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Acquired Aplastic Anemia Therapies: Immunosuppressive Therapy Versus Alternative Donor Hematopoietic Cell Transplantation

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Abstract

Immunosuppressive therapy for acquired severe aplastic anemia improves pancytopenia but has a significant risk of relapse (40%) and clonal evolution to myeloid neoplasms (15%), especially in patients older than 40. Yet, current guidelines for newly diagnosed severe aplastic anemia patients over the age of 40 recommend immunosuppressive therapy instead of curative allogeneic stem cell transplantation. Upfront allogeneic stem cell transplants are restricted to the rare patient who is not only young but also has a matched sibling donor. This article will discuss practice-changing data on the recent advances in upfront alternative donor hematopoietic cell transplants that could rewrite current treatment algorithms.

Keywords: Aplastic anemia; Immunosuppressive therapy; Stem cell transplantation

Introduction

Acquired aplastic anemia (AA) is a life-threatening bone marrow (BM) failure syndrome from autoreactive T cells destroying hematopoietic stem and progenitor cells (HSPC). The modified Camitta criteria define disease severity (Table 1) [1]. Eighty percent of AA is idiopathic, and 20% is inherited. Other causes of pancytopenia and hypocellularity, such as hypoplastic myelodysplastic syndrome (MDS), should be ruled out (Table 2) [1]. The focus of this article is acquired idiopathic AA. There are two to three cases per million per year in the West and up to three-fold higher incidence in Asia [2]. The peak incidence of AA is at age 10 to 25 years and later after age 60 years. This article will discuss practice-changing data on the recent advances in upfront alternative donor hematopoietic cell transplants that could rewrite current treatment algorithms.

Current guidelines recommend a matched sibling donor (MSD) allogeneic hematopoietic cell transplantation (HCT) for severe and very severe aplastic anemia (SAA/VSAA) patients 40 years or younger. Patients older than 40 receive immunosuppressive therapy (IST) with eltrombopag (EPAG), horse anti-thymocyte globulin (hATG), and cyclosporine (CSA). Alternative donor allogeneic HCT is reserved for those who fail a cycle of IST [2]. Although IST helps improve pancytopenia, the response is not durable, and the risk of clonal disease persists.

The enigma of clonal diseases in AA was alluded to by Dr. Dameshek in 1967, who proposed a riddle: "what do AA, paroxysmal nocturnal hemoglobinuria (PNH), and hypoplastic leukemia have in common?" [3]. The riddle still needs to be fully solved, but there has been progress. Clonal disease is inherent to AA, regardless of IST, with evolution to PNH and myeloid neoplasia (MN), such as MDS and acute myeloid leukemia (AML). Even AA patients who do not progress to clonal diseases can have underlying clonal hematopoiesis.

Pathogenesis of Clonal Evolution in AA Treated With IST

Human leukocyte antigen (HLA) class I alleles, such as HLA-B*14:02, occur at greater frequency in patients with autoimmune disease, such as AA [4]. HLA molecules and other major histocompatibility complex-like molecules, such as glycosylphosphatidylinositol (GPI), present pathogenic antigens that unleash an immune attack by $CD8^+$ cells resulting in diminished HSPC in the marrow of AA patients [5, 6]. The precise antigen specificity that launches this immune attack is unknown but may be viral, such as hepatitis [6].

Escape from immune destruction: *PIGA* mutations

After IST, the surviving HSPCs are under selection pressure to repopulate the marrow. Immune-resistant HSPC clones without GPI anchors are selected, leading to secondary PNH and complement-mediated hemolysis. However, the absence of GPI anchors allows immune escape because of reduced antigen presentation and abrogation of the immune attack on HSPC - a silver lining [7]. PNH has a loss of function of the phosphatidylinositol glycan anchor biosynthesis class A (*PIGA*) gene on chromosome Xq22.2. PNH patients lack GPI

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Table 1. Modified Camitta Criteria to Assess Severity of Aplastic Anemia

	Diagnostic criteria
Severe aplastic anemia (SAA)	Bone marrow cellularity < 25% (or 25-50% if < 30% of residual cells are hematopoietic) and two of the following: 1) Peripheral blood absolute neutrophil count (ANC) < 0.5×10^9/L; 2) Peripheral blood platelet count < 20×10^9/L; or 3) Peripheral blood reticulocyte count < 60×10^9/L
Very severe aplastic anemia (VSAA)	Criteria for SAA and ANC < 0.2×10^9/L
Non-severe aplastic anemia (NSAA)	Bone marrow cellularity < 25% (or 25-50% if < 30% of residual cells are hematopoietic) and peripheral blood cytopenia not fulfilling criteria for SAA or VSAA

proteins, such as CD55 and CD59, leading to susceptibility to complement-mediated hemolysis.

Immune escape: *HLA* mutations

Another immune escape mechanism to reduce antigen presentation is inactivating somatic mutations in HLA genes [8]. Single nucleotide array karyotyping revealed deletions or uniparental disomy (UPD) in chromosome 6p, the site of HLA class I, in 14% of AA [8, 9]. HLA alleles such as A*02:01, B*14:02, and B*40:02 are overrepresented in AA patients, and these are the alleles typically lost in 6pUPD. In other words, these HLA alleles present antigens to cytotoxic T cells to launch the immune attack on the HSPC, and the loss of these HLA alleles allows for immune escape [10-12]. HLA loss (hazard ratio (HR): 4.87 (95% confidence interval (CI): 2.16 - 11), P = 0.00014), HLA-B*14:02 genotype (HR: 2.47 (95% CI: 1.01 - 6.25), P = 0.048), and age 40 years or older (HR: 2.47, (95% CI: 1.2 - 6.28), P = 0.017) were associated with high-risk clonal evolution [8]. Older patients have greater age-related clonal hematopoiesis than pediatric patients. For this age group over 40, upfront transplants should be considered rather than the recommended IST.

Myeloid driver mutations

Seventy percent of AA patients harbor somatic mutations [5, 12, 13]. The most common somatic mutations are *BCOR* and its ligand *BCORL1*, the DTA triad (*DNMT3A, TET2, ASXL1*), and *PIGA*, occurring either at diagnosis or early in the course. Trisomy 8 occurs in 20% of AA at diagnosis [5, 12, 13]. After IST, HSPC with myeloid driver somatic mutations, such as *RUNX1* or *SETBP1*, can emerge and gain clonal dominance by Darwinian selection from a fitness advantage over unmutated HSPC [12, 13]. Oligoclonal hematopoiesis, under the pressure of older age or poor response to IST, could develop chromosomal abnormalities such as loss of chromosome 7, causing MN [5, 13].

In AA, unfavorable somatic mutations, such as *ASXL1*, *RUNX1*, and *TP53*, compared with favorable somatic mutations, such as *BCOR/BCORL1* and *PIGA*, have a higher risk of progression to MN (40% vs. 3%) and worse survival (40% vs. 60%) [12, 13]. After IST, 40-50% of AA patients can have polyclonal HSPC recovery; 20-30% can have immune escape by HLA somatic mutations, such as 6pUPD; 20-25% have immune escape by *PIGA* mutations; and 10-15% can develop myeloid driver mutations triggering MN [5, 13].

Long-Term Outcomes With IST

In 2017, the US Food and Drug Administration (FDA) approved adding EPAG to hATG and CSA (EPAG-IST) in newly diagnosed SAA patients based on a prospective phase II study at the National Institutes of Health (NIH) showing improved hematologic response rates [14]. Complete response (CR) was defined by hemoglobin ≥ 10 g/dL, absolute neutrophil count ≥ $1{,}000 \times 10^9$/L, and platelets ≥ 100×10^9/L. EPAG is a thrombopoietin receptor agonist promoting the expansion and differentiation of megakaryocytes and HSPC, improving all cell lineages [14]. Optimal responses were seen with 6 months of EPAG beginning on the first day of IST with hATG for 4 days and CSA for 2 years. At 6 months, EPAG-IST had 94% overall response rate (ORR) and 58% CR vs. 60% ORR and 10% CR with historic-IST (hATG and CSA) [14]. The faster, more robust hematologic responses with EPAG were confirmed in a prospective randomized phase III study comparing EPAG-IST to historic-IST (6-month ORR/CR 68%/32% vs. 41%/20%) [15]. Still, a third of patients did not respond to EPAG-IST (Table 3) [15]. Adding EPAG did not significantly improve

Table 2. Aplastic Anemia Versus Hypoplastic Myelodysplastic Syndrome

	Aplastic anemia	Hypoplastic myelodysplastic syndrome
Dysplasia	Erythroid lineage only	Bilineage/trilineage; granulocytic, megakaryocytic also
Blasts	None	Present-normal or increased
Abnormal localization of immature precursors	No	Yes
Cytogenetics	6p uniparental disomy, -7/deletion 7q, +8, +15	-5/deletion 5q, -7/deletion 7q, +8

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Table 3. RACE[a] Conducted Between 2015 and 2019 in Patients With Acquired Severe or Very Severe Aplastic Anemia Aged 15 Years or Older With Karnofsky Performance Status at Least 50-60% or Greater

	Group A	Group B
Therapy	Horse ATG 40 mg/kg/day × 4 days IV + cyclosporine PO for 12 months with taper over next 12 months and discontinuation at 24 months	EPAG 150 mg PO, day 14 to 6 months, or to 3 months if in CR + horse ATG 40 mg/kg/day × 4 days IV + cyclosporine for 12 months with taper over next 12 months and discontinuation at 24 months
Number of patients	101	95
Age, median (range) years	52 (15 - 81) years	55 (16 - 77) years
Response at 3 months		
Complete response	10%	22%
Overall response	31%	59%
Response at 6 months		
Complete remission	20%	32%
Overall response	41%	68%
Complete remission at 12 months	33%	52%
Median time to first response	8.8 months	3 months
Number of patients who had stem cell transplantation	12 patients	11 patients
Relapse at 18 months	11% (95%CI: 2 - 20)	19% (95% CI: 9 - 29)
2-year event-free survival	34% (95% CI: 24 - 44)	46% (95% CI: 36 - 57)
2-year overall survival	85% (95% CI: 78 - 92)	90% (95% CI: 82 - 97)
Multivariate analysis for worse OS and relapse risk	Age > 40 years	Age > 40 years
Percentage of patients with NGS somatic mutations at diagnosis	29%	31%
Percentage of patients with NGS somatic mutations at 6 months	66%	51%

[a]Randomized multicenter trial of horse anti-thymocyte globulin (ATG) + cyclosporine with or without EPAG as first line. OS: overall survival; NGS: next-generation sequencing: CR: complete remission; EPAG: eltrombopag; IV: intravenous; PO: *per os*; CI: confidence interval.

overall survival (OS). It modestly improved 2-year event-free survival (EFS) (46% vs. 34%), where events were: no response at 6 months, allogeneic HCT, clonal evolution, relapse, additional AA therapy, and death. In multivariable analysis, only those over 40 had worse OS and relapse risk [15].

Relapse After IST

After a median follow-up of 4 years in the NIH study, there was a cumulative incidence of relapse of 39% in the EPAG-IST group vs. 56% in a historic-IST group, but this was not statistically significant (P = 0.07) [16]. Early relapse occurred at 6 months when EPAG was discontinued, pointing to EPAG's primarily short-term expansion of HSPC. Lowering CSA to maintenance levels at 6 months led to relapse from the resurgence of autoreactive lymphocytes. Late relapses occurred after 2 years when CSA was stopped [16]. Two-thirds of the relapses occurred before 2 years. The median time to relapse was faster with EPAG-IST (324 days) than with historic-IST (774 days). Historic-IST had the same 4-year relapse rate as EPAG-IST, 33% vs. 39% (P = 0.09) [16]. In other words, stopping EPAG forfeited the superior response rate. The durability of IST is poor. Adding EPAG to IST did not improve the durability of the response. The major cause of death was infection from prolonged neutropenia [16].

Only older age was associated with more relapse amongst all variables tested, such as telomere length, somatic mutations, and blood counts at baseline or 6 months. Compared with patients 18 to 40 years of age, those aged 40 - 60 had more relapse (HR: 2.29, 95% CI: 1.52 - 4.85, P = 0.03) as did those 60 years or older (HR: 2.89, 95% CI: 1.52 - 5.48, P = 0.001) [16].

Clonal Evolution After IST

AA has an inherent risk for clonal evolution to PNH and MN. In 2014, EPAG monotherapy was approved in the US for relapsed SAA with a 40% response but with a 20% clonal evolution rate [17]. Based on this, there was concern adding EPAG to hATG and CSA could increase the risk of MN. However, in the NIH study of newly diagnosed SAA patients, the cumulative incidence of clonal evolution was 15% with both EPAG-IST and historic-IST [14]. Patients older than 40 had a significantly greater risk of clonal evolution than younger patients. High-risk clonal evolution, such as deletion 7, *ASXL1*, or *RUNX1* mutations, occurred in 5.7% of the EPAG-IST group, like

Table 4. Clonal Evolution to Secondary MN in Nontransplanted AA Patients

N = 882 patients	
10-year cumulative incidence of MN overall	12.80%
10-year cumulative incidence of MN for CR vs. no CR with IST	8.5% vs. 15.7%, P = 0.02
10-year cumulative incidence of MN for >35 years vs ≤ 35 years of age	20.6% vs. 6.6%, P < 0.001
Median time from diagnosis to MN	4.5 years (IQR: 1.8 - 7.7 years)
MN type	MDS 75%
	AML 18%
	MDS/MPN 7%
Clonal burden at diagnosis vs. at time of MN diagnosis	20% vs. 30%, P = 0.001
Mutations at AA diagnosis vs. at the time of MN progression	*BCOR/L1*, *PIGA*, *HLA* mutations decreased vs. myeloid mutations *ASXL1, RUNX1, SETBP1* increased

IST: immunosuppressive therapy; MN: myeloid neoplasm; AA: aplastic anemia; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; MPN: myeloproliferative neoplasm; HLA: human leukocyte antigen; IQR: interquartile range; CR: complete response.

the historic-IST group. However, the time to high-risk clonal evolution was earlier with EPAG-IST, 6 months vs. 2 years with historic-IST [14]. The 58% mortality was high due to the development of MDS or AML, for which even allogeneic HCT had a poor prognosis. Low-risk clonal evolution such as deletion 13q, trisomy 8, and 5q deletion occurred in 9.1% of EPAG-IST patients at 4 years [14]. In the NIH study, EPAG was discontinued at the onset of low-risk clonal abnormalities. None of the low-risk clonal abnormalities evolved into MN.

In a retrospective multicenter study, 1,008 AA patients with or without PNH underwent next-generation sequencing (NGS) to detect somatic mutations at diagnosis and follow-up between 1972 and 2020 (Table 4) [13]. Of note, no patient developed MN or PNH with an upfront allogeneic HCT after a median 8.2-year follow-up (interquartile range (IQR): 5.7 - 10.6), and the 10-year OS was 86.7% (77.8-92.1%). Of the remaining 882 non-transplanted patients, the largest cohort to date, the 10-year OS was 76.4%. At 10 years, the cumulative incidence of MN was 12.8% in AA, 13.1% in AA/PNH, and 3.4% in PNH patients. Due to the lower risk of MN, primary PNH had better 10-year OS than AA or AA/PNH (95.2% vs. 72.1% vs. 88.8%, P < 0.001) [13]. Patients older than 35 had a higher 10-year cumulative incidence of MN than younger patients (20.6% vs. 6.6%, P < 0.001). Those not in CR with IST had a greater 10-year cumulative incidence of MN than those in CR (15.7% vs. 8.5%, P = 0.02) [13]. Older age and poor response to IST were independent predictors of MN and survival. The presence of a small PNH clone at diagnosis predicted better 10-year OS (83.9% vs. 70.7%, P = 0.02) and a higher rate of evolution to secondary PNH (19.8% vs. 4.7%, P < 0.001).

The median time from diagnosis of AA to MN was 4.5 years (IQR: 1.8 - 7.7 years). Most patients who progressed to MN developed MDS (75%), followed by AML in 18% and myelodysplastic/myeloproliferative neoplasm in 7% [13]. The 5-year OS after MN diagnosis was 40%. BM blasts 5% or greater were independent predictors of OS (HR: 3.64, 95% CI: 1.82 - 7.30, P < 0.001). The MDS cases were high risk by the revised International Prognostic Scoring System (R-IPSS) due to the prevalence of poor-risk cytogenetics such as monosomy 7. Deletion 7/7q MN was usually associated with *ASXL1, SETBP1, RUNX1*, and *RAS* pathway mutations. Secondary MN with normal karyotype had a unique signature of *DNMT3A, FLT3,* and *NPM1* mutations, whereas MN with complex karyotype had diverse molecular mutations. In contrast to *de-novo* MDS, AA-associated MDS had higher R-IPSS scores and more chromosome 7 abnormalities (53% vs. 11%), *ASXL1* mutations (24% vs. 12%), and *RUNX1* mutations (21% vs. 8%) [13].

Myeloid mutations at diagnosis were found in 18% of patients, more commonly in AA than in PNH. At diagnosis, a third of patients had *PIGA* mutations, followed by *BCOR/L1, ASXL1*, and *TET2* mutations. Patients with myeloid driver mutations (such as *RUNX1* and *SETBP1*) at AA diagnosis were older with a higher risk of progression to MN in contrast to the more favorable group with *PIGA* and *BCOR/L1* mutations (P < 0.001). At evolution to MN, expanding myeloid driver mutations swept away *PIGA* and somatic *HLA* mutations. Compared with the diagnosis of AA, the time of MN progression had higher mutational and clonal burdens (median variant allele frequency 20% vs. 30%, P = 0.001). Even though 10% of mutations at MN evolution were already present at AA diagnosis or early in the course, there was no difference in the time to MN evolution.

The phase III RACE study performed prospective BM NGS sampling at diagnosis and follow-up [15]. At diagnosis, a third of patients had somatic mutations. At 6 months, the prevalence of somatic mutations increased, indicating oligoclonal hematologic recovery. However, EPAG-IST did not increase the prevalence of somatic mutations over historic-IST (Table 3) [15]. Long-term results from the RACE study will help elucidate the clinical and biological factors predicting the progression of oligoclonal hematopoiesis to MN.

After IST, BM recovery is oligoclonal and prone to mutations resulting in MN. Patients treated with IST need life-long monitoring by BM biopsies with cytogenetics and NGS to allow timely intervention with allogeneic HCT for MN. Even so, allogeneic HCT for monosomy 7 AML, for example, provides a 2-year leukemia-free survival of only 28.5% and a 2-year OS of 34.9% [18]. Secondary MN has an abysmal prognosis.

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The goal of AA therapy should be to avoid MN with a curative allogeneic HCT upfront in fit patients. After HCT, there is polyclonal hematopoietic recovery. No patient with an upfront allogeneic HCT developed MN at a median of 8.2 years' follow-up [13]

Allogeneic HCT

Current treatment guidelines for SAA/VSAA recommend MSD allogeneic HCT for fit patients 40 years or younger. Patients over 40 receive IST with EPAG, hATG, and CSA regardless of matched donor availability. Even patients younger than 40 without an MSD undergo IST, as unrelated donor searches take up to 4 months. Alternative donor HCT is consigned to the role of salvage therapy for those who fail a cycle of IST, as only a third of patients will respond to a second course of IST [2]. Although IST helps improve pancytopenia, the response is not durable, and the risk of MN persists [13-16]. Two-year EFS is only 46% [15]. However, refinements in graft-vs-host disease (GVHD) prophylaxis and alternative donor HCT with readily accessible haploidentical donors could transform AA therapy.

Age at HCT

The median age for IST in the RACE study, for example, was 55 years [15]. In the past, allogeneic HCT was restricted to younger patients; however, recent advancements in HLA matching, conditioning regimens, and supportive care have expanded the use of transplantation to fit older patients.

Shin et al [19] showed comparable outcomes in SAA patients ≤ 40 years (15 - 40 years) or older (40 - 63 years) after MSD allogeneic HCT with fludarabine, cyclophosphamide, and rabbit ATG (FCATG) conditioning [19]. There was no difference in the incidences of 3-month grade II-IV acute GVHD (9.5% vs. 9.3%, P = 0.42), 5-year chronic GVHD (8.1% vs. 9.5%, P = 0.80), 5-year transplant-related mortality (5.4% vs. 11.1%, P = 0.91), 5-year failure-free (73.7% vs. 81.0%, P = 0.73); and 5-year OS rates (93.7% vs. 88.9%, P = 0.20) in the younger or older age group [19].

A joint European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) study of AA patients 50 years or older undergoing first MSD or matched unrelated donor (MUD) allogeneic HCT between 2005 and 2014 after the failure of IST revealed age had no impact on OS [20]. The median age at transplant was 57.8 years (range: 50 - 77.7 years). Out of all the variables tested, including age and graft type with BM or peripheral blood stem cell (PBSC), only Karnofsky performance status (KPS) < 90% was associated with poorer survival [20]. The 3-year probability of OS in patients with KPS 90-100% vs. KPS < 90% was 66% (range: 57-75%) vs. 57% (range: 47-76%), P = 0.02 [20]. The mortality risk for patients aged 65 to 78 years vs. 50 to 64 years was not significantly different (HR: 1.3, 95% CI: 0.81 - 1.81, P = 0.343).

Fludarabine, cyclophosphamide, and alemtuzumab (FCC) with CSA for GVHD prophylaxis in MSD and MUD allogeneic HCT avoids using total body irradiation (TBI) in conditioning and methotrexate in GVHD prophylaxis. Alemtuzumab effectively reduces GVHD, allowing the safe use of PBSC grafts to increase stem cell dose and lower the risk of graft failure [21]. At King's College Hospital, 45 SAA patients received FCC-conditioned allogeneic HCT. Seventy-three percent had MUD, and 84.5% had PBSC grafts. Most patients had failed IST. The graft failure rate was low (2.2%), as was the acute GVHD grade I - II rate at 13% and mild chronic GVHD at 13%. The 5-year OS and EFS were 93% and 91%, respectively. Patients older or younger than 50 or with MSD or MUD had similar outcomes. In patients older than 50, OS was 98% with the hematopoietic cell transplantation comorbidity index (HCT-CI) score of < 3, compared with 76% with an HCT-CI score of 3 or more [22]. Performance status and HCT-CI should guide eligibility for transplant rather than only chronological age.

Upfront Haploidentical HCT

The likelihood of a sibling being HLA-matched is 25%. The prospect of finding an MUD is 75% for Caucasians of European ancestry and much less for ethnic minorities, for example, only 16% for South or Central Americans, because ethnic minorities have more HLA polymorphism and smaller donor pools in national registries [23]. Thus, curative upfront transplants are restricted to the rare AA patient who is not only young but also has an MSD. Recently, the donor pool has expanded with the successful use of haploidentical HCT from first- and second-degree relatives [24]. Patients share a haplotype with each parent or child, half of their siblings, and half of their second-degree relatives, such as grandparents, aunts, uncles, nieces, nephews, and grandchildren [24]. A haploidentical donor is available for almost everyone, irrespective of race/ethnicity. Unrelated donor searches take up to 4 months, whereas haploidentical donors are available in a month.

Posttransplant cyclophosphamide (PTCY), an S-phase drug, kills proliferating alloreactive host and donor effector T cells and promotes the recovery of regulatory donor T cells, enhancing tolerance and suppressing graft rejection and GVHD [25]. The PTCY platform allows for transplantation across HLA barriers, such as haploidentical HCT, without severe GVHD. Haploidentical HCT using PBSC or BM with PTCY have comparable outcomes to MSD and MUD HCT in hematological malignancies [26-28]. Furthermore, the low rates of GVHD and graft rejection with PTCY allow for the safe and effective use of haploidentical HCT in non-malignant diseases, such as sickle cell anemia and AA, where the graft-versus-tumor effect is not needed [24, 29].

At Johns Hopkins, a phase II prospective study in 27 newly diagnosed SAA patients with a median age of 25 years (range: 3 - 65 years) used upfront haploidentical bone marrow transplant (BMT) with rabbit ATG, fludarabine, cyclophosphamide, and TBI 2 Gy - 4 Gy conditioning [24]. GVHD prophylaxis consisted of PTCY on day +3 and day +4 after stem cell infusion, mycophenolate mofetil from day +5 to 35, and tacrolimus from day +5 with a target level of 10 - 15 µg/L. The patients

undergoing upfront HCT had KPS of 60% or greater, similar to the RACE study of upfront IST with KPS of 50-60% or more [15]. The first 10 patients stopped tacrolimus without taper at day +365 if there was no GVHD. The remaining patients discontinued tacrolimus at day +180 without taper, provided there was no GVHD. Of the first seven patients who received 2 Gy TBI conditioning, three had primary graft failure. Due to the need for more immunosuppression in newly diagnosed SAA patients to ensure engraftment, the subsequent 20 patients received 4 Gy TBI in a single fraction, and none developed graft failure. The cumulative incidence of grade I - II acute GVHD on day +100 was 7%, and mild chronic GVHD at 2 years was 4%. No patient had grade III - IV acute GVHD or moderate/severe chronic GVHD. The 3-year OS was 92% (95% CI; 83-100%). However, in the TBI 4 Gy group, the 3-year OS was 100% and treatment-related mortality 0%. These results are encouraging, especially since half the patients had VSAA for whom early mortality with IST is 10% due mainly to infections from prolonged neutropenia as the time to hematologic response with IST is 3 months vs. 3 weeks with HCT [15, 24].

Neutrophil engraftment occurred by day 17, and platelet engraftment by day 25.5. At 12 months, 96% had CR (hemoglobin ≥ 10 g/dL, absolute neutrophil count ≥ 1,000 × 10^9/L, and platelets ≥ 100 × 10^9/L). No secondary MN occurred during follow-up. Most importantly, 24 patients returned to school or work. Although there is no randomized comparison, these outcomes contrast with the RACE study, where EPAG-IST had 52% 12-month CR, 90% 2-year OS, and only 46% 2-year EFS [15]. With IST, CSA must continue for 2 years to avoid relapse, whereas haploidentical BMT allows patients to stop tacrolimus by 6 months to 1 year.

The Johns Hopkins PTCY platform for SAA is also suitable for matched donor transplants. Three patients with MSD, six with MUD, and one with 7/8 mismatched unrelated donor (MMUD) BMT with the PTCY platform had 3-year OS 100% [30]. These results are on par with upfront MSD transplants.[19]

Of note, Xu et al [31] found no difference in the outcomes of upfront haploidentical HCT or MSD HCT. The 9-year OS was 87.1±2.5% for haploidentical donors and 89.3±3.7% for MSD (P = 0.173). The 9-year failure-free survival was 86.5±2.6% for haploidentical donors and 88.1±3.8% for MSD (P = 0.257) [31]. Thus, haploidentical HCT can be an option for upfront treatment of SAA/VSAA if an MSD is not available.

The EBMT conducted a meta-analysis of retrospective studies of upfront alternative donor HCT (haploidentical, MUD, MMUD) vs. IST in SAA [32]. The pooled 5-year odds ratio for OS was statistically significant at 0.44 (95% CI: 0.23 - 0.85) in favor of upfront alternative donor HCT. However, the EMBT meta-analysis included retrospective studies, mainly of pediatric patients undergoing alternative donor transplants with heterogeneous conditioning regimens without PTCY. The current review also highlights the promise of upfront alternative donor transplantation with PTCY in adults with SAA.

Haploidentical HCT in Relapsed SAA

After IST, the 15-year OS is 63%. However, for those under 20 years, the 15-year OS is 89%; for those 60 years or older, the OS falls to 32% [33]. With IST, there is only 23% 15-year EFS, with events such as transplant, relapse, MDS, AML, and death [33]. Even patients younger than 20 had only 27% 15-year EFS, whereas those 60 years or older had 15-year EFS of 12% [33]. Thus, failure-free survival after IST is poor in both younger and older patients with AA after IST.

Treatment after relapse has poor outcomes. The only FDA-approved therapy for relapsed SAA in the USA is EPAG monotherapy, with a 40% response but a 20% clonal evolution rate [17]. Just a third of patients will respond to second-line IST [2]. Transplantation is considered after failure of a cycle of IST.

Eight relapsed/refractory SAA patients, either lacking MSD or MUD or failing unrelated or cord blood transplant, received haploidentical PBSC transplant with the Baltimore regimen of fludarabine, cyclophosphamide and TBI 2 Gy [34]. GVHD prophylaxis comprised day +3 and day +4 PTCY, mycophenolate mofetil day +5 to day +35, and tacrolimus day +5 to maintain therapeutic levels 10 - 15 µg/L for 9 months and then tapered by 12 months if there was no GVHD. Six patients engrafted, but two had graft failure due to persistent donor-specific antibodies. Relapsed AA patients have more allosensitization after months of transfusions, raising the risks of donor-specific antibodies and graft rejection.

There was only one case of acute GVHD grade 2 of the skin. No chronic GVHD occurred. Whereas there was stable mixed T-cell chimerism with the FCC regimen, the Baltimore regimen achieved full donor T-cell and myeloid chimerism [21, 34]. Thus, granulocyte colony stimulating factor (G-CSF)-mobilized PBSC can optimize cell dose for haploidentical HCT in AA [34].

A phase II prospective study found relapsed/refractory SAA patients could be salvaged by haploidentical BMT using the Johns Hopkins PTCY protocol with ATG, fludarabine, cyclophosphamide, and TBI 2 Gy with 1-year OS 81% (Table 5) [30, 35]. The GVHD incidence was low. Four patients had primary graft failure, mainly because of infusion of less than the optimal cell dose of 4 × 10^8 nucleated marrow cells/kg recipient's ideal body weight.

In an EBMT report on haploidentical HCT for relapsed SAA with PTCY regimens, age, graft source (PBSC or BM), or adding *in-vivo* T-cell depletion with ATG did not affect survival or GVHD-free survival [36]. Even though TBI 2 Gy conditioning is feasible for relapsed AA after IST failure, treatment-naive SAA may need greater immunosuppression with TBI 4 Gy to ensure engraftment [24, 34]. Importantly, the EBMT meta-analysis showed a statistically significant 5-year odds ratio for OS of 0.31 (95% CI: 0.15 - 0.64) in favor of upfront rather than salvage alternative donor transplants in SAA [32].

Future Prospective HCT Studies in Newly Diagnosed SAA

The TransIT phase III study (Table 6) [37] in newly diag-

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Table 5. Haploidentical Hematopoietic Cell Transplantation in Severe Aplastic Anemia

	DeZern phase 2 single center	DeZern phase 2 multicenter
	Newly diagnosed SAA	Relapsed/refractory SAA (BMTCTN 15-02)
Number	27	31
Year	2016 - 2020	2017 - 2020
Median time from diagnosis to HCT	78 (12 - 249) days	10.8 (4.5 - 109.5) months
Donors/graft source	Haploidentical/bone marrow	Haploidentical/bone marrow
Median age, range	25 (3 - 63) years	24.9 (2.1 - 70.3) years
Conditioning	ATG, FLU, CY, TBI 2 - 4 Gy	ATG, FLU, CY, TBI 2 Gy
GVHD prophylaxis	PTCY, mycophenolate mofetil, tacrolimus	PTCY, mycophenolate mofetil, tacrolimus
Graft failure (GF)	3/7 with TBI 2 Gy; 0/20 with TBI 4 Gy	Primary GF n = 4; Secondary GF n = 1
Cumulative incidence of acute GVHD at day +100	Grade I - II 7%	Grade II 16%
cGVHD	At 3 years mild cGVHD 4%	1-year moderate cGVHD 26%
Overall survival (OS)	3-year OS 92% but with TBI 4 Gy: 3-year OS 100%	1-year OS 81% (95% CI: 62 - 91)
Causes of death	Graft failure with infections (viral)	Graft failure, fungal infection, interstitial pneumonia
Neutrophil engraftment	17 days (range 14 - 88)	17 days (range 1 - 69 days, IQR: 15 - 19)
Day +28 cumulative incidence neutrophil engraftment	96% (95% CI: 87 - 100)	94% (95% CI: 72 - 99)
Platelet engraftment	25.5 days	23 days (range 1 - 49, IQR: 17 - 33)
Day +100 cumulative incidence of platelet transfusion independence	88% (95% CI: 74 - 100)	77% (95% CI: 57 - 89)

HCT: hematopoietic cell transplantation; SAA: severe aplastic anemia; BMTCTN: Blood and Marrow Transplant Clinical Trials Network; TBI: total body irradiation; cGVHD: chronic graft-vs-host disease; IQR: interquartile range; ATG: anti-thymocyte globulin; FLU: fludarabine; CY: cyclophosphamide; PTCY: posttransplant cyclophosphamide; GVHD: graft-vs-host disease; CI: confidence interval.

nosed SAA patients younger than 25 without MSD will help answer whether upfront allogeneic BMT using ≥ 9/10 unrelated donors with FCATG and TBI 2 Gy conditioning has better failure-free survival than IST with hATG and CSA [37]. In adults over 25 years with newly diagnosed SAA lacking MSD, the CUREAA phase II study will analyze GVHD-failure-free survival of upfront haploidentical or > 7/10 unrelated donor BMT with the Johns Hopkins PTCY platform ATG, fludarabine, cyclophosphamide, TBI 4 Gy (Table 6) [37]. Both studies could be practice-changing, expanding the role of alternative donor transplants as initial therapy for newly diagnosed SAA.

Conclusions

Adding EPAG to hATG and CSA improves the 12-month CR rate to 52% vs. 33% with hATG and CSA but leaves the risk of relapse at 40% and MN at 15% unchanged [5, 13, 15, 16]. The response to IST is slow (3 months) and lacks durability. The primary cause

Table 6. Future Prospective Studies of Upfront Hematopoietic Cell Transplantation in Newly Diagnosed Severe Aplastic Anemia Patients Without a Matched Sibling Donor

Study	Goal	Age years	Donor	Graft source	Conditioning	GVHD prophylaxis	Primary endpoint
TransIT BMTCTN 22-02 phase III	235 patients	≤ 25	IST hATG + CSA vs. 10/10 or 9/10 unrelated donor	BM	FLU, CY, ATG, and TBI 2 Gy	CSA and MTX	Time to treatment failure
CUREAA BMTCTN 22-07 phase II	60 patients	> 25	Haploidentical or 10/10, 9/10, or 8/10 unrelated donor	BM	FLU, CY, ATG, and TBI 4 Gy	PTCY, tacrolimus and mycophenolate mofetil	GVHD-failure-free survival at 1 year

BMTCTN: Blood and Marrow Transplant Clinical Trials Network; hATG: horse anti-thymocyte globulin; CSA: cyclosporine; BM: bone marrow; FLU: fludarabine; CY: cyclophosphamide; TBI: total body irradiation; MTX: methotrexate; PTCY: posttransplant cyclophosphamide; GVHD: graft-vs-host disease.

of death is infection from prolonged neutropenia [16]. There is a relentless pattern of relapse and clonal disease such that the 15-year EFS is only 27% in patients younger than 20, whereas those 60 years or older had a 15-year EFS of 12%, indicating IST is not curative [33]. Older age increases the risk of relapse and MN after IST [14, 17]. The median time to MN onset was only 4.5 years [13]. Yet, current guidelines stipulate older patients proceed with IST rather than a curative allogeneic HCT [2]. After upfront allogeneic HCT for SAA, no patient developed MN at a median of 8.2 years' follow-up [13]. Longer follow-up is needed to determine the late effects of allogeneic HCT with TBI 2 - 4 Gy conditioning in SAA. For example, three decades of follow-up in sickle cell disease revealed TBI 2 - 4 Gy-based conditioning for allogeneic HCT had a 1.7% 10-year incidence of leukemia and MDS, and a 0.7% 10-year incidence of solid tumors [38].

At present, upfront HCT is restricted to the rare AA patient who is not only young but also has an identical twin or MSD. An EBMT/CIBMTR study of AA patients 50 years or older undergoing MSD or MUD HCT revealed age had no impact on survival [20]. Performance status and HCT-CI should guide eligibility for transplant rather than only age. The donor pool has recently expanded with successful haploidentical HCT from first- and second-degree relatives using the PTCY platform [24]. Upfront haploidentical BMT in SAA resulted in 3-year OS 100% with low rates of mild GVHD [24]. Faster neutrophil recovery in 3 weeks (vs. 3 months with IST) lowers the risk of infections [15, 24]. Xu et al found no difference in the outcomes of upfront haploidentical or MSD HCT [31]. A haploidentical donor is available for almost everyone. Unrelated donor searches take up to 4 months, whereas haploidentical donors are available in a month.

Thus, haploidentical HCT can be an option for first-line curative therapy if an MSD is unavailable for fit newly diagnosed SAA patients who meet eligibility criteria. IST is an option for newly diagnosed SAA patients who are not eligible for transplant. Results of the prospective randomized study of IST and alternative donor transplants for newly diagnosed SAA patients lacking MSD are eagerly awaited [37].

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Conflict of Interest

None to declare.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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