrow transplantation with phenotypically identical or partially matched marrow from unrelated donors is a feasible method for patients lacking an HLA-identical sibling donor. Fatal septic complications would seem to be a major problem. GVHD occurs more frequently than with identical sibling donor transplants and contributes to the cause of death in some patients. But the frequency of severe GVHD is not correlated with the degree of mismatch in DR-matched patients (Table 6). The infections which occur are probably due to the higher incidence of GVHD. The long-term outcome is doubtful, however, with regard to the clinical status of the patients in Iowa City (Table 7). More than half of the survivors suffer from chronic bronchitis, which is well known as a GVHD equivalent. These patients with GVHD of the lung have clinical problems with the trapped-air phenomenon and restrictive bronchitis.

It is not known whether in transplants from fully HLA-matched (A, B, D, DR) unrelated donors the possibility of graft failure or GVHD is due to undetermined histocompatibility antigens outside the major locus, or whether different DP and DQ antigens are responsible for these reactions. Basic research in HLA typing requires intensification to illuminate the correlations between different HLA antigens or minor antigens and graft failure or GVHD.

### C. Mismatched Family Donors

Bone marrow transplantation from related phenotypically identical or related mismatched donors has been performed in greater number in Seattle than elsewhere [6]. A total of 105 patients have been grafted: 41 with acute leukemia in remission, 51 with acute leukemia in relapse, 5 with chronic granulocytic leukemia (CGL) in chronic phase, and 8 with CGL in blast crisis. Engraftment was delayed in a significant number of patients, thus resulting in persistent granulocytopenia. The risk of GVHD was higher in mismatched transplantation than in the control group, and this risk increased with the degree of HLA disparity (Fig. 1). The survival of patients with one unshared antigen was the same as in the control group (Fig. 2). These data clearly demonstrate that bone marrow transplantation with mismatched family donors is feasible, that results with one antigen mismatch are good, but that engraftment and GVHD problems have to be considered.

### D. Strategies of Bone Marrow Transplantation in Childhood

Data concerning bone marrow transplantation with unrelated donors and partially

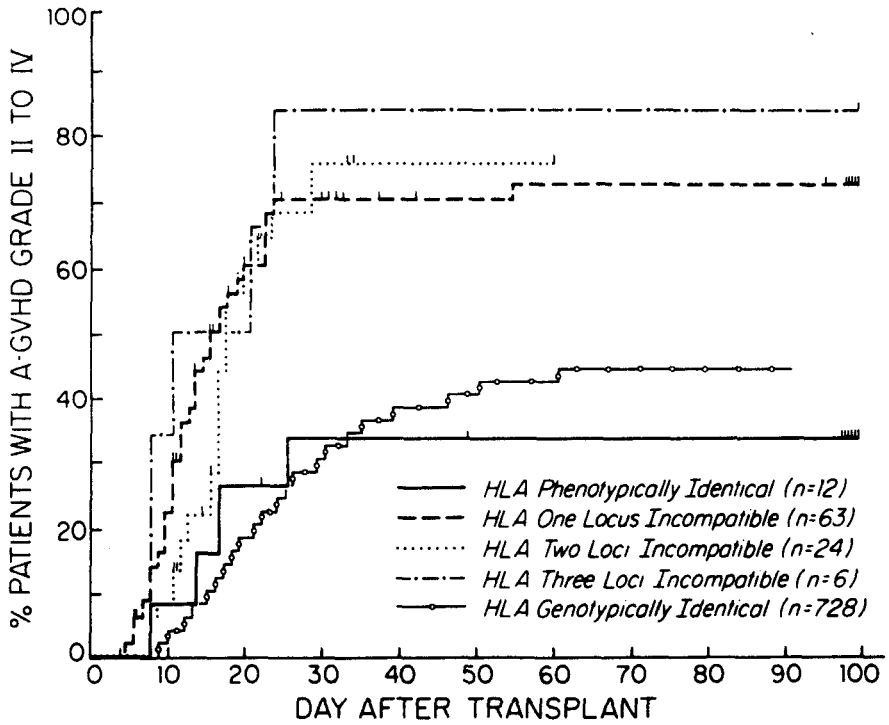


**Fig. 1.** GVHD incidence in 105 patients after BMT with phenotypically identical or mismatched family donors. (After [6])

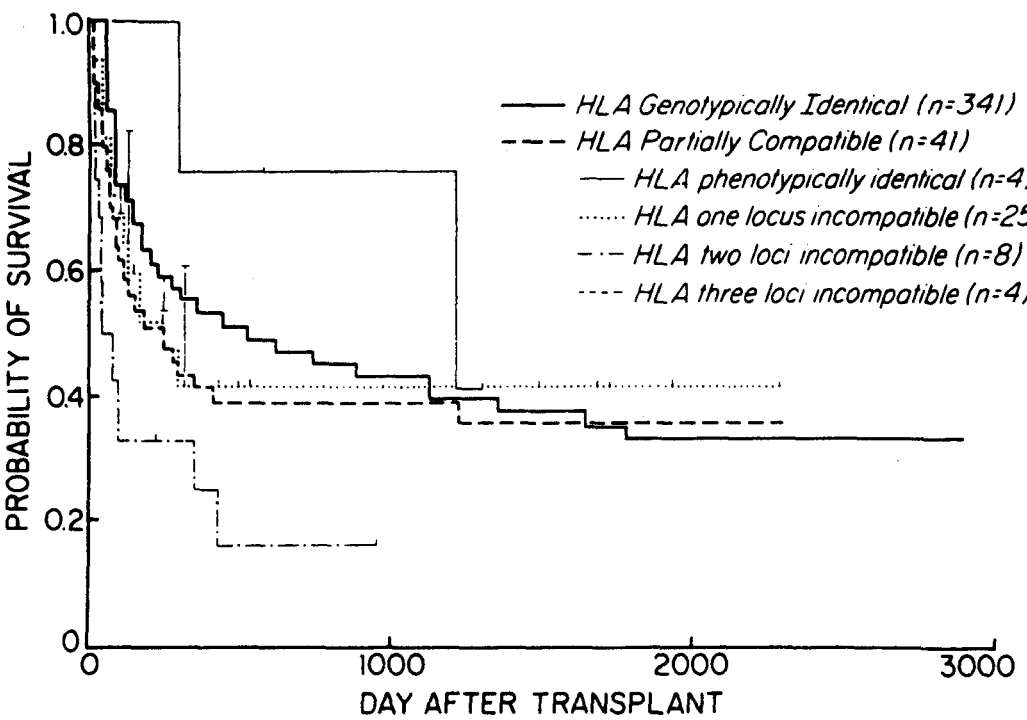


**Fig. 2.** Survival of 105 patients grafted from phenotypically matched or mismatched family donors. (After [6])

**Table 8.** Strategies for bone marrow transplantation in childhood leukemia in Germany (After [7]). Mismatch transplantation in the absence of an HLA-Identical sibling donor

| | Sibling donor 1Ag-mismatch > 1Ag-mismatch | | Unrelated donor 1Ag-mismatch > 1Ag-mismatch | |
|---|---|---|---|---|
| CML | + | $(+)_T$ | + | o |
| ALL 1.CR | o* | o | o | o |
| ALL 2.CR | + | $+_T$ | $+_T$ | $(+)_T$ |
| AML 1.CR | $(+)_{(T)}$ | o | o | o |
| AML 2.CR | $+_{(T)}$ | $(+)_T$ | $+_T$ | $(+)_T$ |

o = not recommended; + = recommended; T = T-cell depletion; (+) = (T) to be discussed; * = to be discussed for high-risk patients

matched donors were presented and discussed in part at the 4th Expert Meeting of the Kind-Philipp Foundation in November 1985. For the pediatric situation in Germany, we have drawn the conclusions presented in Table 8 [7].

## E. New Developments to Prevent GVHD, Engraftment Failure, and Relapse of Leukemia

Even in the absence of an HLA-identical sibling, bone marrow transplantation can still offer a curative chance for some patients using other donors. But the main problems of engraftment, GVHD, and GVHD-related infections have to be solved.

Controlled studies in Iowa City concerning the relevance of T-cell depletion for GVHD prophylaxis in mismatched bone marrow transplantation are now in progress. For mismatched transplantation in immunodeficient patients, it can be concluded [8] that significant GVHD does not occur but that engraftment failure can be a problem with T-cell depletion. Promising initial results have been obtained in matched bone marrow transplantation through the use of such monoclonal antibodies as Campath I in vitro for T-cell depletion and in vivo, after bone marrow transplantation, for GVHD prophylaxis [9]. The combination of T-cell depletion in vitro and use of LFA1 monoclonal antibody in vivo after bone marrow transplantation has been successfully employed in Paris in two patients with osteopetrosis and the Wiskott-Aldrich syndrome. The patients underwent rapid engraftment and did not develop GVHD [10]. It can be speculated that with the help of this protocol, the engraftment problems can be resolved. Intensification of total body irradiation (TBI) and chemoconditioning have been associated with a significant increase in toxicity, but there are some interesting data on the combination of TBI and total nodal irradiation to prevent engraftment failure and relapse after bone marrow transplantation. As far as chemotherapy as a conditioning regimen is concerned, no promising new approach offering a difference in survival rates is in sight. Nevertheless, preliminary data on the escalation of cyclophosphamide up to the dose used in aplastic anemia indicate that survival can be improved by decreasing the relapse rate.

The GVHD-related infections and immunodeficiency are the major cause of death in mismatched transplantation in the largest number of cases available from Iowa City. Through consequent administration of trimethoprim for prophylaxis of pneumocystis carinii, prophylactic use of 7S immunoglobulins, adequate herpes virus prophylaxis with acyclovir and perhaps CMV hyperimmunoglobulin, and total decontamination with elimination of gram-negative bacteria, the problems with infections may prove to be of minor importance.

Both improvement in the prophylactic treatment of graft failure and GVHD and improvement in the prophylaxis of GVHD-related infections may lead to increased survival rates in mismatched bone marrow transplantation.

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