TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Cardiovascular Medicine and Haematology

Retrospective evaluation of patients who underwent allogeneic stem cell transplantation for bone marrow failure

Tuba Ersal , Vildan Özkocaman

Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Bursa Uludag University, Bursa, Turkey

A B S T R A C T

Background Bone marrow failure is a disease that develops due to different etiologies. Aplastic anaemia (AA) and hypocellular myelodysplastic syndrome (HMDS) are the most common bone marrow failure disorders. Treatment options include supportive therapy, immunosuppressive therapy, and allogeneic hematopoietic stem cell transplantation (allo-HCT). Allo-HCT is the only curative treatment option. This study aimed to retrospectively evaluate the demographic characteristics, treatment, and transplantation results of patients who underwent Allo-HCT for bone marrow failure.

Methods This single-centre retrospective study enrolled 11 patients (9 with severe AA and 2 with HMDS) who underwent allo-HCT for bone marrow failure. The patients' records until 17.08.2023 were analysed. Age, gender, diagnosis, donor age and gender, type of transplantation, pre-transplant ferritin levels, time to transplantation, volume of infused product, number of CD34+ cells in the infused product, post-transplant engraftment times, discharge time, transplant-related complications, post-transplant follow-up and overall survival times were obtained.

Results Eleven patients underwent 12 allo-HCTs for bone marrow failure. Seven patients were male, and four were female. The median age was 40, and seven patients were ≥ 40 years old at the time of transplantation. Eleven transplants were performed from HLA fully matched siblings and one from a 9/10 matched sibling donor. Bone marrow was used as a stem cell source in 8 transplants and peripheral blood in 4 transplants. The conditioning regimen was fludarabine/cyclophosphamide/anti-thymocyte globulin in all patients. The median time from diagnosis to transplantation was five months. The median time for neutrophil engraftment was 23 days. The median platelet > 20.000/mm^3 engraftment time was 16 days. A statistically significant positive correlation was found between ferritin levels and platelet > 20.000/mm^3 engraftment (days) (r = 0.653, p = 0.040) and platelet > 50.000/mm^3 engraftment (days) (r = 0.720, p = 0.029). There was a statistically significant negative correlation between the number of infused CD34 positive cells (10^6/kg) and platelet > 50.000/mm^3 engraftment (days) (r = -0.670, p = 0.024). Patients were discharged in a median of 23 days. Acute graft versus host disease (GvHD) was observed in one patient, while chronic GvHD was not observed in any patient. The median overall survival time was 48 months, and the median post-transplant follow-up was 37 months. Secondary malignancy and MDS were not detected in any patient during the follow-up period. All 11 patients who underwent Allo-HCT from a matched sibling donor are alive and continue to have a complete haematological response. There was no increase in mortality and morbidity in patients aged 40 years and older.

Conclusions In patients with severe AA and high-risk HMDS without comorbidities between the ages of 40 and 50, allo-HCT should be considered as first-line treatment in the presence of an HLA-matched sibling donor.

Turk J Int Med 2023;5(4):262-270
DOI: 10.46310/tjim.1359793

Keywords: *Acquired severe aplastic anemia, bone marrow failure, myelodysplastic syndrome, allogeneic stem cell transplantation.*

Received: *September 13, 2023;* ***Accepted:*** *October 24, 2023;* ***Published Online:*** *29 October 2023*

How to cite this article: *Ersal T, Özkocaman V. Retrospective evaluation of patients who underwent allogeneic stem cell transplantation for bone marrow failure.Turk J Int Med 2023;5(4):262-270. DOI: 10.46310/tjim.1359793*

Address for Correspondence:
Tuba ERSAL, MD., Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Uludag University, 16059 Bursa, Turkey
E-mail: tubaersal@uludag.edu.tr

INTRODUCTION

Bone marrow failure is a group of disorders that develop due to different etiologies. The leading causes of acquired bone marrow failure include aplastic anaemia (AA) and hypocellular myelodysplastic syndrome (HMDS). AA is defined as pancytopenia with hypocellular bone marrow without infiltration or fibrosis. Supportive therapy, immunosuppressive therapy (IST), and allogeneic stem cell transplantation (allo-HCT) are among the treatment options. Supportive therapy includes erythrocyte and platelet transfusion, prevention and treatment of infections, thrombopoietin mimetic eltrombopag, and iron chelation. Standard first-line IST combines horse-derived anti-thymocyte globulin (ATG) and cyclosporine-A (CsA).[1] HLA typing should be performed at the time of diagnosis for all newly diagnosed AA patients who may be potential transplant candidates. Allo-HCT is the only curative treatment option. However, it may only be a suitable option for some patients. Although the approach is still being determined because of the rarity of the diseases, bone marrow transplantation should be the first-line treatment in patients with severe AA, especially in patients aged < 40 years if there is an HLA-compatible sibling donor.[2] The appropriate age limit for transplantation is gradually increasing. Transplant-related morbidity and mortality is gradually improving with advances in treatment. A limit between 35 and 50 years of age has been proposed depending on the patient's comorbidities in selected patients who are medically fit for patients between 41 and 60.[3] IST is applied in patients unsuitable for allo-HCT.[4]

Myelodysplastic syndrome (MDS) is a clonal bone marrow neoplasm characterised by morphological dysplasia findings in hematopoietic cells, peripheral cytopenia(s), ineffective hematopoiesis, recurrent genetic abnormalities, and increased risk of transformation to acute myeloid leukaemia.[5] The role of allo-HCT in treating low-risk MDS has yet to be fully established. It has been shown that progression-free and overall survival rates of patients with multiple molecular abnormalities are significantly reduced compared with patients who do not carry mutations. It may be recommended that these patients and patients with TP53 mutation be closely monitored, the HLA typing should be studied, and they should be directed to HCT.1 HMDS is an MDS subgroup comprising 10-15% of MDS patients characterised by bone marrow hypocellularity. IST is an essential component of the clinical approach in patients with HMDS; early allo-HCT should also be considered in some patients.[6]

In this study, we retrospectively evaluated the allo-HCT results of patients diagnosed with acquired severe AA and HMDS. It was aimed to determine the clinical characteristics and transplantation results of patients who underwent allo-HCT for bone marrow failure.

MATERIAL AND METHODS

Patient selection

The study included patients over 18 who underwent allo-HCT and were diagnosed with acquired severe AA and HMDS in our haematology department between January 2016 and April 2023. The conditioning regimen: fludarabine (30 mg/m^2/day; days -8, -7, -6, -5) + cyclophosphamide (300 mg/m^2/day; days -8, -7, -6, -5) + ATG (rabbit sourced; 3.75 mg/kg/day; days -4, -3, -2, -1) in all patients. Graft versus host disease (GvHD) prophylaxis: methotrexate 10 mg/m^2 IV on day +1 and CsA 3 mg/kg/day on day -1 were administered to all patients. After transplantation, all patients received prophylactic acyclovir, trimethoprim-sulfamethoxazole, triflucan, and ciprofloxacin.

Response assessment

Neutrophil and platelet engraftment was defined as absolute neutrophil count > 500/mm^3 and platelet count > 20000/mm^3 on three consecutive days without transfusion support, respectively. Primary graft failure (GF) was defined as failure to achieve engraftment 28 days after HCT. Secondary GF was described as a neutrophil count < 500/mm^3 after initial engraftment. Post-treatment blood counts were classified as complete response (CR), partial response (PR), and no response.1 Standard criteria were used for stage 2-4 acute GvHD and chronic GvHD.7,8 Chimerism determination was routinely performed in the 1st post-transplant month. Post-transplant cytomegalovirus (CMV) follow-up by PCR was performed twice a week in peripheral blood for the first 100 days.

Statistical analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". The data were analysed for normality, and Shapiro-Wilk values were determined as $p < 0.05$. Therefore, the Spearman correlation test was used to determine the relationship between continuous variables. $p < 0.05$ was considered statistically significant.

RESULTS

Twelve allo-HCTs were performed in 11 patients with bone marrow failure (9 severe AA and 2 HMDS). The median age was 40, and seven patients were ≥ 40 years old at the time of transplantation. Allo-HCT was administered as first-line treatment in 9 patients and second-line therapy in 2 patients. The median time from initial diagnosis to transplantation was five months. Patient and transplant characteristics were summarised in Table 1.

The median time to neutrophil > 500/mm^3 engraftment was 23 days, and the median time to platelet 20000/mm^3 engraftment was 16 days.

Table 1. Patient (n: 11) and transplant (n: 12) characteristics.

Number of transplants	12
Transplant for the second time	1
Recipient Gender (female/male)	4/7
Recipient transplant age (years)	40 (21:55)
Diagnosis	
Severe aplastic anaemia	9 (81.8)
Hypocellular MDS	2 (18.1)
Donor	
Sibling	12 (100)
Age (years) median, (min-max)	39.5 (25:63)
Diagnosis-transplant time (months)	5 (2:35)
Number of transfusions (U)	
Erythrocyte suspension	11.5 (5:55)
Platelet suspension	12.5 (2:69)
Pre-transplant ferritin level (µg/L)	1291 (284:3970)
Conditioning regime	
Flu/Cy/ATG	12 (100)
HLA matching	
9/10	1 (8.3)
10/10	11 (91.6)
Stem cell source	
Bone marrow	8 (66.6)
Peripheral blood	4 (33.3)
Infused product volume (cc)	
Bone marrow	1250 (320:1500)
Peripheral blood	520 (105:720)
Number of infused CD34+ cells (10^6/kg)	
Bone marrow	0.98 (1:5.4)
Peripheral blood	5.67 (2:6.65)
Infused product CD34+ cell count (µL)	
Bone marrow	76 (52:812)
Peripheral blood	1149 (192:4991)

MDS: myelodysplastic syndrome, CsA: cyclosporine A, ATG: antithymocyte globulin.
The values were expressed as n (%) or median (minimum: maximum).

Table 2. Results of transplantation.

Engraftment time (days)	
Neutrophils >500/mm^3	23 (13:31)
Platelets >20.000/mm^3	16 (11:24)
Platelets >50.000/mm^3	22 (14-33)
Engraftment failure	1 (8.3)
Discharge duration (days)	23 (20:39)
Chimerism 30 days after transplantation	6 (60)
100	4 (40)
85-100	
Complication after transplantation	
FEN	5 (41.6)
Grade 1-2 mucositis	4 (33.3)
Grade 1-2 nausea and vomiting	9 (75)
GvHD	
Acute	1 (8.3)
Chronic	0
CMV infection after transplant	
Yes	6 (54.5)
One time	6 (54.5)
Two times	3 (27.2)
No	5 (45.4)
Hematological Response	
Complete remission	11 (91.6)
No response	1 (8.3)
Last status	
Alive	11 (100)
Exitus	0
Post-transplant follow-up time (months)	37.48 (4.30:92.63
Overall survival (months)	48.20 (9.30:95.17

The values were expressed as n (%) or median (minimum maximum).

Post-transplant patients were complicated with febrile neutropenia (FEN), grade 1-2 mucositis, and grade 1-2 nausea-vomiting. No focus of infection was found in 3 of 5 patients complicated with FEN, and the response was obtained with piperacillin-tazobactam. *E.coli* was also grown in blood culture in 2 patients, and a response was received with meropenem. Patients were discharged on the median 23rd day (20-39 days). CMV infection was observed in six patients. All of these were in the first 100 days of transplantation. Three patients experienced CMV reactivation for the second time after the 100th day of transplantation. CMV-DNA negativity was achieved in all patients with oral valganciclovir treatment. The chimerism of 6 patients who could be chimerised in the first month was 100%, and four patients had an

Table 3. The relationship between engraftment times and various variables.

		Neutrophil >500/mm^3 engraftment (day)	Platelet >20.000/mm^3 engraftment (day)	Platelet >50.000/mm^3 engraftment (day)
Recipient transplant age	r	0.361	0.018	–0.067
	p	0.249	0.956	0.846
Donor age	r	0.445	0.198	0.169
	p	0.147	0.538	0.620
Pre-transplant ferritin (µg/L)	r	0.445	0.653*	0.720*
	p	0.197	0.040	0.029
Infused product volume (cc)	r	0.549	0.250	0.483
	p	0.065	0.433	0.133
Number of CD34+ infused cells (10^6/kg)	r	–0.507	–0.531	–0.670*
	p	0.092	0.076	0.024
Number of infused product CD34+ cells (µL)	r	–0.532	–0.346	–0.579
	p	0.075	0.270	0.062

A correlation was significant at 0.05 level (Spearman correlation test).

85-100% donor profile. Acute GvHD was observed in one patient, while chronic GvHD was not observed in any patient. After transplantation, one transplant was considered non-responsive, and the others were complete responders. Although chimerism was 100% in the unresponsive patient, a second allo-HCT was performed 15 months after the first transplant due to secondary graft failure from another fully matched sibling (patient number 8 in Table 4). The results of transplantation were summarised in Table 2.

There was a statistically significant positive correlation between ferritin levels and platelet > 20.000/mm^3 engraftment (day) (r = 0.653, p = 0.040) and platelet > 50.000/mm^3 engraftment (day) (r = 0.720, p = 0.029). A statistically significant negative correlation was found between the number of infused CD34 positive cells (10^6/kg) and platelet > 50.000/mm^3 engraftment (days) (r = –0.670, p = 0.024) (Table 3).

No statistically significant difference was found between CMV infection and age groups (< 40 and ≥ 40 years) (p = 0.558) and between neutrophil and platelet engraftment times and age groups (< 40 and ≥ 40 years) (p = 0.104 and p = 0.682, respectively). One patient was complicated by BK virus (during her second transplant) (transplant number 11 in Table 5). Pregnancy was detected in one patient in the 5th month of transplantation (patient number 6 in Table 4). No complications or disease recurrence were observed during pregnancy. Delivery was performed uneventfully by standard vaginal delivery at 39 weeks.

The median follow-up period was 48 months, and the median post-transplant follow-up period was 37 months. All patients were still in our follow-up after transplantation; complete haematological responses

Table 4. Data of the study patients at the time of diagnosis.

Patient no	Gender	Diagnosis	Neutrophil (/mm^3)	Haemoglobin (g/dL)	Platelets (/mm^3)	Corrected reticulocyte (%)	Transfusion dependence
1	Male	SAA	50	7.6	13000	0.2	Yes
2	Male	HMDS	780	9.5	13700	0.9	Yes
3	Male	SAA	480	8.1	26000	0.6	Yes
4	Male	SAA	640	8.1	9600	0.5	Yes
5	Male	SAA	990	7.5	18000	2.4	Yes
6	Female	SAA	330	5.7	21000	0.7	Yes
7	Male	AA	1100	13	54000	1.3	No
8	Female	SAA	1600	3.9	8000	0.4	Yes
9	Male	SAA	600	4.9	3900	0.4	Yes
10	Female	SAA	480	9.1	4400	0.3	Yes
11	Female	HMDS	1500	6.1	19000	1.1	Yes

SAA: severe aplastic anaemia, HMDS: hypocellular myelodysplastic syndrome.

Table 5. Transplantation data of the patients

HCT no	Age	Diagnosis	Year	Time until HCT (month)	HLA compatibility	Stem cell source	Number of infused CD34+ cells (10^6/kg)	Neutrophil ET (day)	Platelet >20000 /mm^3 ET (day)	GF	Acute GvHD	Chronic GvHD	OS (month)	Last status
1	46	SAA	2016	3	10/10	BM	2.04	26	18	No	No	No	95	Alive
2	47	HMDS	2017	7	10/10	PBSC	6.63	14	12	No	No	No	85	Alive
3	40	SAA	2018	4	10/10	BM	1.37	31	19	No	No	No	61	Alive
4	36	SAA	2018	6	9/10	BM	1.26	21	21	No	No	No	62	Alive
5	21	SAA	2019	2	10/10	BM	1	25	21	No	No	No	49	Alive
6	25	SAA	2020	3	10/10	BM	5.4	15	13	No	No	No	47	Alive
7	40	SAA	2021	35	10/10	BM	2	25	11	No	No	No	66	Alive
8*	54	SAA	2022	9	10/10	PBSC	2	30	24	Yes	No	No	29	Alive
9	36	SAA	2022	3	10/10	PBSC	4.72	13	14	No	No	No	21	Alive
10	27	SAA	2023	3	10/10	BM	1.25	20	13	No	No	No	9	Alive
11*	55	SAA	2023	22	10/10	BM	1.6	27	18	No	No	No	29	Alive
12	46	HMDS	2023	30	10/10	PBSC	6.65	18	13	No	Yes	No	34	Alive

HCT no: hematopoietic stem cell transplantation number, ET: engraftment time, GF: graft failure, GvHD: graft versus host disease, OS: overall survival, SAA: severe aplastic anaemia, HMDS: hypocellular myelodysplastic syndrome, BM: bone marrow, PBSC: Peripheral blood stem cells.

* Numbers 8 and 11 were data from two different transplants of the same patient.

continued. Secondary malignancy and MDS were not detected in any patient during the follow-up period. Patient data were given in Tables 4 and 5.

DISCUSSION

Severe AA is a life-threatening disease with a high mortality rate due to bleeding and infections, and therefore, effective treatment is essential.[9] In severe AA, allo-HCT with an HLA-compatible sibling donor is recommended in patients under 40.[2] In young patients with poor risk characteristics in HMDS, HLA typing should be analysed. Allo-HCT should be considered in appropriate patients. Forty years is the cut-off age for first-line HCT from a fully matched sibling donor in most centres. Today, improved treatment conditions and decreasing transplant-related morbidity and mortality have raised the recommended age for transplantation. Although the cut-off age for HCT is shifting towards 50 years, a consensus has yet to emerge.

In our study, the median age at recipient transplantation was 40 years, and seven patients were 40 or older. The oldest patient was 55 years old. There was no correlation between the patient's age and engraftment duration. Only the patient with secondary engraftment failure was the oldest, and successful engraftment was achieved in the second allo-HCT. No statistically significant difference between patients under and over 40 regarding engraftment times was found. Therefore, the upper age limit of HCT from a fully matched sibling donor can be raised above 40 years for appropriate patients. For patients over 40 years of age with a fully HLA-matched sibling donor, patients with severe AA or high-risk HMDS with a low probability of response to IST can be transplanted in experienced transplantation centres if they do not have comorbidities and are willing for transplantation.

The risk of chronic GvHD increases with using Peripheral blood stem cells (PBSC) as a stem cell source. Therefore, bone marrow as a stem cell source is recommended for all patients with AA. PBSC are an alternative stem cell source when bone marrow cell collection is contraindicated, or the donor is unwilling to donate bone marrow. Despite early engraftment with the use of PBSC, it has been shown that inferior results are obtained, especially in young patients.[10] A study confirmed the survival advantage of bone marrow grafting in all age groups.[11] Our study's major stem cell source was bone marrow. Acute GvHD developed in 8.3% of the patients. The stem cell source was peripheral blood in this patient with acute GvHD. No patient developed chronic GvHD. Therefore, we reported relatively low GvHD rates compared to the literature.[9-13] Although acute GvHD can be controlled in almost all cases and is associated with a very low risk of death, chronic GvHD remains a problem. Cumulative incidences ranging from 0% to 44% have been reported when the marrow is used as a graft source.[8,14-17] The incidence of chronic GvHD was 16% in patients in whom bone marrow grafts were limited to $\leq 2.5 \times 10^8$/kg nucleated cells.10 It was thought that the low rate of chronic GvHD in our study might be related to the low number of cells in the infused product.

Our cohort's median time to neutrophil and platelet engraftment was within the range reported in the literature.[12-14] The amount of CD34 positive cells in the infused product (10^6/kg) did not correlate with neutrophil and platelet > 20.000/mm^3 engraftment time (days). However, there was a statistically significant negative correlation between the number of CD34 positive cells in the infused product (10^6/kg) and platelet > 50.000/mm^3 engraftments (days) ($r = -0.670$, $p = 0.024$). In agreement with our results, a study conducted in allo-HCT patients suggests that low CD34+ cell counts in allografts may be associated with delayed platelet engraftment.[18]

Most of our study patients were red cell transfusion-dependent before transplantation and had high ferritin levels. A significant positive correlation was found between ferritin elevation and platelet engraftment times. Some studies have reported lower OS among patients with high pre-transplant ferritin levels.[19,20] This was not observed in our study cohort due to the small sample size.

A low stem cell dose is known to increase the risk of GF, and a bone marrow stem cell dose of at least 2×10^6 CD34+ cells/kg is recommended.[21] Fatal GF is frequently seen in 3-5% of patients with severe AA. The aetiology of GF includes previous immunosuppressive therapy, excessive transfusion, advanced age, viral infection, and drug effects. GF is a life-threatening complication of HCT. Therapeutic strategies for GF include cytokine therapy, immunosuppressive therapy, donor leukocyte infusion (DLI), allogeneic PBSC, and second HCT.15 The median number of in-

fused CD34+ cells in our study was 0.98 × 10^6/kg in bone marrow-derived products and 5.67 × 10^6/kg in PBCS. While primary GF was not observed in any of the patients, secondary GF was observed in one transplant whose stem cell source was PBCS. Similarly, there were cases in the literature that were successfully treated for GF.[13]

In our study, no fatal infection was observed in the post-transplant period. FEN developed in 41.6% of patients after transplantation. The median duration of FEN was +11th day of transplantation. There was no growth in the cultures of 3 of these patients, while gram-negative bacteria growth was observed in 2 patients. The incidence of CMV infection was 50%. This rate was within the range reported in the literature.11,14 We also observed that CMV infection was significantly higher in patients transplanted after the COVID-19 pandemic (33% before and 67% after COVID-19).

The limitations of our study included the fact that it was a single-centre retrospective study and the number of patients was relatively small.

CONCLUSIONS

We concluded that allo-HCT should be considered first-line treatment in patients aged 40-50 with SAA who have HLA-matched sibling donors without comorbidities. Patients aged 40-50 years with a diagnosis of HMDS and high-risk characteristics should be evaluated for sibling HLA antigen compatibility, and transplant-eligible patients with fully matched sibling donors should be considered for Allo-HCT as first-line treatment.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa Uludag university, Bursa, Turkey. (Decision number: 2023-17/12, date: 19.10.2023).

Authors' Contribution

Study Conception: TE, VÖ; Study Design: TE, VÖ; Literature Review: TE, VÖ; Critical Review: TE, VÖ; Data Collection and/or Processing: TE, VÖ,; Analysis and/or Data Interpretation: TE, VÖ; Manuscript preparing: TE, VÖ.

REFERENCES

1. Killick SB, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, Hillmen P, Ireland R, Kulasekararaj A, Mufti G, Snowden JA, Samarasinghe S, Wood A, Marsh JC; British Society for Standards in Haematology. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. 2016 Jan;172(2):187-207. doi: 10.1111/bjh.13853. Erratum in: Br J Haematol. 2016 Nov;175(3):546.
2. Bacigalupo A. How I treat acquired aplastic anemia. Blood. 2017 Mar 16;129(11):1428-36. doi: 10.1182/blood-2016-08-693481.
3. Tichelli A, Marsh JC. Treatment of aplastic anaemia in elderly patients aged >60 years. Bone Marrow Transplant. 2013 Feb;48(2):180-2. doi: 10.1038/bmt.2012.224.
4. Rice C, Eikema DJ, Marsh JCW, Knol C, Hebert K, Putter H, Peterson E, Deeg HJ, Halkes S, Pidala J, Anderlini P, Tischer J, Kroger N, McDonald A, Antin JH, Schaap NP, Hallek M, Einsele H, Mathews V, Kapoor N, Boelens JJ, Mufti GJ, Potter V, Pefault de la Tour R, Eapen M, Dufour C. Allogeneic hematopoietic cell transplantation in patients aged 50 years or older with severe aplastic anemia. Biol Blood Marrow Transplant. 2019 Mar;25(3):488-95. doi: 10.1016/j.bbmt.2018.08.029.
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-405. Blood. 2016 Jul 21;128(3):462-463. doi: 10.1182/blood-2016-06-721662.
6. Karantanos T, DeZern AE. Biology and clinical management of hypoplastic MDS: MDS as a bone marrow failure syndrome. Best Pract Res Clin Haematol. 2021 Jun;34(2):101280. doi: 10.1016/j.beha.2021.101280.
7. Flowers ME, Kansu E, Sullivan KM. Patho-

physiology and treatment of graft-versus-host disease. Hematol Oncol Clin North Am. 1999 Oct;13(5):1091-112, viii-ix. doi: 10.1016/s0889-8588(05)70111-8.
8. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995 Jun;15(6):825-8.
9. Zhang Y, Huo J, Liu L, Shen Y, Chen J, Zhang T, Chen X, Pang A, Yang D, Zhang R, Ma Q, Zhai W, He Y, Wei J, Jiang E, Han M, Zheng Y, Feng S. Comparison of hematopoietic stem cell transplantation outcomes using matched sibling donors, haploidentical donors, and immunosuppressive therapy for patients with acquired aplastic anemia. Front Immunol. 2022 Feb 1;13:837335. doi: 10.3389/fimmu.2022.837335.
10. Schrezenmeier H, Passweg JR, Marsh JC, Bacigalupo A, Bredeson CN, Bullorsky E, Camitta BM, Champlin RE, Gale RP, Fuhrer M, Klein JP, Locasciulli A, Oneto R, Schattenberg AV, Socie G, Eapen M. Worse outcome and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA-matched sibling donor transplants for young patients with severe acquired aplastic anemia. Blood. 2007 Aug 15;110(4):1397-400. doi: 10.1182/blood-2007-03-081596.
11. Bacigalupo A, Socié G, Schrezenmeier H, Tichelli A, Locasciulli A, Fuehrer M, Risitano AM, Dufour C, Passweg JR, Oneto R, Aljurf M, Flynn C, Mialou V, Hamladji RM, Marsh JC; Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT). Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. Haematologica. 2012 Aug;97(8):1142-8. doi: 10.3324/haematol.2011.054841.
12. Sangiolo D, Storb R, Deeg HJ, Flowers ME, Martin PJ, Sandmaier BM, Kiem HP, Nash RA, Doney K, Leisenring WM, Georges GE. Outcome of allogeneic hematopoietic cell transplantation from HLA-identical siblings for severe aplastic anemia in patients over 40 years of age. Biol Blood Marrow Transplant. 2010 Oct;16(10):1411-8. doi: 10.1016/j.bbmt.2010.04.005.
13. Wilfred G, Ong TC, Sh Shahnaz SAK, Wah HK, Carlo ES, Jameela S, Mui Tan S. Allogeneic hematopoietic stem cell transplantation in severe aplastic anemia: A single centre experience in Malaysia. Blood Cell Ther. 2022 Apr 8;5(2):45-53. doi: 10.31547/bct-2021-018.
14. Gallo S, Woolfrey AE, Burroughs LM, Storer BE, Flowers ME, Hari P, Pulsipher MA, Heimfeld S, Kiem HP, Sandmaier BM, Storb R. Marrow grafts from HLA-identical siblings for severe aplastic anemia: does limiting the number of transplanted marrow cells reduce the risk of chronic GvHD? Bone Marrow Transplant. 2016 Dec;51(12):1573-8. doi: 10.1038/bmt.2016.198.
15. Ciurea SO, de Lima M, Cano P, Korbling M, Giralt S, Shpall EJ, Wang X, Thall PF, Champlin RE, Fernandez-Vina M. High risk of graft failure in patients with anti-HLA antibodies undergoing haploidentical stem-cell transplantation. Transplantation. 2009 Oct 27;88(8):1019-24. doi: 10.1097/TP.0b013e3181b9d710.
16. Huang LF, Li L, Jia JS, Yang Y, Lin SY, Meng FK, Zhang DH, He GS. Frontline therapy options for adults with newly diagnosed severe aplastic anemia: Intensive immunosuppressive therapy plus eltrombopag or matched sibling donor hematopoietic stem cell transplantation? Transplant Cell Ther. 2022 Sep;28(9):586.e1-586.e7. doi: 10.1016/j.jtct.2022.05.027.
17. Storb R, Prentice RL, Sullivan KM, Shulman HM, Deeg HJ, Doney KC, Buckner CD, Clift RA, Witherspoon RP, Appelbaum FA, Sanders JE, Stewart PS, Thomas ED. Predictive factors in chronic graft-versus-host disease in patients with aplastic anemia treated by marrow transplantation from HLA-identical siblings. Ann Intern Med. 1983 Apr;98(4):461-6. doi: 10.7326/0003-4819-98-4-461.
18. Chang YJ, Xu LP, Liu DH, Liu KY, Han W, Chen YH, Yu-Wang, Chen H, Wang JZ, Zhang XH, Zhao XY, Huang XJ. Platelet engraftment in patients with hematologic malignancies following unmanipulated haploidentical blood and marrow transplantation: effects of CD34+ cell dose and disease status. Biol Blood Marrow Transplant. 2009 May;15(5):632-8. doi: 10.1016/j.bbmt.2009.02.001.
19. Armand P, Kim HT, Cutler CS, Ho VT, Koreth J, Alyea EP, Soiffer RJ, Antin JH. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. Blood. 2007 May 15;109(10):4586-8. doi: 10.1182/blood-2006-10-054924.
20. Platzbecker U, Ehninger G, Bornhäuser M. Prog-

nostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem-cell transplantation. Blood. 2007 Oct 15;110(8):3083; author reply 3083-4. doi: 10.1182/blood-2007-05-089839.

21. Pulsipher MA, Lehmann LE, Bertuch AA, Sasa G, Olson T, Nakano T, Gilio A, Burroughs LM, Lipton JM, Huang JN, Dickerson K, Bertaina A, Zhuang C, Malsch M, Fleming M, Weller E, Shimamura A, Williams DA. A study assessing the feasibility of randomization of pediatric and young adult patients between matched unrelated donor bone marrow transplantation and immune-suppressive therapy for newly diagnosed severe aplastic anemia: A joint pilot trial of the North American Pediatric Aplastic Anemia Consortium and the Pediatric Transplantation and Cellular Therapy Consortium. Pediatr Blood Cancer. 2020 Oct;67(10):e28444. doi: 10.1002/pbc.28444.