Biol Blood Marrow Transplant 25 (2019) 1970−1974

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Allogeneic – Adult

High Graft-versus-Host Disease-Free, Relapse/Rejection-Free Survival and Similar Outcome of Related and Unrelated Allogeneic Stem Cell Transplantation for Aplastic Anemia: A Nationwide Swedish Cohort Study

Krista Vaht[1,2,*], Magnus Göransson[3], Kristina Carlson[4], Cecilia Isaksson[5], Stig Lenhoff[6], Anna Sandstedt[7], Bertil Uggla[8], Jacek Winiarski[9], Per Ljungman[10,11], Per-Ola Andersson[2,12], Mats Brune[1,2]

[1] *Section of Hematology and Coagulation, Sahlgrenska University Hospital, Gothenburg, Sweden*
[2] *Institute of Medicine, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden*
[3] *Department of Pediatrics, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden*
[4] *Department of Hematology, Uppsala University Hospital, Uppsala, Sweden*
[5] *Department of Hematology, Cancer Centre, University Hospital, Umeå, Sweden*
[6] *Department of Hematology, Skåne University Hospital, Lund University, Lund, Sweden*
[7] *Department of Hematology, Linköping University Hospital, Linköping, Sweden*
[8] *Section of Hematology Department of Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden*
[9] *Astrid Lindgren Children's Hospital, Karolinska University Hospital, Huddinge and CLINTEC, Karolinska Institutet, Stockholm, Sweden*
[10] *Centre of Allogeneic Stem Cell Transplantation Unit (CAST), Karolinska University Hospital, Stockholm, Sweden*
[11] *Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden*
[12] *Department of Medicine, Södra Älvsborg Hospital Borås, Borås, Sweden*

Article history:
Received 18 February 2019
Accepted 28 May 2019

Key Word:
Aplastic anemia
Allogenic stem cell transplantation
Graft-versus-host disease-free
Relapse/rejection-free survival
Real-world data

ABSTRACT

Allogeneic stem cell transplantation (SCT) as primary treatment for aplastic anemia (AA) is being increasingly used. Yet, age, stem cell source, and donor type are important outcome factors. We have recently performed a nationwide cohort study of all patients with AA in Sweden diagnosed from 2000 to 2011 and now present outcome data on SCT patients. In total, 68 patients underwent SCT, and 63% of them had failed immunosuppressive therapy. We found that, with a median follow-up of 109 months (range, 35 to 192 months), 5-year overall survival (OS) for all patients was 86.8%, whereas graft-versus-host disease-free, relapse/rejection-free survival (GRFS) at 5 years was 69.1%. There was no survival impact regarding the donor type or stem cell source. Patients aged ≥40 years had a higher transplant-related mortality (29.4% versus 7.8%; $P = .023$), which translated into a lower 5-year OS: 70.6% versus 92.2% ($P = .022$) and a trend of lower GRFS (52.9% versus 74.5%; $P = .069$). In conclusion, we found in this real-world setting that both OS and GRFS were high, but SCT for patients with AA aged ≥40 years is problematic, and clinical trials addressing this issue are warranted.

INTRODUCTION

Current guidelines for the management of aplastic anemia (AA) recommend an upfront allogeneic hematopoietic stem cell transplantation (SCT) for patients who are <40 years of age with a sibling donor, whereas older patients or patients without a related donor should receive primary immunosuppressive therapy [1] (IST). Thus, SCT is routinely considered only for a minority of patients with newly diagnosed AA. However, there is increasing evidence indicating improved overall survival (OS) after unrelated donor SCT from approximately 50% in the 1970s to 76% in the early 2000s [2–6]. Nevertheless, patient age still appears to be the most important factor influencing the treatment results. Patients who are >40 years old have an OS rate of about 60%, which apparently has been unchanged during the past 15 years [7,8]. There are several probable explanations. High risk of infections, lack of an optimal conditioning regimen, and excessive rates of graft-versus-host disease (GVHD) all have been suggested as major obstacles to improve outcomes of older patients [7–9].

Furthermore, both severe acute GVHD (aGVHD) and chronic GVHD (cGVHD) have substantial effects on patient outcomes, which in many cases are not fully assessed by the conventional endpoints, that is, OS or relapse-free survival

Financial disclosure: See Acknowledgments on page 1974.
* Correspondence and reprint requests: Krista Vaht, MD, Section of Hematology and Coagulation, Department of Medicine, Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden.
E-mail address: krista.vaht@vgregion.se (K. Vaht).

https://doi.org/10.1016/j.bbmt.2019.05.032
1083-8791/

and transplant-related mortality (TRM). Thus, a novel composite endpoint, GVHD-free, rejection-free survival (GRFS), was recently introduced and represents more ideal recovery after SCT without ongoing morbidity [10]. GRFS events are defined as acute grade III to IV GVHD, cGVHD requiring systemic treatment, disease relapse, or death from any cause. It has been mainly used to evaluate the outcomes of SCT for malignant hematologic diseases, especially acute myeloid leukemia [11–13]. In a nonmalignant disease, GRFS could be even more clinically meaningful because disease relapse is an uncommon event that suggests a more important role for long-term GVHD morbidity.

Moreover, most contemporary publications regarding SCT for AA are registry-based or single-center studies, whereas nationwide studies describing real-world data are scarce [14,15]. We recently reported data in a nationwide study of the incidence, treatment, and outcomes of all patients with AA diagnosed in Sweden between 2000 and 2011 [16]. We found that over 60% of the patients were primarily treated with immunosuppressive therapy (mainly antithymocyte globulin [ATG]), and only 10% underwent first-line SCT. There were no differences in the response rate to ATG among age groups, and we found an excellent OS of responding patients. Still, 52 patients were treated with second-line ATG, and the common reasons for second ATG were lack of donor (38%) or patients' age (46%). Patients with very severe AA (VSAA) responded poorly to both first- and second-line ATG, which was translated into worse survival, suggesting the need for a different treatment approach [17].

In this report, we present detailed data from all allografted patients in our previous study. We focused on the effects of disease severity, stem cell source, age, and transplantation timing on patient survival. We also report the causes of death and the composite endpoint, GRFS.

PATIENTS AND METHODS

As described previously, we retrospectively identified all cases of acquired AA in patients diagnosed in Sweden between 2000 and 2011, and the data on incidence, overall outcome, and results of immunosuppressive therapy with ATG were recently published [16,17]. In the present study, we included all patients with AA who underwent SCT. Patients underwent transplantation either as the primary treatment or as second- or third-line measures after a failure of 1 or more ATG courses. Patients were allografted at 6 Swedish university hospitals: 6 adult and 4 pediatric centers. The study was approved by the Regional Ethics Review Board in Gothenburg.

AA diagnosis was defined according to the criteria by Camitta et al. [18]. GVHD was graded using patient medical records according to the National Institutes of Health 2014 criteria [19]. Graft failure was classified as (1) primary graft failure (neutrophil counts not reaching 0.5×10^9/L) and (2) graft rejection or secondary graft failure (a decrease in neutrophil counts to $<0.5 \times 10^9$/L after achieving a neutrophil count of $> 0.5 \times 10^9$/L) [20].

Statistical Analysis

OS was defined as the time from transplantation until the date of death or the last follow-up. The Kaplan-Meier method and log-rank test were used to calculate and compare OS and GRFS. In the GRFS calculation, grade III to IV aGVHD, cGVHD requiring systemic treatment, relapse (defined as graft rejection/failure), and death were considered the events [10]. Cumulative incidence functions were used to estimate GRFS event incidence in competing risks setting. Examining graft failure, death was considered a competing event; to study aGVHD, both rejection, death, and cGVHD were competing events, and for cGVHD, rejection and death were competing events. The statistical analyses were performed by SPSS version 25 (SPSS, Chicago, Illinois) or Stata for Macintosh version 13.1 (StataCorp, College Station, Texas).

RESULTS

Basic Data

Details of the entire patient cohort (n = 257) have been described previously [16]. A total of 68 patients (26.5%) underwent SCT, and their characteristics are presented in Table 1. Median age at transplantation was 22 years (range, 2 to 65 years), and 17 patients were ≥40 years of age. Sixty-three percent of the patients had been treated with 1 or more courses of IST. Transplantations by year and the type of donor are presented in Supplementary Table S1. During the time period, 13 patients were planned to undergo SCT, 9 of whom responded to first-line (n = 5), second-line (n = 3), and third-line (n = 1) ATG (6 complete remissions [CRs], 3 partial remissions [PRs]), and 4 did not survive because of infections (n = 3) and acute respiratory distress syndrome (n = 1).

Table 1
Patient Characteristics

Patients	First-Line SCT (n = 25)	Later SCT (n = 43)
Age, median (range), yr	18 (6-61)	29 (2-65)
Children ≤18 yr, n	13	14
Patients ≥40 yr, n	5	12
Sex (female/male), n	11/14	24/19
Donor type, n		
Unrelated donor	4	32
Sibling donor	21*	11
CMV, recipient/donor, n		
Positive/negative	9	10
Negative/positive	2	5
Matched	14	28
Stem cell source, BM/PB/CB	22/3/0	32/10/1
NSAA/SAA/VSAA (at time of transplant), n	2/16/7	1†/21/21
Previous ATG treatments, n		
1		28
2		14
3		1
Interval Dx-Tx days, median (range)	70 (17-255)	265 (87-2960)

CMV indicates cytomegalovirus; PB, peripheral blood; CB, cord blood; NSAA, non-severe aplastic anemia; SAA, severe aplastic anemia; Dx, diagnosis; Tx, transplantation.
* Including 2 monozygotic twin donors.
† NSAA with clonal evolution.

Stem Cell Donors and Stem Cell Source

Donors were unrelated donors (URDs, n = 36) or related (sibling) donors (RDs, n = 32). Two of the RDs were monozygotic twins. Seven URD recipients were mismatched at 1 or more loci. Stem cell sources were unmanipulated: bone marrow (BM, n = 54) or peripheral blood stem cells (PBSCs, n = 13). One patient received a double cord blood graft.

Conditioning Regimen

Patients receiving a graft from an RD were conditioned with cyclophosphamide combined with ATG (n = 20) or together with a third agent, fludarabine (n = 8). Cyclophosphamide alone was administered to 4 patients. Patients who received transplants from an URD were conditioned with fludarabine and cyclophosphamide with (n = 25) or without ATG (n = 3), for some combined with total-body irradiation, 2 Gy (n = 9) or 6 Gy total lymph node irradiation (n = 12). Seven patients received fludarabine-free conditioning: cyclophosphamide and ATG with (n = 3) or without 2 Gy total-body irradiation (n = 4). Two patients received busulfan-based conditioning because of clonal evolution and suspected transformation to a myelodysplastic syndrome.

Post-Transplantation Immunosuppression

Immunosuppression was given as cyclosporine (n = 35) or tacrolimus (n = 8) in combination with methotrexate (1 to 4 doses). Patients who did not receive methotrexate (n = 24) were treated with cyclosporine alone (n = 7) or in combination with mycophenolate (n = 8), post-transplantation cyclophosphamide (n = 1), sirolimus (n = 1), or tacrolimus with (n = 6) or without sirolimus (n = 1). One patient did not receive any immunosuppression. Median treatment duration with calcineurin inhibitors for patients surviving for ≥4 weeks was 436 days (range, 28 to 3184 days).

Graft Failure

Engraftment data are presented in Supplementary Table S2. Graft failure was confirmed in 8 of 65 (12.3%) patients (3 patients died within 16 days and were not included in the analysis). Three patients did not engraft, 1 patient rejected the graft before day +100, and 4 patients rejected the graft after day +100. Six patients were retransplanted (3 without conditioning). Four of them had engraftment, and 1 patient died at 28 days after the second transplant without engraftment. For 1 patient, the retransplant resulted in poor graft function, and this patient is still alive after undergoing 2 additional transplantations.

GVHD

Twenty-five patients (38.5%; 3 early deaths are not included in the analysis) developed grade I to IV aGVHD: 21 of them after BM transplantation and 4 after PBSC transplantation. The aGVHD grade distribution was 76% grade I, 8% grade II, 12% grade III, and 4% grade IV. Seventeen of the patients with aGVHD (68%) received a transplant from an URD. Border-significant differences in aGVHD between RD and URD recipients were seen: 27% versus 49% (*P* = .07). Eleven (16.2%) patients developed cGVHD: 23% after URD transplantation and 10% after an RD transplant (*P* = .168). Chronic GVHD grades were mild (n = 5), moderate (n = 5), or severe (n = 1). The stem cell source did not influence the incidence of cGVHD: 17.6% for BM and 15.4% for PBSCs. There was a tendency for more aGVHD in <40-year-old patients: 45% versus 19% (*P* = .062), whereas the difference in cGVHD incidence was not significant: 14% versus 24% (*P* = .321). At 1-year post-transplantation, 7 patients had ongoing cGVHD requiring systemic treatment.

OS and GFRS

The median follow-up for surviving patients was 109 months (range, 35 to 192 months). Five-year OS for all patients was 86.8% (Figure 1A). Ten patients died after transplantation with a median time to death of 53 days (range, 5 to 3184 days). Six patients (8.8%) died within 100 days, 3 of them within the first 16 days after transplantation. Causes of death were infection (n = 5), GVHD (n = 3), intracranial bleeding (n = 1), and multiorgan failure (n = 1). TRM of the entire cohort was 13.2%, which was significantly higher for ≥40-year-old patients (29.4%) than in younger patients (7.8%), *P* = .023. First-line transplantation was associated with a tendency for better OS: 5-year OS 96% versus 81.4% for later transplantation (*P* = .095). Patients aged <40 years had

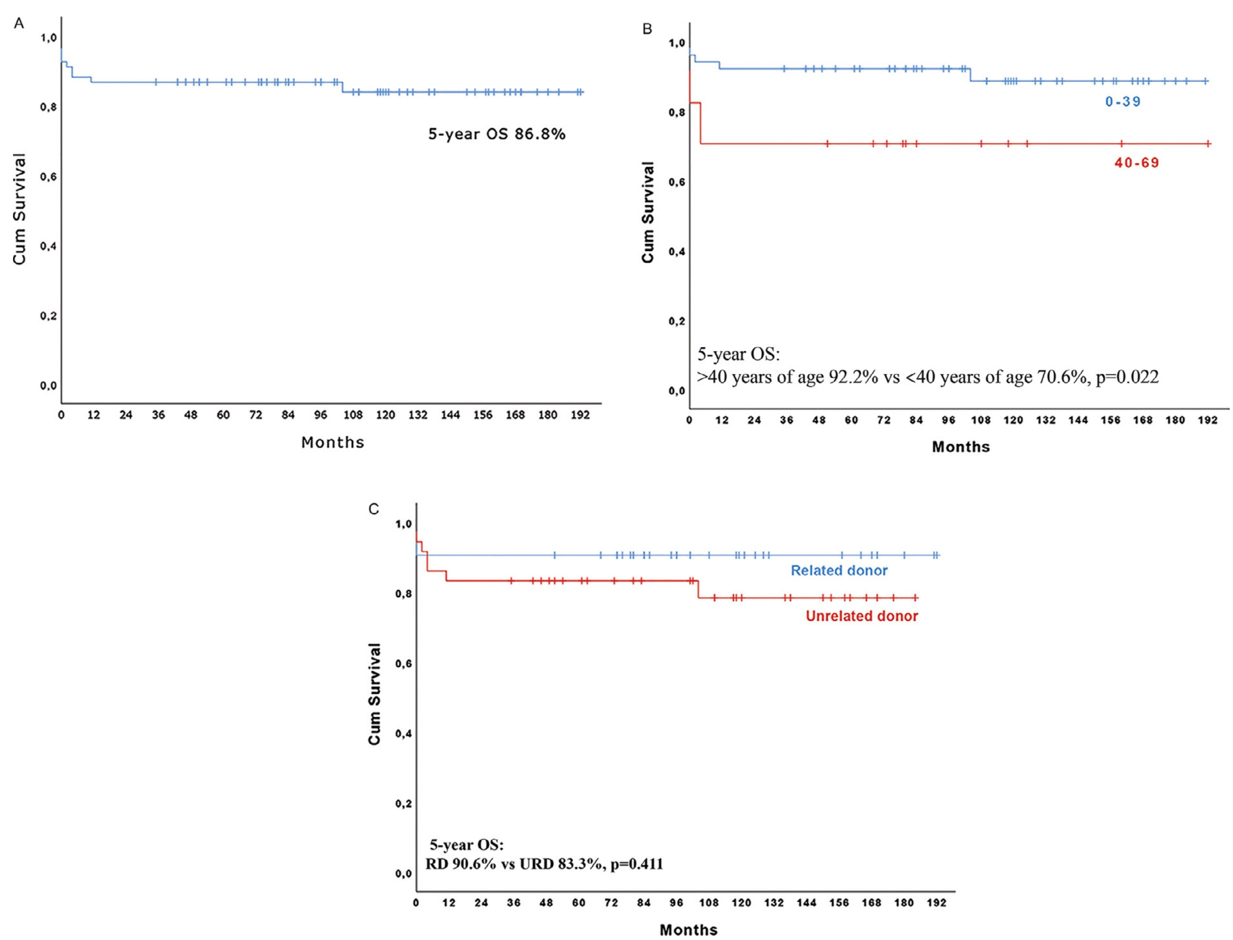

Figure 1. (A) Overall survival of all patients. (B) Overall survival according to age groups. (C) Overall survival according to the donor type.

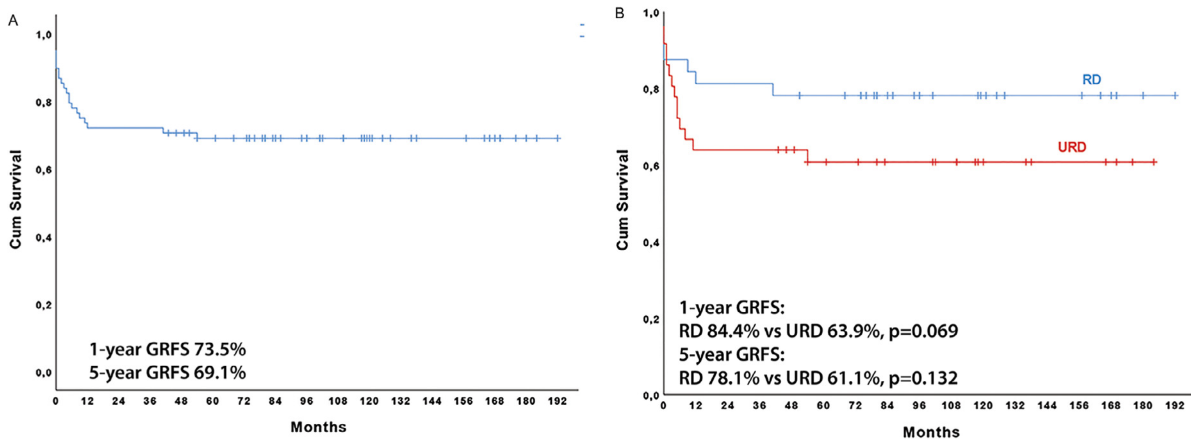

Figure 2. (A) GRFS. (B) GRFS according to the donor type.

significantly better 5-year OS than patients aged ≥40 years, 92.2% versus 70.6%, respectively (P = .022) (Figure 1B).

There was no survival difference between RD and URD recipients regarding all patients (5-year OS: 90.6% versus 83.3%, P = .411) (Figure 1C) or <40-year-old patients (RD, 95.2%; URD, 90%; P = .508). Yet, for patients ≥40 years old, there was a numerical but no statistical difference in OS (RD, 81.8%; URD, 50%; P = .255). To compare children with adults, we also divided patients into ≤18- and ≥19-year age groups and found a trend for better 5-year OS in children: 96.3% and 80.5%, respectively (P = .064). However, when comparing young adults (19 to 39 years of age) with children (≤18), there was no difference (87.5%; P = .246).

Disease severity grade before transplantation was not associated with survival (non-severe aplastic anemia [NSAA], 100%; severe aplastic anemia [SAA], 83.8% [P = .464] or VSAA, 89.3% [P = .561]). Likewise, there was no significant difference in OS regarding the stem cell source: 85.2% for BM and 100% for PBSCs (P = .148).

In the entire patient cohort, GRFS at 1 and 5 years was 73.5% and 69.1%, respectively (Figure 2A). Cumulative incidence of rejection, death, grade III to IV aGVHD, and systemic treatment requiring cGVHD at 1 year were 4.4% (95% confidence interval [CI], 1.4% to 13.1%), 13.2% (95% CI, 7.1% to 23.9%), 5.9% (95% CI, 2.2% to 14.9%), and 11.8% (95% CI, 6.1% to 22.2%), respectively. When dividing patients into age groups of <40 and ≥40 years, GRFS at 1 and 5 years was 80.4% versus 52.9% (P = .024) and 74.5% versus 52.9% (P = .069), respectively. When comparing ≤18- and ≥19-year age groups, 1-year GRFS was 88.8% and 63.4% (P = .025), whereas it was 70.8% for the 19- to 39-years age group (P = .114). For RD and URD recipients, there was a nonsignificant difference in GRFS at 1 and 5 years: 84.4% versus 63.9% (P = .069) and 78.1% versus 61.1% (P = .132), respectively (Figure 2B). We also compared different GRFS events at 1 year in the different age groups and donor types (<40 versus ≥40 years and RD versus URD), but because of low event numbers, we found no statistical differences (Supplementary Figure S1).

There was also a nonsignificant difference in GRFS when comparing patients who underwent transplantation during 2000 to 2005 compared with 2006 to 2012 (1 year, 66.7% versus 77.3%, P = .286; 5 years, 58.3 versus 75%, P = .140).

DISCUSSION

In this nationwide cohort study, we found that patients with AA diagnosed between 2000 and 2011 in Sweden, who underwent transplantation, had a good outcome with a 5-year overall survival of 87%, even though most patients were allografted after 1 or more courses of IST. In addition, the clinically important combined endpoint of GRFS at 5 years was high (69.1%). Reasons for this favorable outcome could be attributed to both the use of conditioning regimens, including ATG for both RD and URD recipients, as well as long-term immunosuppression post-transplantation. Indeed, in a study from the European Group for Blood and Marrow Transplantation (EBMT) Severe Aplastic Anemia Working Party, in 1448 patients with AA (URD, n = 508; RD, n = 940) allografted between 2005 and 2009 [2], the use of ATG in the conditioning regimen was found to have a positive effect on survival. In another recent population-based Latin American study, superior event-free survival was observed for patients conditioned with ATG-based regimens compared with other regimens (79% versus 61%, P = .001) [14]. Furthermore, the current British AA guidelines recommend the use of ATG in the conditioning regimen regardless of the stem cell source in addition to 9 months of continuous cyclosporine followed by 3 months of tapering [1].

The outcome of URD transplantation for AA appears to be similar that of RD transplants. Dufour et al. [3] showed that upfront use of unrelated donor grafts in an age group up to 20 years was associated with very good survival (96%), which was similar to historical results with identical sibling donors (OS: 91%) and statistically better than results with URD transplants after failed immunosuppressive therapy (OS: 71% P = .02). URD transplantation in other age groups was almost entirely conducted after 1 or more courses of IST. The EBMT study from 2015 showed that URD transplantations were associated with significantly more grade II to IV aGVHD and cGVHD, but mortality was not significantly higher compared with RD transplantations [2]. In our study, although most URD grafts were performed after failed IST, RD and URD recipients had a similar survival rate (90.6% and 83.3%, respectively).

Age is still one of the most important factors for survival after SCT [2,7,21–25]. In the EBMT Severe Aplastic Anemia Working Party study from 2015, negative predictors of survival apart from no ATG in the conditioning regime were the use of PBSCs, time lag from diagnosis to transplantation of >180 days, and patient age of >20 years. In our study, patients aged 0 to 19 and 20 to 39 years had similar outcomes, whereas patients aged >40 years had a worse survival, mostly because of a higher TRM. The underlying reasons for this difference are unclear. However, we found that patients aged >40 years had a significantly longer time from diagnosis to transplantation compared with younger patients (255 versus 142 days, respectively, $P = .025$). Moreover, in the small group of patients aged >40 years who underwent an upfront transplantation, 4 of 5 were long-term survivors. Yet, there are data suggesting that the outcome of this age group does not appear to have changed during the latest years [7]. Nevertheless, in the Latin American study, describing RD recipients between 1990 and 2014, patients aged >40 years (n = 58) had a 5-year survival of 75%, which is similar to our patient cohort. We have previously reported that patients with VSAA, in a population-based setting, responded poorly to both first- and second-line ATG with a 5-year survival of only 53% [17]. At the same time, our transplantation data showed an almost 90% 5-year survival for all patients with VSAA and 75% in the ≥40-year-old age group, suggesting that selected patients with VSAA also above the age of 40 years should be counseled for an allograft as first-line therapy.

Our study has limitations, mainly the retrospective nature and the small number of patients in each subgroup. Nevertheless, it is a nationwide study including all transplanted patients with AA diagnosed in Sweden from 2000 to 2011 with a long follow-up time and with complete treatment data.

In conclusion, we found in a real-world setting that survival of patients with AA who underwent allografting was similar regardless of the stem cell source and donor type. Younger patients did particularly well, and almost 70% of all patients were alive without transplant- or disease-related morbidity. However, SCT for patients with AA aged ≥40 years was associated with a poorer prognosis. This inferior outcome, apart from any intrinsic effect of age, may be caused by the longer time from diagnosis, more pretransplantation immunosuppression courses, and accompanying infections. Together, this may indicate that earlier transplant could improve the results for older patients, and prospective clinical trials addressing this issue are warranted.

ACKNOWLEDGMENTS

The authors thank Mitchell Arico from Edanz Group for editing a draft of this manuscript.

Financial disclosure: This study was supported by grants from the Gothenburg Medical Society, the Swedish state under the agreement between the Swedish government and the country councils, the ALF-agreement (ALFGBG-719481), and the Borås Cancer Foundation.

Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.05.032.

REFERENCES

1. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. *Br J Haematol*. 2016;172:187–207.
2. Bacigalupo A, Socie G, Hamladji RM, et al. Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis. *Haematologica*. 2015;100:696–702.
3. Dufour C, Veys P, Carraro E, et al. Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia: a study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT. *Br J Haematol*. 2015;171:585–594.
4. Marsh JC, Pearce RM, Koh MB, et al. Retrospective study of alemtuzumab vs ATG-based conditioning without irradiation for unrelated and matched sibling donor transplants in acquired severe aplastic anemia: a study from the British Society for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2014;49:42–48.
5. Choi YB, Yi ES, Lee JW, Sung KW, Koo HH, Yoo KH. Immunosuppressive therapy versus alternative donor hematopoietic stem cell transplantation for children with severe aplastic anemia who lack an HLA-matched familial donor. *Bone Marrow Transplant*. 2017;52:47–52.
6. Maury S, Balere-Appert ML, Chir Z, et al. Unrelated stem cell transplantation for severe acquired aplastic anemia: improved outcome in the era of high-resolution HLA matching between donor and recipient. *Haematologica*. 2007;92:589–596.
7. Giammarco S, Peffault de Latour R, Sica S, et al. Transplant outcome for patients with acquired aplastic anemia over the age of 40: has the outcome improved? *Blood*. 2018;131:1989–1992.
8. Bacigalupo A, Giammarco S, Sica S. Bone marrow transplantation versus immunosuppressive therapy in patients with acquired severe aplastic anemia. *Int J Hematol*. 2016;104:168–174.
9. Meyers G, Maziarz RT. Is it time for a change? The case for early application of unrelated allo-SCT for severe aplastic anemia. *Bone Marrow Transplant*. 2010;45:1479–1488.
10. Holtan SG, DeFor TE, Lazaryan A, et al. Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. *Blood*. 2015;125:1333–1338.
11. Solh M, Zhang X, Connor K, et al. Factors predicting graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation: multivariable analysis from a single center. *Biol Blood Marrow Transplant*. 2016;22:1403–1409.
12. Tan J, Wang Y, Yu SJ, Ma YY, Lei HY, Liu QF. Prognostic factors on graft-versus-host disease-free and relapse-free survival after allogeneic hematopoietic stem cell transplantation for adults with acute leukemia. *Leuk Res*. 2017;59:1–7.
13. Solomon SR, Sizemore C, Zhang X, et al. Current graft-versus-host disease-free, relapse-free survival: a dynamic endpoint to better define efficacy after allogenic transplant. *Biol Blood Marrow Transplant*. 2017;23:1208–1214.
14. Gomez-Almaguer D, Vazquez-Mellado A, Navarro-Cabrera JR, et al. The Latin American experience of allografting patients with severe aplastic anaemia: real-world data on the impact of stem cell source and ATG administration in HLA-identical sibling transplants. *Bone Marrow Transplant*. 2017;52:41–46.
15. Devillier R, Dalle JH, Kulasekararaj A, et al. Unrelated alternative donor transplantation for severe acquired aplastic anemia: a study from the French Society of Bone Marrow Transplantation and Cell Therapies and the EBMT Severe Aplastic Anemia Working Party. *Haematologica*. 2016;101:884–890.
16. Vaht K, Goransson M, Carlson K, et al. Incidence and outcome of acquired aplastic anemia: real-world data from patients diagnosed in Sweden from 2000-2011. *Haematologica*. 2017;102:1683–1690.
17. Vaht K, Goransson M, Carlson K, et al. Low response rate to ATG-based immunosuppressive therapy in very severe aplastic anaemia: a Swedish nationwide cohort study. *Eur J Haematol*. 2018;100:613–620.
18. Camitta BM, Thomas ED, Nathan DG, et al. Severe aplastic anemia: a prospective study of the effect of early marrow transplantation on acute mortality. *Blood*. 1976;48:63–70.
19. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21:389–401. e381.
20. Bacigalupo A, Socie G, Lanino E, et al. Fludarabine, cyclophosphamide, antithymocyte globulin, with or without low dose total body irradiation, for alternative donor transplants, in acquired severe aplastic anemia: a retrospective study from the EBMT-SAA Working Party. *Haematologica*. 2010;95:976–982.
21. Locasciulli A, Oneto R, Bacigalupo A, et al. Outcome of patients with acquired aplastic anemia given first line bone marrow transplantation or immunosuppressive treatment in the last decade: a report from the European Group for Blood and Marrow Transplantation (EBMT). *Haematologica*. 2007;92:11–18.
22. Scheinberg P, Wu CO, Nunez O, Young NS. Predicting response to immunosuppressive therapy and survival in severe aplastic anaemia. *Br J Haematol*. 2009;144:206–216.
23. Gupta V, Eapen M, Brazauskas R, et al. Impact of age on outcomes after bone marrow transplantation for acquired aplastic anemia using HLA-matched sibling donors. *Haematologica*. 2010;95:2119–2125.
24. Dufour C, Pillon M, Passweg J, et al. Outcome of aplastic anemia in adolescence: a survey of the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica*. 2014;99:1574–1581.
25. Dufour C, Pillon M, Socie G, et al. Outcome of aplastic anaemia in children: a study by the severe aplastic anaemia and paediatric disease working parties of the European group blood and bone marrow transplant. *Br J Haematol*. 2015;169:565–573.