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ORIGINAL ARTICLE

# Bone marrow transplants from mismatched related and unrelated donors for severe aplastic anemia

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**For patients with acquired severe aplastic anemia without a matched sibling donor and not responding to immunosuppressive treatment, bone marrow transplantation from a suitable alternative donor is often attempted. We examined risks of graft failure, graft-versus-host disease and overall survival after 318 alternative donor transplants between 1988 and 1998. Sixty-six patients received allografts from 1-antigen and 20 from >1-antigen mismatched related donors; 181 from matched and 51 from mismatched unrelated donors. Most patients were young, had had multiple red blood cell transfusions and poor performance score at transplantation. We did not observe differences in risks of graft failure and overall mortality by donor type. The probabilities of graft failure at 100 days after 1-antigen mismatched related donor, >1-antigen mismatched related donor, matched unrelated donor and mismatched unrelated donor transplants were 21, 25, 15 and 18%, respectively. Corresponding probabilities of overall survival at 5 years were 49, 30, 39 and 36%, respectively. Although alternative donor transplantation results in long-term survival, mortality rates are high. Poor performance score and older age adversely affect outcomes after transplantation. Therefore, early referral for transplantation should be encouraged for patients who fail immunosuppressive therapy and have a suitable alternative donor.**

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## Introduction

Patients with acquired severe acquired aplastic anemia (SAA) were among the first to benefit from allogeneic bone marrow transplantation (BMT). In fact, the first clinical trials comparing transplant to non-transplant treatment was in patients with SAA receiving BMT vs androgens.[1,2] Bone marrow transplantation from an HLA-identical sibling is a well-established first-line treatment for young patients with SAA with excellent long-term results.[3–7] Imunosuppressive treatment with antithymocyte globulin and cyclosporine is an alternative therapy for patients without an HLA-matched related donor, patients with non-severe aplastic anemia, or older patients at higher risk of transplant-related morbidity and mortality.[8–10] Results of both treatment modalities are considered acceptable. Younger patients with severe neutropenia have better outcomes using an upfront transplant strategy and older patients and those with less severe disease are more likely to benefit from immunosuppression as first-line treatment,[9] since patients with severe neutropenia have a higher risk of infection-related deaths during nontransplant therapy while older patients are more likely to develop severe graft-versus-host disease (GVHD) after transplantation. Current practice guidelines do not recommend transplantation from an alternative donor as first-line treatment.[9–11]

Transplantation from donors other than HLA-identical relatives can be successful, with first reports of unrelated donor transplantation dating back to the early 1970s.[12–16] There are relatively few studies focusing on alternative related or unrelated donor transplantation for SAA.[13,17–20] Probabilities of overall survival after unrelated donor transplant range from 29 to 50%, but most series are small with short follow-up. Information at the level of detail required for decision making, such as outcome of transplants from 1-antigen-mismatched siblings as a first-line treatment vs later in the disease course, outcome using relatives with more than one mismatch, unrelated donor transplantation as upfront vs salvage treatment with information on the degree of HLA-matching, is lacking.

This report focuses on outcomes of patients transplanted for SAA with donors other than HLA-identical siblings and reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

## Patients and methods

### *Data sources*

The CIBMTR comprises a voluntary working group of more than 450 transplant centers worldwide that contribute data on consecutive hematopoietic stem cell transplantations to a Statistical Center at the Health Policy Institute of the Medical College of Wisconsin. The CIBMTR collects data at two levels: Registration and Research. Participating centers are required to report all consecutive transplants. Registration data include disease type, age, sex, disease, date of diagnosis, disease stage at transplantation, graft type, conditioning regimen, post-transplant disease progression and survival, development of a new malignancy and cause of death. All participating transplant teams contribute Registration data. Research data are collected on selected subsets of registered patients, selected using a randomized weighted scheme and include detailed pre- and post-transplant data. All patients are followed longitudinally, with yearly follow-up. Computerized checks for errors, physician reviews of submitted data and on-site audits of participating centers ensure the data quality.

### *Patients*

This study included 318 recipients of transplants from donors other than HLA-identical relatives transplanted between 1988 and 1998 and reported to the CIBMTR by 112 transplant centers in 29 countries. High-resolution typing at HLA-A, B and DR was available for only 6% of 1-antigen mismatched related donor–recipient pairs, 1% of >1-antigen mismatched related donor–recipient pairs, 25% of matched unrelated donor–recipient pairs and 10% of mismatched unrelated donor–recipient pairs. Therefore, donor–recipient compatibility at HLA-A, B, and DR loci were based on low-resolution typing. Donor–recipient compatibility at HLA-C was not considered, as this was available for only 11% of 1-antigen mismatched related donor–recipient pairs, 3% of >1-antigen mismatched related donor–recipient pairs, 20% of matched unrelated donor–recipient pairs and 9% of mismatched unrelated donor–recipient pairs. One hundred and eighty-one patients received HLA-matched unrelated donor transplants, 51 received HLA-mismatched related donor transplants, and 86 received HLA-mismatched related donor transplants. Median follow-up of survivors was 59 (12–144) months for 1-antigen mismatched related donor patients, 90 (69–112) months for >1-antigen mismatched related donor patients, 62 (3–139) months for matched unrelated donor patients and 61 (8–136) months for mismatched unrelated donor patients. Nine recipients of peripheral blood transplants were excluded, as were nine patients in whom HLA reports were not obtained for confirmation of donor–recipient HLA disparity.

### *End points*

The primary outcomes studied were graft failure, acute and chronic GVHD and overall survival. The absence of hematopoietic recovery (absolute neutrophil count (ANC) $\geqslant 500/\mu$l) and initial neutrophil recovery with later declines to $<500/\mu$l were considered graft failures. Acute and chronic GVHD were defined as grade II–IV acute GVHD and any chronic GVHD (limited or extensive), respectively.[21,22] For analyses of overall survival, failure was death from any cause; surviving patients were censored at the date of last contact.

### *Statistical analysis*

Characteristics of patients were compared using the $\chi^2$ test for categorical variables and the Kruskal–Wallis test for continuous variables. For univariate analysis of graft failure and GVHD, cumulative incidence curves accommodating competing risks (i.e. death from other causes) were used, and for overall survival, the Kaplan–Meier estimator was used.

Assessment of potential risk factors for outcomes of interest were evaluated in multivariate analyses using Cox proportional hazards regression.[23,24] Variables considered in multivariate analysis are listed in Table 1. First, we determined if there was an interaction between type of donor and the factor being examined and tested for proportional hazards for each factor in the Cox model

**Table 1** Variables tested in Cox proportional hazards regression models

*Main effect variable*[a]
- Type of donor: Match unrelated[b] vs mismatched unrelated vs 1-antigen mismatched related vs >1-antigen mismatched related

*Patient-related variables*
- Age at transplant: <21 years[b] vs ⩾21 years
- Gender: female[b] vs male
- Karnofsky performance status at transplant: <90%[b] vs ⩾90%

*Disease-related variables*
- Prior treatment: none[b] vs ATG + CsA ± other vs ATG ± other vs CsA ± other vs androgen ± other vs other
- Courses of ATG: 0[b] vs 1 vs ⩾2 vs missing
- Number of transfusions: 0–20[b] vs 21–50 vs >50
- Conditioning regimen: Cy + antibodies ± other[b] vs Cy + LFR ± other vs Cy + TBI ± other vs others
- Time from diagnosis to transplant: <3 months[b] vs 3–6 months vs 6–12 months vs >12 months

*Treatment-related variables*
- Donor age: <21 years[b] vs ⩾21 years
- Donor–recipient sex match: male–male[b] vs female–male vs male–female vs female–female
- Donor–patient relationship: other relative[b] vs sibling
- Year of transplant: 1988–1994[b] vs 1995–1998
- GVHD prophylaxis: MTX ± CsA ± others[b] vs CsA ± other (not MTX) vs T-depletion ± other
- Growth factors post transplant: no[b] vs yes

[a]Included in all models.
[b]Baseline group.
CsA, cyclosporine; Cy, cyclophosphamide; LFR, limited field radiation; TBI, total body irradiation; GVHD, graft-versus-host disease; MTX = methotrexate.

using time-dependent covariates. As there were no time-varying effects, the final multivariate model was built using a forward stepwise model selection approach. All models included the main effect term reflecting donor type, that is, matched unrelated vs mismatched unrelated vs 1-antigen mismatched related vs >1-antigen mismatched related (match unrelated donor transplantation being the reference group). Factors significant at the 5% level were kept in the final model. Examination for center effects was performed using a random effects model.[25] We found no evidence of correlation between center and any of the outcomes. All *P*-values are two-sided. All analyses were performed using SAS version 8.0.

## Results

Table 2 shows patient, disease, and transplant characteristics of the 318 patients included in the study. Seventeen percent of alternative related donor transplant were carried out as first-line treatment compared to about 5% of unrelated donor transplants. Approximately 40% of patients in the four groups had poor performance scores at the time of transplantation. Recipients of unrelated donor transplants had a longer interval between diagnosis and transplant and had more red blood cell transfusions prior to transplant than recipients of related donor transplants. Eighty-nine percent of the patients received pre-transplant conditioning with cyclophosphamide (Cy) plus either antibodies (mainly antithymocyte globulin), or irradiation (limited field (LFR) or total body irradiation (TBI)). Six percent of patients received pre-transplant conditioning with Cy alone. Graft-versus-host disease prophylaxis was with cyclosporine (CSA) with or without other agents. Fourteen percent of grafts were T-cell depleted. A third of patients received growth factors post transplant (initiated within 7 days of infusion of graft) to accelerate hematopoietic recovery. Unrelated donor transplants were more frequent in the later 1990s whereas alternative related donor transplants were distributed equally across the decade. The decision to proceed to transplant, choice of donor and other characteristics, such as choice of conditioning regimen and GVHD prophylaxis were determined by transplant centers.

### *Graft failure*

Graft failure was evaluable in 315 of 318 patients. The probabilities of primary or secondary graft failure at 100 days post transplant were 21 (95% confidence interval (CI) 12–32)%, 25 (95% CI 9–45)%, 15 (95% CI 10–20)% and 18 (95% CI 9–29)% after 1-antigen mismatched related, >1-antigen mismatched related donor, matched unrelated donor and mismatched unrelated donor transplants, respectively (Table 3, Figure 1). In multivariate analysis, risks of graft failure did not differ significantly by donor type (Table 4). However, graft failure was more likely in recipients with poor performance score at transplantation.

### *Graft-versus-host disease*

Graft-versus-host disease was evaluable in 316 of 318 patients. Probabilities of grades 2–4 acute GVHD at 100 days post-transplant were 35 (95% CI 24–47)%, 15 (95% CI 3–33)%, 48 (95% CI 40–55)% and 37 (95% CI 25–51)% after 1-antigen mismatched related, >1-antigen mismatched related donor, matched unrelated donor and mismatched unrelated donor transplants, respectively (Table 3, Figure 2). There were no significant differences in risks of acute GVHD by donor type except that recipients of >1-antigen mismatched related donor transplants had a lower risk of developing acute GVHD than recipients of matched unrelated transplants. Approximately a third of recipients of >1-antigen mismatched related donor transplants received T-cell depleted grafts compared to 11% of recipients of matched unrelated donor transplants and this may explain the lower rate of GVHD.

Five year probabilities of chronic GVHD (limited or extensive) were 19 (95% CI 11–30%), 23 (95% CI 7–44%), 29 (95% CI 22–36%) and 24 (95% CI 13–36%) after 1-antigen mismatched related, >1-antigen mismatched related donor, matched unrelated donor and mismatched unrelated donor transplants, respectively (Figure 3). In multivariate analysis, risks of chronic GVHD did not differ significantly by donor type (Table 4). However, chronic GVHD was more likely in older patients (⩾21 years) and those with good performance scores at transplantation.

### *Overall mortality*

The 5-year probabilities of overall survival were 49 (95% CI 36–60%), 30 (95% CI 12–50%), 39 (95% CI 31–46%) and 36 (95% CI 23–50%) after 1-antigen mismatched related, >1-antigen mismatched related donor, matched unrelated donor and mismatched unrelated donor transplants, respectively (Figure 4). In multivariate analysis, risks of mortality did not differ significantly by donor type (Table 4), but mortality was significantly higher in older patients, and in those with poor performance scores at transplant. Thirty-five of 66 (53%) recipients of 1-antigen mismatched related, 14 of 20 (70%) >1-antigen mismatched related donor, 109 of 181 (60%) matched unrelated donor and 33 of 51 (65%) mismatched unrelated donor transplants died (Table 5). There were no significant differences in causes of death by donor type.

## Discussion

Reported results of alternative donor transplantation for SAA are rather heterogeneous and most but not all series are limited by small numbers of patients. The largest series to date described 154 patients who underwent matched or mismatched unrelated donor bone marrow transplant with an estimated overall survival of 56%.[26] The current study examined outcomes after HLA-mismatched related and HLA-matched and mismatched unrelated donor transplantation for SAA between 1988 and 1998. We did not observe significant differences in risks of graft failure or mortality by donor type. Survival rates were 30–49% at 5-years post-transplant in the four groups, which is comparable to

**Table 2** Characteristics of patients receiving alternative related or unrelated donor bone marrow transplants for SAA between 1988 and 1998, by type of donor

| *Variables* | *Mismatched related donor* | | | | *Unrelated donor* | | | |
|---|---|---|---|---|---|---|---|---|
| | *No. eval* | *1-antigen mismatch* | *No. eval* | *>1-antigen mismatch* | *No. eval* | *Match* | *No. eval* | *Mismatch* |
| Number of patients | | 66 | | 20 | | 181 | | 51 |
| Age, median (range) (years)* | 66 | 14 (1–46) | 20 | 19 (<1–41) | 181 | 16 (1–55) | 51 | 10 (2–44) |
| *Age at transplant* (years)* | 66 | | 20 | | 181 | | 51 | |
| ⩽10 | | 19 (29) | | 6 (30) | | 54 (30) | | 30 (59) |
| 11–20 | | 27 (41) | | 7 (35) | | 73 (40) | | 11 (21) |
| 21–30 | | 11 (17) | | 4 (20) | | 32 (18) | | 5 (10) |
| 31–40 | | 8 (12) | | 3 (15) | | 12 (7) | | 3 (6) |
| >40 | | 1 (1) | | 0 | | 10 (5) | | 2 (4) |
| Male sex | 66 | 42 (64) | 20 | 10 (50) | 181 | 96 (53) | 51 | 35 (69) |
| Karnofsky score ⩾90% | 66 | 38 (58) | 20 | 13 (65) | 181 | 109 (60) | 51 | 30 (59) |
| *Prior treatment** | 66 | | 20 | | 181 | | 51 | |
| None | | 12 (18) | | 3 (15) | | 10 (6) | | 2 (4) |
| ATG + CsA ± other | | 19 (29) | | 4 (20) | | 91 (50) | | 31 (61) |
| ATG ± other (not CsA, not androgens) | | 10 (15) | | 5 (25) | | 25 (14) | | 5 (10) |
| CsA ± other (not ATG, not androgens) | | 5 (8) | | 4 (20) | | 14 (8) | | 2 (4) |
| Androgens ± other | | 14 (21) | | 2 (10) | | 33 (18) | | 9 (17) |
| Other[a] | | 6 (9) | | 2 (10) | | 8 (4) | | 2 (4) |
| *Courses of ATG* | 20 | | 9 | | 84 | | 28 | |
| 1 | | 12 (60) | | 8 (89) | | 55 (65) | | 18 (64) |
| 2 | | 6 (30) | | 1 (11) | | 21 (25) | | 6 (21) |
| 3 | | 1 (5) | | 0 | | 0 | | 1 (4) |
| 4 | | 1 (5) | | 0 | | 8 (10) | | 3 (11) |
| *Number of transfusions* | 64 | | 20 | | 177 | | 51 | |
| 0–20 | | 15 (24) | | 9 (45) | | 38 (22) | | 8 (16) |
| 21–50 | | 18 (28) | | 1 (5) | | 40 (23) | | 9 (17) |
| >50 | | 25 (39) | | 9 (45) | | 84 (47) | | 29 (57) |
| Transfusions given, # unk | | 6 (9) | | 1 (5) | | 15 (8) | | 5 (10) |
| *Conditioning regimen** | 66 | | 20 | | 181 | | 51 | |
| Cy + antibodies ± others | | 24 (36) | | 8 (40) | | 69 (38) | | 14 (27) |
| Cy + LFR ± others | | 11 (17) | | 1 (5) | | 17 (9) | | 3 (6) |
| Cy + TBI ± others | | 16 (24) | | 11 (55) | | 79 (44) | | 29 (57) |
| Cy alone | | 4 (6) | | 0 | | 2 (1) | | 1 (2) |
| Cy + BU ± others | | 7 (11) | | 0 | | 8 (5) | | 4 (8) |
| Others[b] | | 4 (6) | | 0 | | 6 (3) | | 0 |
| *Donor recipient sex match* | 65 | | 20 | | 173 | | 50 | |
| M–M | | 15 (23) | | 6 (30) | | 49 (28) | | 23 (46) |
| M–F | | 11 (17) | | 5 (25) | | 40 (23) | | 7 (14) |
| F–M | | 26 (40) | | 4 (20) | | 41 (24) | | 11 (22) |
| F–F | | 13 (20) | | 5 (25) | | 43 (25) | | 9 (18) |
| *Donor/patient relationship* | 66 | | 20 | | NA | | NA | |
| Sibling | | 41 (62) | | 8 (40) | | | | |
| Parent/children | | 22 (33) | | 11 (55) | | | | |
| Other relative | | 3 (5) | | 1 (5) | | | | |
| *HLA class mismatch** | 66 | | 20 | | 181 | | 51 | |
| None | | 0 | | 0 | | 181 (100) | | 0 |
| I | | 41 (62) | | 9 (45) | | | | 45 (88) |
| II | | 25 (38) | | 0 | | | | 4 (8) |
| I and II | | 0 | | 11 (55) | | | | 2 (4) |
| Time from diagnosis to transplant, median (range) (months)* | 66 | 7 (<1–99) | 20 | 4 (1–40) | 179 | 13 (2–245) | 51 | 11 (4–124) |

**Table 2** Continued

| *Variables* | *Mismatched related donor* | | | | *Unrelated donor* | | | |
|---|---|---|---|---|---|---|---|---|
| | *No. eval* | *1-antigen mismatch* | *No. eval* | *>1-antigen mismatch* | *No. eval* | *Match* | *No. eval* | *Mismatch* |
| *Time from dx to tx (months)** | 66 | | 20 | | 179 | | 51 | |
| <3 | | 13 (20) | | 8 (40) | | 10 (5) | | 0 |
| 3–6 | | 17 (26) | | 7 (35) | | 28 (16) | | 8 (16) |
| 6–12 | | 15 (22) | | 1 (5) | | 41 (23) | | 20 (39) |
| >12 | | 21 (32) | | 4 (20) | | 100 (56) | | 23 (45) |
| *Year of transplant** | 66 | | 20 | | 181 | | 51 | |
| 1988–1989 | | 17 (26) | | 3 (15) | | 18 (10) | | 1 (2) |
| 1990–1991 | | 12 (18) | | 5 (25) | | 27 (15) | | 8 (16) |
| 1992–1993 | | 10 (15) | | 5 (25) | | 44 (24) | | 12 (24) |
| 1994–1995 | | 11 (17) | | 5 (25) | | 47 (26) | | 14 (27) |
| 1996–1998 | | 16 (24) | | 2 (10) | | 45 (25) | | 16 (31) |
| *GVHD prophylaxis** | 66 | | 20 | | 181 | | 51 | |
| MTX ± CsA ± other | | 51 (77) | | 7 (35) | | 125 (69) | | 24 (47) |
| CsA ± other | | 6 (9) | | 6 (30) | | 37 (20) | | 18 (35) |
| T-depletion ± other | | 9 (14) | | 7 (35) | | 19 (11) | | 9 (18) |
| G-CSF or GM-CSF within 7 days pre-tx | 66 | 17 (26) | 20 | 6 (30) | 181 | 65 (36) | 51 | 17 (33) |
| Median FU of survivors (months) | | 59 (12–144) | | 90 (69 -112) | | 62 (3–139) | | 61 (8–136) |

Abbreviations: SAA = severe aplastic anemia; eval = evaluable; dx = diagnosis; tx = transplant; CsA = cyclosporine; HLA = human leukocyte antigen; DNA = deoxyribonucleic acid; CY = cyclophosphamide; LFR = limited field radiation; TBI = total body irradiation; BU = busulfan; GVHD = graft-versus-host disease; MTX = methotrexate; G-CSF = granulocyte-colony stimulating factor; GM-GSF = granulocyte–macrophage colony-stimulating factor; FU = follow-up; unk = unknown.
[a]Other type of treatments were cytokines alone, corticosteroids alone, corticosteroids + FK506 and corticosteroids + cytokines.
[b]Other conditioning regimen were cyclophosphamide + monoclonal antibody; total body irradiation + atg; total body irradiation.
**P*-value <0.05.

**Table 3** Univariate analysis of transplant outcomes among patients receiving alternative related or unrelated donor bone marrow transplants for SAA between 1988 and 1998, by type of donor

| *Outcomes* | *Mismatched related donor* | | | | *Unrelated donor* | | | |
|---|---|---|---|---|---|---|---|---|
| | *1-antigen mismatch* | | *>1-antigen mismatch* | | *Match* | | *Mismatch* | |
| | *No. eval* | *Prob (95% CI)*[a] | *No. eval* | *Prob (95% CI)*[a] | *No. eval* | *Prob (95% CI)*[a] | *No. eval* | *Prob (95% CI)*[a] |
| *Graft failure* | 66 | | 20 | | 178 | | 51 | |
| At 100 days | | 21 (12–32) | | 25 (9–45) | | 15 (10–20) | | 18 (9–29) |
| At 1 year | | 26 (16–37) | | 25 (9–45) | | 17 (12–23) | | 24 (13–36) |
| Acute GVHD at 100 days, grades (2–4) | 66 | 35 (24–47) | 20 | 15 (3–33) | 179 | 48 (40–55) | 51 | 37 (25–51) |
| *Chronic GVHD* | 66 | | 20 | | 179 | | 51 | |
| At 1 year | | 18 (9–28) | | 23 (7–44) | | 26 (20–33) | | 22 (11–34) |
| At 3 years | | 19 (11–30) | | 23 (7–44) | | 29 (22–36) | | 24 (13–36) |
| At 5 years | | 19 (11–30) | | 23 (7–44) | | 29 (22–36) | | 24 (13–36) |
| *Survival* | 66 | | 20 | | 181 | | 51 | |
| At 1 year | | 49 (36–60) | | 35 (16–55) | | 49 (41–56) | | 41 (28–54) |
| At 3 years | | 49 (36–60) | | 35 (16–54) | | 41 (34–49) | | 39 (26–52) |
| At 5 years | | 49 (36–60) | | 30 (12–50) | | 39 (31–46) | | 36 (23–50) |

Abbreviations: eval = evaluable; CI = confidence interval; prob = probability; GVHD = graft-versus-host disease.
[a]Probabilities of acute GVHD, chronic GVHD and graft failure were calculated using the cumulative incidence estimate. Survival was calculated using the Kaplan–Meier product limit estimate.

earlier published reports.[18,19,27–29] Recent data from the Japan Marrow Donor Program indicate higher survival rates with unrelated donor transplantation.[26] Our cohorts differ in that donor–recipient HLA disparity in the current study was determined by low or intermediate resolution. In contrast, donor–recipient HLA disparity in the Japanese

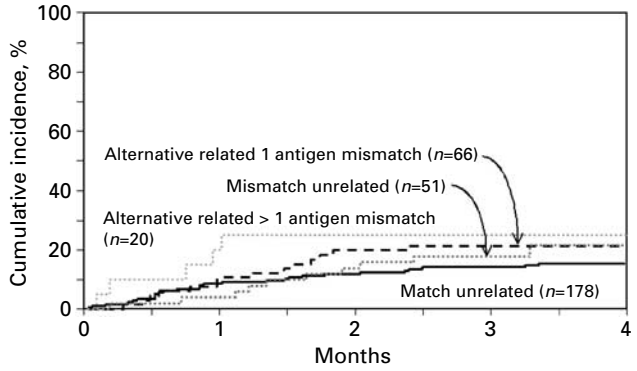


**Figure 1** Cumulative incidence of graft failure after unrelated or mismatched related bone marrow transplantation for severe acquired aplastic anemia, by donor type.

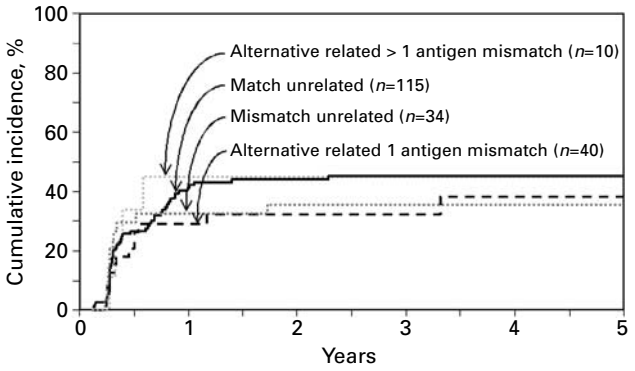


**Figure 3** Cumulative incidence of chronic graft-versus-host disease of any grade after unrelated or mismatched related bone marrow transplantation for severe acquired aplastic anemia, by donor type.

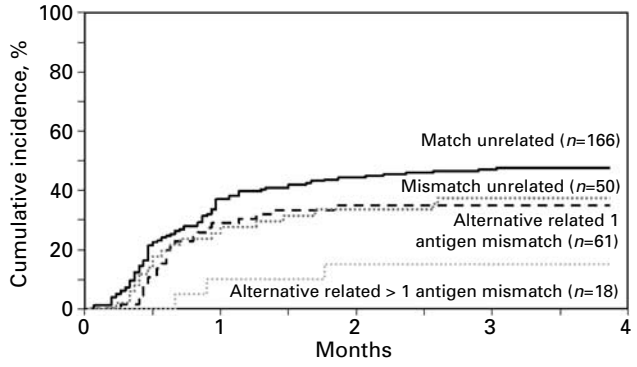


**Figure 2** Cumulative incidence of acute grade II–IV graft-versus-host disease after unrelated or mismatched related bone marrow transplantation for severe acquired aplastic anemia, by donor type.

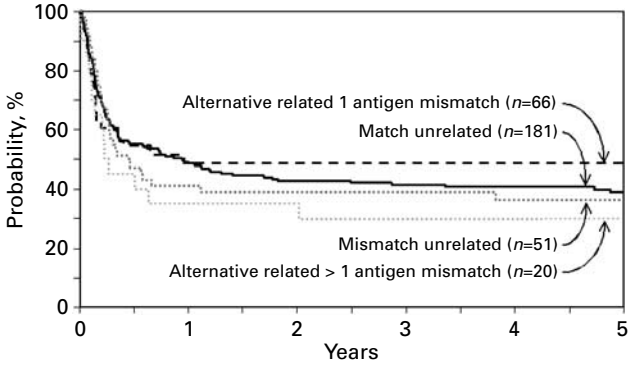


**Figure 4** Probability of survival after unrelated or mismatched related bone marrow transplantation for severe acquired aplastic anemia, by donor type.

study was determined using high-resolution techniques. Although donor–recipient compatibility was not a significant prognostic factor in either study, it is likely that a generally higher degree of mismatch in the current study had an adverse effect on post transplant survival.[30] Consistent with other reports, mortality was higher among older recipients and among those with a poor performance score at transplant in all groups. This suggests early referral might be beneficial for patients in whom transplantation is considered and who have a suitable related or unrelated donor.

We did not observe an effect of time from diagnosis to transplant on overall survival even though unrelated donor transplants were performed considerably longer after diagnosis than alternative related donor transplants. However, effects of time interval between diagnosis and transplant are not easy to model as conflicting biases may be operating. Whereas, earlier transplantation may be favorable because of fewer therapies and transfusions, it can be unfavorable where selection for transplantation is due to intolerance or lack of response to initial immunosuppression. Late transplantation can be favorable because patients dying from early disease related complications are excluded, but can be unfavorable when patients who have had good responses to immunosuppression are excluded. We also did not have information on patients in whom a donor search was initiated but who did not survive to transplant. We did not observe an effect of prior treatment, including the use of androgens and survival after transplantation.

Donor–recipient HLA compatibility was determined based on low-resolution techniques as less than half the study population had high-resolution HLA typing data; this is a major limitation of the current analysis. Assignment of HLA compatibility based on low-resolution techniques may have lead to the inclusion of mismatched donor–recipient pairs in the matched group, especially in the unrelated setting, and may explain our inability to detect differences in transplant-outcomes by donor type. Additionally, we were unable to examine the impact of HLA-C as less than half of the study population had HLA-C typing data. Because of this, some practical issues related to donor selection remain unanswered. For example, it is not clear whether a fully high-resolution matched unrelated donor is preferable over a mismatched family donor. We observed graft failure rates of 17–26%, but did not observe significant differences between the groups. Our inability to observe differences may be explained by relatively small numbers of patients in each of the groups and the use of low-resolution methods to classify donor–recipient

**Table 4** Multivariate analysis of graft failure, acute and chronic GVHD and death among patients receiving alternative related or unrelated donor bone marrow transplants for SAA

| *Variables* | N | *Relative risk (95% CI)* | P-*value* |
|---|---|---|---|
| *Graft failure* | | | |
| Type of donor[c] | | | |
| (1) Match unrelated donor | 178 | 1.00[a] | $P^{b}_{overall} = 0.404$ |
| (2) Mismatched unrelated donor | 51 | 1.35 (0.69–2.64) | $P_{12} = 0.379$ |
| (3) 1-antigen mismatched related donor | 66 | 1.54 (0.85–2.80) | $P_{13} = 0.152$ |
| (4) >1-antigen mismatched related donor | 20 | 1.77 (0.69–4.56) | $P_{14} = 0.239$ |
| Other significant covariates | | | |
| Karnofsky performance status at transplant | | | |
| <90% | 126 | 1.00[a] | |
| ⩾90% | 189 | 0.38 (0.23–0.63) | 0.0002 |
| *Acute GVHD* | | | |
| Type of donor[c] | | | |
| (1) Match unrelated donor | 179 | 1.00[a] | $P^{b}_{overall} = 0.04$ |
| (2) Mismatched unrelated donor | 51 | 0.68 (0.42–1.12) | $P_{12} = 0.134$ |
| (3) 1-antigen mismatched related donor | 66 | 0.68 (0.43–1.09) | $P_{13} = 0.107$ |
| (4) >1-antigen mismatched related donor | 20 | 0.26 (0.08–0.84) | $P_{14} = 0.023$ |
| *Chronic GVHD* | | | |
| Type of donor[c] | | | |
| (1) Match unrelated donor | 179 | 1.00[a] | $P^{b}_{overall} = 0.719$ |
| (2) Mismatched unrelated donor | 51 | 1.12 (0.59–2.12) | $P_{12} = 0.721$ |
| (3) 1-antigen mismatched related donor | 66 | 0.74 (0.40–1.37) | $P_{13} = 0.341$ |
| (4) >1-antigen mismatched related donor | 20 | 1.15 (0.41–3.21) | $P_{14} = 0.787$ |
| Other significant covariates | | | |
| Age at transplant | | | |
| <21 years | 225 | 1.00[a] | |
| ⩾21 years | 91 | 1.78 (1.11–2.85) | 0.016 |
| Karnofsky performance status at transplant | | | |
| <90% | 127 | 1.00[a] | |
| ⩾90% | 189 | 2.93 (1.58–5.44) | 0.001 |
| *Overall mortality* | | | |
| Type of donor[c] | | | |
| (1) Match unrelated donor | 181 | 1.00[a] | $P^{b}_{overall} = 0.52$ |
| (2) Mismatched unrelated donor | 51 | 1.10 (0.99–1.84) | $P_{12} = 0.62$ |
| (3) 1-antigen mismatched related donor | 66 | 0.86 (0.58–1.25) | $P_{13} = 0.42$ |
| (4) >1-antigen mismatched related donor | 20 | 1.33 (0.76–2.32) | $P_{14} = 0.32$ |
| Other significant covariates | | | |
| Age at transplant | | | |
| <21 years | 227 | 1.00[a] | |
| ⩾21 years | 91 | 1.35 (1.02–1.84) | 0.05 |
| Karnofsky performance status at transplant | | | |
| <90% | 128 | 1.00[a] | |
| ⩾90% | 190 | 0.52 (0.39–0.69) | <0.001 |

Abbreviations: CI = confidence interval; GVHD = graft-versus-host disease; RR = relative risk.
*Graft failure*:
[a]Reference group.
[b]Three degrees of freedom.
[c]Other pairwise comparisons: 3 vs 2: RR = 1.14 (0.55–2.39), $P = 0.72$; 4 vs 2: RR = 1.31 (0.46–3.72), $P = 0.61$; 4 vs 3: RR = 1.14 (0.42–3.11), $P = 0.79$.
*Acute GVHD*:
[a]Reference group.
[b]Three degrees of freedom.
[c]Other pairwise comparisons: 3 vs 2: RR = 1.00 (0.55–1.84), $P = 0.99$; 4 vs 2: RR = 0.39 (0.11–1.31), $P = 0.13$; 4 vs 3: RR = 0.39 (0.12–1.28), $P = 0.12$.
*Chronic GVHD*:
[a]Reference group.
[b]Three degrees of freedom.
[c]Other pairwise comparisons: 3 vs 2: RR = 0.66 (0.30–1.45), $P = 0.30$; 4 vs 2: RR = 1.03 (0.33–3.19), $P = 0.97$; 4 vs 3: RR = 1.55 (0.50–4.77), $P = 0.44$.
*Overall survival*:
[a]Reference group.
[b]Three degrees of freedom.
[c]Other pairwise comparisons: 3 vs 2: RR = 0.77 (0.48–1.25), $P = 0.30$; 4 vs 2: RR = 1.20 (0.64–2.26), $P = 0.56$; 4 vs 3: RR = 1.55 (0.84–2.89), $P = 0.16$.

HLA disparity. Nevertheless, in the current study, no patients lost their graft a year or later after transplant. The current study, with a median follow-up of at least 5 years in all groups, shows that in patients with acquired SAA alternative donor transplantation results in long-term survival in a considerable proportion of patients.

**Table 5** Causes of death

| | *Mismatched related donor* | | *Unrelated donor* | |
|---|---|---|---|---|
| | *1-antigen mismatch* | *>1-antigen mismatch* | *Match* | *Mismatch* |
| Number of patients | 66 | 20 | 181 | 51 |
| Number of deaths | 35 | 14 | 109 | 33 |
| *Causes of death* | | | | |
| Graft failure | 11 (31) | 1 (7) | 13 (12) | 4 (12) |
| Infection | 8 (23) | 4 (29) | 20 (18) | 4 (12) |
| IPN | 1 (3) | 3 (22) | 6 (6) | 4 (12) |
| ARDS | 1 (3) | 1 (7) | 4 (4) | 0 |
| GVHD | 2 (6) | 1 (7) | 16 (15) | 6 (18) |
| Organ failure | 4 (11) | 2 (14) | 18 (16) | 4 (12) |
| Secondary malignancy | 0 | 1 (7) | 2 (2) | 1 (3) |
| Hemorrhage | 4 (11) | 0 | 7 (6) | 4 (12) |
| TTP | 1 (3) | 0 | 3 (3) | 0 |
| GVHD and IPN | 2 (6) | 1 (7) | 3 (3) | 1 (3) |
| Others | 1 (3) | 0 | 17 (15) | 5 (16) |

Abbreviations: eval = evaluable; GVHD = graft-versus-host disease; IPN = interstitial pneumonia; ARDS = adult respiratory distress syndrome; TTP = thrombotic thrombocytopenic purpura.

Nevertheless, overall mortality remains high and is primarily due to graft failure, GVHD and infectious complications. Overall the population analyzed was young, only one-third of patients are above 20 and few were above 40. Extrapolation of results to older patient cohorts is therefore impossible. We were unable to identify patient or donor characteristics or a transplant strategy likely to result in improved outcomes. In a small series of patients ($n = 9$) who received highly purified CD34+ progenitor cells from matched or mismatched unrelated donors, there were no reports of acute or chronic GVHD.[28] These results are encouraging and need to be validated in a larger series prior to wide spread adoption in the setting of alternative donor transplants. In this study we have not seen a significant effect of year of transplantation, one would hope that with improved typing technology better donor selection would be possible. This study was limited to patients transplanted up to 1998. Future studies should also address the question whether advances in HLA-typing and donor matching strategies (i.e. high-resolution typing at HLA-A, B, C and DRB1) will translate into higher survival for patients with SAA. This study provides a benchmark against which, future improvement is to be measured.

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