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Haploidentical Donor Bone Marrow Transplantation for Severe Aplastic Anemia

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Synopsis

Hematopoietic stem cell transplantation (BMT) is the only curative treatment for severe aplastic anemia (SAA). BMT from an HLA matched sibling donor is the standard of care for young patients; immunosuppressive therapy (IST) is used for older patients or those lacking matched sibling donors. Patients with refractory or relapsed disease are increasingly treated with HLA haploidentical BMT. Historically, haploidentical BMT led to high rates of graft rejection and graft-versus-host disease (GVHD). High dose cyclophosphamide which mitigates the risk of GVHD is a major advance. Here we provide an overview of the haploidentical BMT approach in SAA.

Keywords

Severe aplastic anemia; Cyclophosphamide; Haploidentical transplant; Graft versus host disease

Introduction

Acquired severe aplastic anemia (SAA) is an immune-mediated hematopoietic stem cell disorder that presents with a hypocellular marrow and pancytopenia^{1,2}. The incidence is roughly 1 in 250,000 individuals per year.^{3,4} Most newly diagnosed patients are managed with immunosuppressive therapy (IST) unless they are young and have a suitable HLA-matched sibling donor for bone marrow transplantation (BMT). IST improves hematopoiesis

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and decreases the early mortality of the disease. Severe AA is not considered overtly malignant, but clonal hematopoiesis is present in over 60% of patients at diagnosis; commonly mutated genes include *PIGA*, *BCOR/BCORL1*, *DNMT3A*, and *ASXL1* among others.^{5–7} This explains the high rate of PNH and MDS that frequently arise from SAA 5 years or more after treatment with IST.^{8–11} Infection (usually fungal) is the most common cause of early death in SAA patients; however, hemorrhage, clonal disease (myelodysplastic syndromes [MDS],¹² leukemia, paroxysmal nocturnal hemoglobinuria [PNH]), and transfusional iron overload are other causes of severe morbidity and mortality.¹³ Improved supportive care has led to significant progress in controlling the acute aspects of the disease (bleeding and infection), but little progress has been made controlling the late complications of severe AA, especially the risk for relapse and secondary clonal disorders following IST. Indeed, SAA that is refractory or relapses after ATG/CSA is associated with a high degree of morbidity and mortality. Curative strategies are desperately needed for these patients.

Allogeneic bone marrow transplantation (alloBMT) addresses both the acute and chronic complications of severe AA, by virtually eliminating the risk of relapse and secondary clonal disease, but introduces the risk of acute and chronic GVHD. Thus, alloBMT from a human leukocyte antigen (HLA) matched sibling donor (MSD) is the standard of care for young, newly diagnosed severe AA patients^{2,14} with long-term survival rates approaching 90% in patients under 20 years^{15,16} and 76% for patients older than 20 years.¹⁶ The less favorable transplant outcomes in older (above age 30–40 years) patients is attributed to reduced engraftment, and higher rates of GVHD¹⁷.

When to apply alternative donor BMT has remained an active research question for many years. More recently, there has been an increase in HLA haploidentical BMT (haplo-BMT) from family members globally^{18–20} for all diseases. For severe AA in particular, a European survey showed that haploidentical donors constituted 6.7%, whereas cord blood is used in 3.2% of transplants in AA.¹⁸ This is only likely to increase as outcomes improve with haploidentical transplant for severe AA. Here, we review the outcomes in relapsed and refractory disease as well as upfront use of haplo-BMT for patients suffering with SAA.

Haploidentical Transplant Strategies

The ideal BMT regimen in AA is one that results in sustained engraftment, minimal toxicity from the regimen, lack of acute or chronic GVHD and allows the majority of patients (old and young) to proceed efficiently to this potentially curative option. In a nonmalignant disease such as AA, it is advantageous to utilize strategies to minimize GVHD.²¹ Multiple approaches are utilized towards this goal. Table 1 reviews results of these studies. As in all of BMT, multiple factors require evaluation prior to alternative donor BMT in AA.

The role of high-dose cyclophosphamide (HiCY) in therapy for Aplastic Anemia

HiCY (50mg/kg/d × 4 days) has a unique history in the context of AA for both transplant and non-transplant therapies. Figure 1 shows the role of cyclophosphamide over the past six decades for AA. The first successful allogeneic BMT in a human was performed for SAA

following conditioning with HiCY.²² Shortly afterwards, reports of complete hematopoietic recovery with host hematopoiesis following allogeneic BMT for SAA began to trickle into the literature^{23,24}. This suggested that HiCY, with its stem cell sparing yet highly lymphocytotoxic properties, could achieve durable complete responses in SAA. This hypothesis was confirmed in the 1990s. A Johns Hopkins report of complete hematologic remission in seven of ten SAA patients treated with high dose cyclophosphamide without BMT proved the potential efficacy of this approach²⁵. Subsequent reports in larger numbers of SAA patients confirmed these results²⁶ but the prolonged aplasia and morbidity of this approach has limited the enthusiasm for HiCY as therapy for SAA.

More recently, the efficacy of HiCY for alloimmunity has been realized as well. HiCY after BMT was shown to inhibit both graft rejection and GVHD in animal models.²⁷ On the basis of these data, and the clinical experience demonstrating the efficacy of HiCY in SAA and other severe autoimmune diseases²⁸ the use of HiCY or specifically post-transplant cyclophosphamide (PTCy) (50 mg/kg/d on days +3 and +4) was found to be highly effective for GVHD prophylaxis. In phase II clinical trials, HiCY after nonmyeloablative haplo-BMT is associated with rates of acute or chronic GVHD similar to those seen with matched allogeneic BMT in hematologic malignancies.^{29–31} This platform to decrease GVHD has been especially effective in nonmalignant diseases such as PNH and sickle cell disease^{32,33} where a graft-versus-tumor effect is not necessary. More recently, it has been used for AA.^{34–37}

Results of Haplo-BMT for SAA

Approaches using Post-transplant Cyclophosphamide

The first reported use PTCy for treating SAA was by DeZern et al with myeloablative conditioning.³⁵ In a pilot study, Clay et al.³⁷ reported the use of haplo-BMT in refractory SAA, using a reduced intensity conditioning with PTCy and mobilized peripheral blood cells (PBSC) in eight patients, with successful engraftment in 6 patients with low acute GVHD and no chronic GVHD. Follow up was 14.8 (7.2–44.4) months. Esteves et al.³⁶ also described haplo-BMT using the Hopkins regimen (described below) in another small cohort with 16 patients, after failure of IST or graft failure following unrelated-donor or cord blood transplant. Their protocol was similar to Clay et al.³⁷. Graft source was bone marrow in 13 and PBSC in three. The 1-year OS was 67.1% (95% CI: 36.5–86.4%).

Previous reports with haplo-BMT without PTCy in SAA have produced heterogeneous results depending on the patient population and are limited by small sample sizes (Table 1).^{36–44} In these series, rejection has been between 6% and 25%, acute GVHD between 12% and 30%, chronic GVHD between 20% and 40%, and overall survival (OS) between 60% and 100%.^{36–45} Limited comparisons can be made across these studies but some differences between studies may be related to infectious complications, donor specific antibodies as well as amount of patients' previous therapies. Nonetheless, in the relapsed and refractory setting, all patients had previously received IST at the time of diagnosis for their SAA and thus this may have impacted more favorably on engraftment with any of the conditioning regimens. Furthermore, the previous use of multiple lines of therapy could have also contributed to the improved engraftment rates over historical reports²¹. Upfront haploidentical transplant

studies are still very early with limited reports in the literature. Most studies have relatively short follow up.

More recently, DeZern et al.³⁴ reported on a prospective phase 2 trial of PTCy for refractory SAA in which 16 patients (median age 30 years, range 11–69) underwent transplant from 13 haploidentical and three unrelated donors. The conditioning consisted of rabbit antithymocyte globulin (ATG) 4.5mg/kg over 3 days, fludarabine (Flu) 30mg/m² for 5 days, Cy 14.5 mg/kg² for 2 days and total body irradiation (TBI) 200cGy (Figure 2). Graft source was bone marrow with target yield of 4 X10⁸ nucleated cells/kg recipient ideal weight. For GVHD prophylaxis, PTCy 50 mg/kg/day IV on days +3 and +4 was administered along with mycophenolate mofetil (MMF) on days +5 through 35 and tacrolimus from day +5 through 1 year. G-CSF was given from day +5 till absolute neutrophil count was more than 1.5 × 10⁹/l for 3 days. There was no graft failure and mild GVHD occurred in two patients. There was evidence for clonality in 37% of the patients pre BMT and this was eliminated post BMT. Furthermore, excellent performance status was noted in all patients after recovery as well. This study is limited by the small sample size and relatively short follow up. This is very similar to what was seen in Brazil using the same regimen, though they did have two patients with secondary graft loss and one primary graft failure.³⁶ Currently haplo-BMT with PTCy is being studied on a national level in the US by the Bone Marrow Transplant Clinical Trials Network (NCT02918292).

Other Strategies Including Upfront Haploidentical Transplant

In a prospective, multicenter study of haplo-BMT for SAA refractory to IST, Xu et al.³⁸ analyzed the outcomes of 101 patients. Conditioning was with IV busulfan (BU) 6.4 mg/kg, Cy 200 mg/kg and rabbit ATG 10mg/kg. Graft source was combined bone marrow and G-CSF-stimulated PBSC. GVHD prophylaxis was with CsA, MMF, and short-term methotrexate. These were compared with 48 patients who had matched-related donor (MRD) BMTs. Haplo-BMT compared with MRD showed more grade II–IV acute GVHD (33.7 vs. 4.2%, P<0.001), more chronic GVHD (22.4 vs. 6.6%, P=0.014) at 1 year, but similar 3-year OS (89.0 vs. 91.0%, P=0.555) and FFS (86.8 vs. 80.3%, P=0.659)³⁸.

Jaiswal et al.⁴⁴ looked at a TBI-sparing regimen in 10 patients (median 35 years, 6–46 years) including horse ATG, at 15 mg/kg from day –8 to day –6, fludarabine 30 mg/m²/day for 5 days and cyclophosphamide 15 mg/kg/day for 2 days with melphalan 120 mg/m² followed by PBSCs and PTCy. This protocol was modified with the introduction of sirolimus on day –7.⁴⁴ Six of the 10 patients were alive; 5 of the 6 received the Day –7 sirolimus. The authors hypothesized that early recovery of regulatory T cells in this small cohort might be indicative of a tolerance induction mechanism that could have resulted from synergism between PTCY and sirolimus.⁴⁴ Additionally, this group used this same platform and added in T cell co-stimulation blockade with abatacept, suggesting a further role of transplant tolerance with this approach.⁴³

Xu et al.⁴⁶ reported on 52 children who received haplo-BMT, with 29 receiving it as salvage and the remaining 23 received it as their upfront therapy, using the BU/Cy/rATG protocol described above.³⁸ Primary engraftment was achieved in 51. The cumulative incidence of aGVHD grade II–IV was 39.2% and of cGVHD was 34.2%, respectively. The 3-year OS and

FFS rates were 84.5% and 82.7% for the whole cohort.⁴⁶ The upfront and salvage haplo patients did very similarly here with non-significant benefit for the upfront group. There were 3-year OS and FFS rates of 87% and 82.6% for the upfront group and 82.6% (p=0.698) and 82.8% (p=0.899) for the salvage cohort. The longer-term FFS of over 80% of the upfront cohort compares quite favorable to previous reports of upfront IST FFS rates⁴⁷.

Upfront haplo-BMT in 158 SAA patients was reported by Xu et al.⁴⁸ based on the Chinese transplant registry. Here, haplo-BMTs were performed in 89 patients based on the BU/Cy/rATG treatment protocol described above,³⁸ and then compared to 69 MRD transplants, conditioned with either Cy+rATG or Cy+Flu+rATG⁴⁸. Haplo-BMT recipients had increased grades II–IV aGVHD (30.3 vs. 1.5%, P<0.001) and cGVHD (30.6 vs. 4.4%, P<0.001) at 1 year but similar extensive cGVHD (3.4 vs. 0%, P=0.426) compared with related transplants. The 3-year OS rates were 86.1 and 91.3% (P=0.358), whereas the 3-year FFS rates were 85.0 and 89.8% (P=0.413) in the haplo-BMT and MRD cohorts, respectively⁴⁸.

Conditioning for Haploidentical Transplant for Aplastic anemia

Reduced intensity or nonmyeloablative conditioning is likely sufficient to balance engraftment and toxicities in this setting. It has previously been shown that TBI-based conditioning regimens reduced the risk of graft rejection but increased GVHD and other late effects.⁴⁹ Standard ATG-based conditioning regimens are employed to aid in engraftment but have also been associated with up to a 30% incidence of cGVHD.^{50,51} Fludarabine has been used in conditioning for patients with both acquired and constitutional aplastic anemia with good results.^{52–55} We favor the use of a conditioning regimen including rATG, fludarabine and TBI with T-cell replete allografts for SAA patients (Figure 2).

Additionally, as described above, both T-cell depleted and T-cell replete^{34,44,56} haploidentical strategies have been reported for multiply relapsed SAA patients lacking a matched donor. Im and colleagues describe 21 patients who underwent fludarabine, cyclophosphamide, 400cGy TBI, and ATG conditioning followed by either CD3/19 or CD3alpha beta/CD19 depleted grafts. OS was reported as 94% at 3 years, without cases of chronic GVHD.⁵⁷ T-replete haploidentical approaches have been taken by Wang (17 children, full intensity conditioning and 4 agent GVHD prophylaxis: OS 71% at 1 year, 20% chronic GVHD)⁴² and Gao (26 adults, reduced intensity conditioning with three agent GVHD prophylaxis: OS 82% at 2 years, GVHD 40%)⁴⁵.

Increasing data are available for a reduced intensity approach followed by T-replete haploidentical transplant and PTCy described above as optimal GVHD prophylaxis with OS approaching 90% and low-GVHD rates.^{34,36,37} Thus, although follow-up is relatively short and numbers do remain small, we conclude from these aggregate data that reduced intensity conditioning regimens followed by haploidentical allografts for SAA patients are an increasingly viable therapeutic option. The multicenter study through the Bone Marrow Transplant Clinical Trials Network (NCT02918292) of haploidentical transplant in relapsed or refractory SAA modelled after the Hopkins approach³⁴ will provide additional experience and clinical outcomes in the arena in the US.

Donor selection

Stem cell choice

Most patients have more than one potential haploidentical donor. The process of choosing among these for the best possible donor is important but remains a controversial topic. The EBMT reviewed outcomes in nearly 700 patients with SAA receiving transplants from HLA-matched siblings. In patients younger than 20 years of age, rates of chronic GVHD (relative risk 2.82; $p = 0.002$) and overall mortality (relative risk 2.04; $p = 0.024$) were higher after transplantation of peripheral blood progenitor cell grafts than after transplantation of bone marrow. In younger patients, the 5-year survival was 85% after marrow transplants but only 73% after PBSC. These data suggest that bone marrow grafts are preferable in this age group^{58,59} but this has not been studied systematically in haploidentical donors. Most centers in the United States favor a bone marrow graft to avoid excessive GVHD in a non-malignant disease; however, in the United Kingdom, PBSC were successfully used without increased rates of GVHD.³⁷ In China many transplants of this nature follow another procedure to optimize cell counts. Haploidentical donors are treated with subcutaneous granulocyte colony-stimulating factor (G-CSF). Marrow grafts are then collected on day 1 with a target mononuclear cell (MNC) count of $2-4 \times 10^8/\text{kg}$ of recipient body weight. Peripheral blood stem cells are also collected by apheresis. The target MNC count from BM and PB was $6-8 \times 10^8/\text{kg}$ of recipient bodyweight. If the MNC count was not sufficient, additional PBSC are collected on the following day.³⁸

Choice of best haploidentical donor

There are often multiple potential haploidentical donor options. These can be first-degree relatives of the patient including biological parents, siblings or half-siblings, or children with 2, 3, or 4 mismatches using DNA-based typing. A unidirectional mismatch in either the graft-versus-host or host-versus-graft direction is considered a mismatch. The donor and recipient are recommended to be identical at a minimum of one allele (at high resolution DNA-based typing) at the following genetic loci: HLA-A, -B, -C, and DRB1 for haploidentical matching. There is nothing in AA that is unique compared to hematologic malignancies that suggests a nonstandard approach to the choice of donor to an AA patient. When more than one donor is available, the donor with the lowest number of HLA allele mismatches will be chosen unless there is HLA cross-match incompatibility or a medical reason to select otherwise. In cases where there is more than one donor with the least degree of mismatch, donors will be selected based on the most favorable combination of HLA compatibility in cross-match testing and ABO compatibility. Prioritization is given to the lowest number of mismatches in the host-versus-graft (HVG) direction to minimize the risk of graft rejection. If there is more than one donor with the least amount of HVG allele mismatches, the suggested prioritization in order of importance includes ABO compatibility, CMV status (use a sero-negative donor for a seronegative recipient or use a sero-positive donor for a sero-positive recipient), younger age, and lighter weight (this rule applies to donors 18 years or older; however, children may also be used as donors if appropriate), and sex of the donor (if all else is equal, males are preferred over nulliparous females over multiparous females).⁶⁰ Youth (age less than 40 years) is increasingly valued when it comes

to choice of any donor and this may begin to take greater priority in the haploidentical donor selection algorithm as well⁶¹.

The challenge of anti-HLA antibodies

Donor-specific anti-HLA antibodies (DSA) have been implicated in graft rejection in solid organ transplantation for many years. More recently their role in BMT has been better defined.⁶² Results in multiple retrospective reviews have suggested that DSA are associated with a higher rate of graft rejection in patients undergoing BMT⁶³ including those from a haploidentical donor⁶⁴. Thus, donors with high levels DSA should be excluded. Anti-HLA desensitization can be employed for low titer DSA in BMT for AA with haploidentical donors but only if there is no haploidentical donor without DSA.^{65,66}

Graft versus Host Disease Prophylaxis

PTCy is becoming standard backbone of GVHD prophylaxis in haplo-BMT. Additionally, oral IST is administered through day 180 or even one year in SAA⁶⁷. This often includes MMF as well as a calcineurin inhibitor. The majority of the more favorable results (seen in table 1) utilize this approach. Methotrexate remains commonly used as well.

Conclusion and Future of Haploidentical Transplants in Aplastic Anemia

In conclusion, haplo-BMT is now a safe and potentially curative option for treating SAA patients who are refractory to IST, have relapsed after IST, or who have acquired a secondary clonal disorder (MDS/PNH) after IST (Figure 3). Current strategies (including PTCy as GVHD prophylaxis) have increased the availability of haplo-BMT to patients previously considered transplant ineligible because they lack a suitable donor or were too high risk for BMT due to the risk GVHD. Ongoing investigations seek to increase this option for these patients through development of further novel therapeutic strategies to optimize haplo-BMT - both in the treatment refractory setting as well the upfront setting. Furthermore, haploidentical transplants are attractive due to low cost and early availability of a donor, although issues of donor-specific antibodies may be potentially problematic^{60,68}. The current results suggest that haplo-BMT should become standard therapy for refractory SAA patients. Upfront haplo-BMT remains investigational, but may be useful for very SAA patients lacking an MSD or MUD who want to consider minimizing risk of clonal evolution post IST.

References

1. Brodsky RA, Jones RJ. Aplastic anaemia. *Lancet*. 2005; 365(9471):1647–1656. [PubMed: 15885298]
2. Scheinberg P, Young NS. How I treat acquired aplastic anemia. *Blood*. 2012; 120(6):1185–1196. [PubMed: 22517900]
3. Young NS, Kaufman DW. The epidemiology of acquired aplastic anemia. *Haematologica*. 2008; 93(4):489–492. [PubMed: 18379007]
4. Alter BP. Bone marrow failure syndromes in children. *Pediatric clinics of North America*. 2002; 49(5):973–988. [PubMed: 12430621]
5. Yoshizato T, Dumitriu B, Hosokawa K, et al. Somatic Mutations and Clonal Hematopoiesis in Aplastic Anemia. *N Engl J Med*. 2015; 373(1):35–47. [PubMed: 26132940]

6. Kulasekararaj AG, Marsh JC. Architectural Clones in Aplastic Anaemia-Lessons Learned from High Throughput Sequencing. Current drug targets. 2015
7. Kulasekararaj AG, Jiang J, Smith AE, et al. Somatic mutations identify a subgroup of aplastic anemia patients who progress to myelodysplastic syndrome. *Blood*. 2014; 124(17):2698–2704. [PubMed: 25139356]
8. Young NS. Acquired bone marrow failure Philadelphia, PA: JB Lippincott; 1995
9. Alter BP. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program 2007 Diagnosis, genetics, and management of inherited bone marrow failure syndromes; 2939
10. Tefferi A, Vardiman JW. Myelodysplastic syndromes. *N Engl J Med*. 2009; 361(19):1872–1885. [PubMed: 19890130]
11. Whitman SP, Archer KJ, Feng L, et al. Absence of the wild-type allele predicts poor prognosis in adult de novo acute myeloid leukemia with normal cytogenetics and the internal tandem duplication of FLT3: a cancer and leukemia group B study. *Cancer Res*. 2001; 61(19):7233–7239. [PubMed: 11585760]
12. Kim SY, Le Rademacher J, Antin JH, et al. Myelodysplastic syndrome evolving from aplastic anemia treated with immunosuppressive therapy: efficacy of hematopoietic stem cell transplantation. *Haematologica*. 2014; 99(12):1868–1875. [PubMed: 25107891]
13. Scheinberg P. Aplastic anemia: therapeutic updates in immunosuppression and transplantation. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2012; 2012:292–300.
14. Eapen M, Horowitz MM. Alternative donor transplantation for aplastic anemia. Hematology Am Soc Hematol Educ Program. 2010; 2010:43–46. [PubMed: 21239769]
15. Storb R, Blume KG, O'Donnell MR, et al. Cyclophosphamide and antithymocyte globulin to condition patients with aplastic anemia for allogeneic marrow transplantations: the experience in four centers. *Biol Blood Marrow Transplant*. 2001; 7(1):39–44. [PubMed: 11215697]
16. Current use and outcomes of hematopoietic stem cell transplantation: CIBMTR Summary Slides 2013
17. Bacigalupo A. Matched and mismatched unrelated donor transplantation: is the outcome the same as for matched sibling donor transplantation? Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2012; 2012:223–229.
18. Passweg JR, Baldomero H, Bader P, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant*. 2017; 52(6):811–817. [PubMed: 28287639]
19. Niederwieser D, Baldomero H, Szer J, et al. Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group including the global survey. *Bone Marrow Transplant*. 2016; 51(6):778–785. [PubMed: 26901703]
20. Xu LP, Wu DP, Han MZ, et al. A review of hematopoietic cell transplantation in China: data and trends during 2008–2016. *Bone Marrow Transplant*. 2017
21. Ciceri F, Lupo-Stanghellini MT, Korthof ET. Haploidentical transplantation in patients with acquired aplastic anemia. *Bone Marrow Transplant*. 2013; 48(2):183–185. [PubMed: 23292235]
22. Thomas ED, Storb R, Fefer A, et al. Aplastic anaemia treated by marrow transplantation. *Lancet*. 1972; 1(7745):284–289. [PubMed: 4109931]
23. Gmur J, Vonfelten A, Rhyner K, Frick PG. Autologous Hematologic Recovery from Aplastic-Anemia Following High-Dose Cyclophosphamide and Hla-Matched Allogeneic Bone-Marrow Transplantation. *Acta Haematologica*. 1979; 62(1):20–24.
24. Sensenbrenner LL, Steele AA, Santos GW. Recovery of Hematologic Competence without Engraftment Following Attempted Bone-Marrow Transplantation for Aplastic-Anemia - Report of a Case with Diffusion Chamber Studies. *Experimental Hematology*. 1977; 5(1):51–58. [PubMed: 319010]

25. Brodsky RA, Sensenbrenner LL, Smith BD, et al. Durable Treatment-Free Remission Following High-Dose Cyclophosphamide for Previously Untreated Severe Aplastic Anemia. *Annals of Internal Medicine*. 2001; 135:477–483. [PubMed: 11578150]
26. Brodsky RA, Chen AR, Dorr D, et al. High-dose cyclophosphamide for severe aplastic anemia: long-term follow-up. *Blood*. 2010; 115(11):2136–2141. [PubMed: 20018919]
27. Luznik L, Engstrom LW, Iannone R, Fuchs EJ. Posttransplantation cyclophosphamide facilitates engraftment of major histocompatibility complex-identical allogeneic marrow in mice conditioned with low-dose total body irradiation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2002; 8(3):131–138.
28. DeZern AE, Petri M, Drachman DB, et al. High-dose cyclophosphamide without stem cell rescue in 207 patients with aplastic anemia and other autoimmune diseases. *Medicine (Baltimore)*. 2011; 90(2):89–98. [PubMed: 21358440]
29. Kasamon YL, Bolanos-Meade J, Prince GT, et al. Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015; 33(28):3152–3161. [PubMed: 26261255]
30. Luznik L, Jones RJ, Fuchs EJ. High-dose cyclophosphamide for graft-versus-host disease prevention. *Current opinion in hematology*. 2010; 17(6):493–499. [PubMed: 20827187]
31. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biology of Blood and Marrow Transplantation*. 2008; 14(6):641–650. [PubMed: 18489989]
32. Tisdale JF, Eapen M, Saccardi R. HCT for nonmalignant disorders. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2013; 19(1 Suppl):S6–9.
33. Bolanos-Meade J, Fuchs EJ, Luznik L, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. *Blood*. 2012; 120(22):4285–4291. [PubMed: 22955919]
34. DeZern AE, Zahurak M, Symons H, Cooke K, Jones RJ, Brodsky RA. Alternative Donor Transplantation with High-Dose Post-Transplantation Cyclophosphamide for Refractory Severe Aplastic Anemia. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2017; 23(3):498–504.
35. DeZern AE, Luznik L, Fuchs EJ, Jones RJ, Brodsky RA. Post-transplantation cyclophosphamide for GVHD prophylaxis in severe aplastic anemia. *Bone Marrow Transplant*. 2011; 46(7):1012–1013. [PubMed: 20838390]
36. Esteves I, Bonfim C, Pasquini R, et al. Haploidentical BMT and post-transplant Cy for severe aplastic anemia: a multicenter retrospective study. *Bone Marrow Transplant*. 2015; 50(5):685–689. [PubMed: 25730184]
37. Clay J, Kulasekararaj AG, Potter V, et al. Nonmyeloablative peripheral blood haploidentical stem cell transplantation for refractory severe aplastic anemia. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2014; 20(11):1711–1716.
38. Xu LP, Wang SQ, Wu DP, et al. Haplo-identical transplantation for acquired severe aplastic anaemia in a multicentre prospective study. *Br J Haematol*. 2016; 175(2):265–274. [PubMed: 27352174]
39. Zhu H, Luo RM, Luan Z, et al. Unmanipulated haploidentical haematopoietic stem cell transplantation for children with severe aplastic anaemia. *Br J Haematol*. 2016; 174(5):799–805. [PubMed: 27263533]
40. Zhang Y, Guo Z, Liu XD, et al. Comparison of Haploidentical Hematopoietic Stem Cell Transplantation and Immunosuppressive Therapy for the Treatment of Acquired Severe Aplastic Anemia in Pediatric Patients. *American journal of therapeutics*. 2017; 24(2):e196–e201. [PubMed: 26872138]

41. Sarmiento M, Ramirez PA. Unmanipulated haploidentical hematopoietic cell transplantation with post-transplant cyclophosphamide in a patient with paroxysmal nocturnal hemoglobinuria and secondary aplastic anemia. *Bone Marrow Transplant.* 2016; 51(2):316–318. [PubMed: 26501768]
42. Wang Z, Zheng X, Yan H, Li D, Wang H. Good outcome of haploidentical hematopoietic SCT as a salvage therapy in children and adolescents with acquired severe aplastic anemia. *Bone Marrow Transplant.* 2014; 49(12):1481–1485. [PubMed: 25133891]
43. Jaiswal SR, Bhakuni P, Zaman S, et al. T cell costimulation blockade promotes transplantation tolerance in combination with sirolimus and post-transplantation cyclophosphamide for haploidentical transplantation in children with severe aplastic anemia. *Transpl Immunol.* 2017
44. Jaiswal SR, Chatterjee S, Mukherjee S, Ray K, Chakrabarti S. Pre-transplant sirolimus might improve the outcome of haploidentical peripheral blood stem cell transplantation with post-transplant cyclophosphamide for patients with severe aplastic anemia. *Bone Marrow Transplant.* 2015; 50(6):873–875. [PubMed: 25798678]
45. Gao L, Li Y, Zhang Y, et al. Long-term outcome of HLA-haploidentical hematopoietic SCT without in vitro T-cell depletion for adult severe aplastic anemia after modified conditioning and supportive therapy. *Bone Marrow Transplant.* 2014; 49(4):519–524. [PubMed: 24464145]
46. Xu LP, Zhang XH, Wang FR, et al. Haploidentical transplantation for pediatric patients with acquired severe aplastic anemia. *Bone Marrow Transplant.* 2017; 52(3):381–387. [PubMed: 27941773]
47. Yoshida N, Kobayashi R, Yabe H, et al. First-line treatment for severe aplastic anemia in children: bone marrow transplantation from a matched family donor versus immunosuppressive therapy. *Haematologica.* 2014; 99(12):1784–1791. [PubMed: 25193958]
48. Xu LP, Jin S, Wang SQ, et al. Upfront haploidentical transplant for acquired severe aplastic anemia: registry-based comparison with matched related transplant. *Journal of hematology & oncology.* 2017; 10(1):25. [PubMed: 28107815]
49. Sanders JE, Woolfrey AE, Carpenter PA, et al. Late effects among pediatric patients followed for nearly 4 decades after transplantation for severe aplastic anemia. *Blood.* 2011; 118(5):1421–1428. [PubMed: 21653322]
50. Konopacki J, Porcher R, Robin M, et al. Long-term follow up after allogeneic stem cell transplantation in patients with severe aplastic anemia after cyclophosphamide plus antithymocyte globulin conditioning. *Haematologica.* 2012; 97(5):710–716. [PubMed: 22180425]
51. Champlin RE, Perez WS, Passweg JR, et al. Bone marrow transplantation for severe aplastic anemia: a randomized controlled study of conditioning regimens. *Blood.* 2007; 109(10):4582–4585. [PubMed: 17272503]
52. Kharfan-Dabaja MA, Otrock ZK, Bacigalupo A, Mahfouz RA, Geara F, Bazarbachi A. A reduced intensity conditioning regimen of fludarabine, cyclophosphamide, antithymocyte globulin, plus 2 Gy TBI facilitates successful hematopoietic cell engraftment in an adult with dyskeratosis congenita. *Bone Marrow Transplant.* 2012; 47(9):1254–1255. [PubMed: 22246089]
53. Dietz AC, Orchard PJ, Baker KS, et al. Disease-specific hematopoietic cell transplantation: nonmyeloablative conditioning regimen for dyskeratosis congenita. *Bone Marrow Transplant.* 2011; 46(1):98–104. [PubMed: 20383216]
54. Marsh JC, Gupta V, Lim Z, et al. Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after allogeneic stem cell transplantation for acquired aplastic anemia. *Blood.* 2011; 118(8):2351–2357. [PubMed: 21518925]
55. Wang SB, Li L, Pan XH, et al. Engraftment of heavily transfused patients with severe aplastic anemia with a fludarabine-based regimen. *Clin Transplant.* 2013; 27(2):E109–115. [PubMed: 23387380]
56. Gupta N, Choudhary D, Sharma SK, Khandelwal V, Dhamija M. Haploidentical hematopoietic SCT for acquired severe aplastic anemia using post-transplant high-dose CY. *Bone Marrow Transplant.* 2015; 50(1):155–156. [PubMed: 25285802]
57. Im HJ, Koh KN, Seo JJ. Haploidentical hematopoietic stem cell transplantation in children and adolescents with acquired severe aplastic anemia. *Korean J Pediatr.* 2015; 58(6):199–205. [PubMed: 26213547]

58. Schrezenmeier H, Passweg JR, Marsh JC, et al. 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; 110(4):1397–1400. [PubMed: 17475907]
59. Bacigalupo A, Socie G, Schrezenmeier H, et al. 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; 97(8):1142–1148. [PubMed: 22315497]
60. McCurdy SR, Fuchs EJ. Selecting the best haploidentical donor. *Semin Hematol*. 2016; 53(4):246–251. [PubMed: 27788762]
61. Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. *Blood*. 2016; 127(2):260–267. [PubMed: 26527675]
62. Morin-Zorman S, Loiseau P, Taupin JL, Caillat-Zucman S. Donor-Specific Anti-HLA Antibodies in Allogeneic Hematopoietic Stem Cell Transplantation. *Front Immunol*. 2016; 7:307. [PubMed: 27570526]
63. Ciurea SO, Thall PF, Wang X, et al. Donor-specific anti-HLA Abs and graft failure in matched unrelated donor hematopoietic stem cell transplantation. *Blood*. 2011; 118(22):5957–5964. [PubMed: 21967975]
64. Ciurea SO, Thall PF, Milton DR, et al. Complement-Binding Donor-Specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2015; 21(8):1392–1398.
65. Gladstone DE, Zachary AA, Fuchs EJ, et al. Partially mismatched transplantation and human leukocyte antigen donor-specific antibodies. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2013; 19(4):647–652.
66. Leffell MS, Jones RJ, Gladstone DE. Donor HLA-specific Abs: to BMT or not to BMT? *Bone Marrow Transplant*. 2015; 50(6):751–758. [PubMed: 25706884]
67. Bacigalupo A, Brand R, Oneto R, et al. Treatment of acquired severe aplastic anemia: bone marrow transplantation compared with immunosuppressive therapy--The European Group for Blood and Marrow Transplantation experience. *Semin Hematol*. 2000; 37(1):69–80. [PubMed: 10676912]
68. Ciurea SO, Champlin RE. Donor selection in T cell-replete haploidentical hematopoietic stem cell transplantation: knowns, unknowns, and controversies. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2013; 19(2):180–184.
69. Gao L, Li Y, Zhang Y, et al. Long-term outcome of HLA-haploidentical hematopoietic SCT without in vitro T-cell depletion for adult severe aplastic anemia after modified conditioning and supportive therapy. *Bone Marrow Transplant*. 2014; 49(4):519–524. [PubMed: 24464145]

Key Points

1. Relapsed and refractory SAA carries a grave prognosis if efforts to renew hematopoiesis and avoid clonal evolution are not pursued.
2. Allogeneic bone marrow transplantation addresses both the acute and chronic complications of severe AA, by virtually eliminating the risk of relapse and secondary clonal disease, but introduces the risk of acute and chronic GVHD.
3. High dose cyclophosphamide (50mg/kg/d $\times$ 4 days) has a unique history in the context of AA for both transplant and non-transplant therapies.
4. Use of post transplantation cyclophosphamide on Days 3 and 4 posttransplant has allowed for expansion of the donor pool to include haploidentical transplants for patient with relapsed and refractory SAA.
5. Rates of GVHD and other transplant related mortality are low with use of post transplantation cyclophosphamide.

Figure 1.
History of Cyclophosphamide in Aplastic Anemia.

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Figure 2.
Schema for Nonmyeloablative Haploidentical Bone Marrow Transplant for Severe Aplastic Anemia Using Post transplantation Cyclophosphamide.

Figure 3.
Current Clinical Approach to the Management of Severe Aplastic Anemia including Haploidentical Bone Marrow Transplant.

Table 1

Results of Haploidentical Bone Marrow Transplant for Severe Aplastic Anemia

<u>Location</u>	<u>Date</u>	<u>N</u>	<u>PRE BMT therapy</u>	<u>Median Age (Range)</u>	<u>Conditioning Regimen</u>	<u>Graft Source</u>	<u>GVHD Prophylaxis</u>	<u>Engraftment</u>	<u>Overall Survival</u>	<u>Median Follow-Up</u>	<u>Acute GVHD</u>	<u>Chronic GVHD</u>
Studies Utilizing Post-transplant Cyclophosphamide as GVHD prophylaxis												
Brazil ³⁶	2010–2014	16	All R/R to IST; no IBMFS included	17 (5–39)	RIC: Flu, CY, TBI (200–600 cGy)	BM 13 PB 3	PTCy +3,4; MMF to D35 CSA/Tacro	15/16; Secondary graft loss 2/16	67.1%	355 days	13 % grade II–IV	20% limited
United Kingdom ³⁷	Prior to 2014	8	4 R/R to IST; 4 failed to engraft after previous BMT	32 (19–57)	RIC: Flu, CY, TBI (200 cGy)	PB (GCSF mobilized)	PTCy +3,4 MMF to D35 CSA/Tacro	6/8	75%	14.8 months (7.2–44.4)	1 Grade 2 aGVHD	0
**Baltimore ³⁴	2011–2016	16 (13 haplo)	All R/R to IST; IBMFS included	30 (11–69)	RIC: rATG, Flu, CY, TBI (200 cGy)	BM	PTCy +3,4 MMF to D35 Tacro	100%	100%	21 months (3–64)	2 Grade 1–2 aGVHD	2 limited
Studies NOT Utilizing Post-transplant Cyclophosphamide as GVHD prophylaxis												
China ⁶⁹	2007–2010	26	All R/R to IST; no IBMFS included	25.4 (18–41)	RIC: rATG, Flu, CY	BM +PB	CSA to D180 MMF to D90 MTX D+1,3,6,11	92.4%	84.6%	1313.2 days (738–2005)	12% grade II–IV	4% extensive
China ⁴⁸	2012–2015	89	None	22 (4–51)	RIC: Bu; CY; rATG	BM +PB	CSA to 1 yr MMF to D60 MTX D+1,3,6,11	98.9%	86.1%	22.6 (7.1–47.6)	30.3% grade II–IV	3.4% extensive
**China ³⁸	2012–2015	101	All R/R to IST; no IBMFS included	19 (2–45)	RIC: Bu; CY; rATG	BM +PB	CSA to 1 yr; MMF to D60; MTX D+1,3,6,11	100% of 97 who survived to Day 28	89%	18.3 months (3–43.6)	33.7 % grade II–IV	10% extensive
Studies in Pediatric Patients												
China ³⁹	2002–2013	36	All R/R to first line tx (only 33% had ATG)	50.5–14	RIC (3 regimens)	PBSCs in 34 1 BM 1UC (matching 3–5/6)	MTX + CSA or tacro or MMF	34/36	86.1% at 5 years	42 months (20–157)	11 with grade II; 2 with grade III	7 limited 1 extensive
China ⁴²	2010–2013	17	All R/R to first line tx (only 5 had ATG)	10 (4–19)	RIC: Bu; Flu; or CY; ATG or ALG	BM +PB	CSA + MTX + basiliximab	17/17 myeloid 16/17 platelet (one secondary)	71.6%	362 (36–1321) days	12 with grade I–II; 1 with grade III–IV	4 limited
**China ⁴⁶	2007–2015	52	29 pts R/R (only 15 had ATG) 23 pts upfront	9 (2–17)	RIC: Bu; CY; rATG	BM +PB	CSA to 1 yr MMF to D60 MTX D+1,3,6,11	96.2%	84.5%	744.5 (100–3294) days	39.2% grade I–II; 13.7 grade III–IV	34.2% (1 extensive)
Peripheral Blood Stem Cell Source												

Location	Date	N	PRE BMT therapy	Median Age (Range)	Conditioning Regimen	Graft Source	GVHD Prophylaxis	Engraftment	Overall Survival	Median Follow-Up	Acute GVHD	Chronic GVHD
India ⁴⁴	2012–2014	10	50% failed IST	35 (6–46)	Flu; CY; rATG, melphalan,	PB	Sirolimus (in 5/10), PTCy, MMF to D35, CSA	90%	60%	2 years	1 patient	2 patients
India ⁴³	2015–2016	10	50% failed IST	12 (4–21)	Flu; CY; rATG, melphalan,	PB	Sirolimus, abatacept, PTCy,	90%	88.9%	NR but >1 year for 8 pts	1 patient grade 2–4	1 patient off IST by 1 year

Prospective study

BMT= bone marrow transplant; R/R = relapsed or refractory; IBMFS= inherited bone marrow failure syndrome; IST= immunosuppressive therapy; GVHD= graft versus host disease; RIC= Reduced Intensity Conditioning; rATG= rabbit anti-thymocyte globulin; BM= bone marrow; PB= peripheral blood; GCSF=granulocyte colony stimulating factor; cGy=centrigray; BU=busulfan; Flu=fludarabine; CY=cyclophosphamide; CSA = cyclosporine; MTX= methotrexate; MMF=mycophenolate mofetil; Tacro=tacrolimus; PTCy= post-transplant cyclophosphamide at 50mg/kg per dose