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Guideline

Allogeneic Hematopoietic Cell Transplantation for the Treatment of Severe Aplastic Anemia: Evidence-Based Guidelines From the American Society for Transplantation and Cellular Therapy

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A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for severe aplastic anemia (SAA). Existing guidance about HCT in SAA is primarily derived from expert reviews, registry data and societal guidelines; however, transplant-specific guidelines for SAA are lacking. A panel of SAA experts, both pediatric and adult transplant physicians, developed consensus recommendations using Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology employing a GRADE guideline development tool. The panel agrees with previous recommendations for the preferential use of bone marrow as a graft source and the use of rabbit over horse antithymocyte globulin (ATG) for HCT conditioning. Fludarabine containing regimens are preferred for patients at high risk of graft failure and those receiving matched unrelated

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or haploidentical donor transplant. Given advancements in HCT, the panel does not endorse the historical 40-year age cut-off for considering upfront HCT in adults, acknowledging that fit older patients may also benefit from HCT. The panel also endorses increased utilization of HCT by prioritizing matched unrelated or haploidentical donor HCT over immunosuppressive therapy in children and adults who lack a matched related donor. Finally, the panel suggests either calcineurin inhibitor plus methotrexate or post-transplant cyclophosphamide-based graft-versus-host disease (GVHD) prophylaxis for matched related or matched unrelated donor recipients. These recommendations reflect a significant advancement in transplant strategies for SAA and highlight the importance of ongoing and further research to revisit current evidence in terms of donor choice, conditioning chemotherapy, GVHD prophylaxis and post-transplant immunosuppression.

INTRODUCTION

Severe aplastic anemia (SAA) is the most common classical hematological disorder in adults for which allogeneic hematopoietic cell transplantation (HCT) is utilized. Characterized by pancytopenia in conjunction with findings of hypocellularity, absence of an abnormal cellular infiltrate and fibrosis within the bone marrow [1]; patients can experience infections, bleeding, organ failure and clonal evolution. Historically, the choice of initial treatment was based on the patient's age, absolute neutrophil count (ANC), co-morbidities and the availability of the most suitable donor type [2]. However, substantial improvements in conditioning regimens, graft-versus-host disease (GVHD) prophylaxis and supportive care have allowed wider acceptance of HCT at all stages of disease. The purpose of this guideline is to assess the evidence for HCT in treating patients with SAA, to offer treatment suggestions based on available evidence along with good practice statements, and to stimulate areas of future research.

GUIDELINE DEVELOPMENT PROCESS

The American Society for Transplantation and Cellular Therapy (ASTCT) Committee on Practice Guidelines directed the overall guideline development process, including protocol review, panel formation, evidence synthesis and manuscript review. The panel included hematologists and transplant physicians (adult and pediatric) who had clinical and research expertise in the management of SAA. The panel utilized the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach using a GRADE guideline development tool (GRADEpro-GDT) to answer research questions [3]. None of the panel members received funding for this guideline development. Conflicts of interest for all members were declared, as per recommendations of Guideline International Network [4].

The steps in the guideline development [5] and evidence-to-decision (EtD) frameworks were followed as per GRADE methodology [6]. Where applicable, mini systematic reviews and meta-analyses were conducted, including studies published through December 2023 to address guideline questions. Meta-analyses were performed using review manager (RevMan) version 5, and risk of bias (RoB) was evaluated using the RoB tool for randomized trials and the ROBINS tool for non-randomized studies [7]. For questions with insufficient data or where systematic review was not feasible, a good practice statement was created. All questions were sent to panel members using the panel voice feature of GRADEpro-GDT to develop recommendations based on evidence synthesized. More than 80% consensus was required before accepting a recommendation.

Interpretation of the Strong and Conditional Recommendations

The Recommendations are labelled as "strong" or "conditional/weak" according to the GRADE approach. For a strong recommendation, the words used are "the guideline panel recommends" while for conditional/weak recommendations the words used are "the guideline panel suggests." Supplemental Table 1 provides explains the quality of evidence and strength of recommendations used in these guidelines [7,8].

Recommendations

Table 1 summarizes the recommendations and the evidence grading.

Table 1
Summary of Recommendations and Evidence Grading

Guideline Question and Recommendation	Quality of Evidence	Strength of Recommendation	Level of Agreement
Disease and patient assessment prior to HCT			
Question 1: How should patients with suspicion of SAA be assessed prior to HCT? The panel recommends that all AA patients should undergo testing to confirm the diagnosis and look for underlying causes of BMF. All newly diagnosed AA should be assessed for indications for HCT and initiation of donor search	Good practice statement	Good practice statement	100%
Question 2: Should an age cutoff of 40 yr be used for adult patients receiving HCT for SAA? Due to improvement in supportive care and conditioning regimen, our panel suggests that upfront HCT may be considered up to 50 yr of age or beyond for patients with severe cytopenias in centers with expertise in HCT	⊕⊕⊕◯ Moderate	Conditional	100%
Decision for HCT			
Question 3: Should MRD or IST be used for newly diagnosed children and young adults patients with SAA ? We recommend upfront MRD-HCT for pediatric and AYA patients presenting with severe aplastic anemia as it offers high cure rates with minimal risk of GVHD, rejection or disease transformation	⊕⊕⊕◯ Moderate	Strong	100%
Question 4: Should MRD-HCT be prioritized over IST for newly diagnosed adults with SAA ? Our panel recommends MRD-HCT as a preferred first-line treatment for patients up to 50 yr of age or beyond	⊕⊕⊕◯ Moderate	Strong	100%
Donor selection			
Question 5: Should HCT be prioritized over IST for children and young adults who lack a MRD? The panel suggests upfront HCT (either MUD or Haplo-HCT) for pediatric patients lacking a MRD. For patients failing the first course of IST, the panel recommends HCT (either MUD or Haplo-HCT) over the second course of IST	⊕◯◯◯ Very Low	Conditional	85.7%
Question 6: Should HCT remain a priority for adults with SAA who lack a a MRD? The panel suggests the use of either MUD or haplo-HCT in preference to IST for patients with SAA lacking a MRD	⊕⊕◯◯ Low	Conditional	88%
Question 7: Should MUD-HCT be prioritized over Haplo-HCT for patients lacking a MRD? The panel suggests either MUD or haplo-HCT for patients lacking a MRD	⊕⊕◯◯ Low	Conditional	86%
HCT procedures			
Question 8: Should rabbit ATG or horse ATG be used in conditioning regimens for SAA patients? The panel recommends rabbit ATG over horse ATG as part of the conditioning regimen	⊕⊕◯◯ Low	Strong	93%
Question 9: Should Fludarabine containing HCT conditioning be prioritized over other regimens for Aplastic Anemia ? The panel recommends Cyclophosphamide-ATG conditioning for pediatric and AYA patients receiving MRD-HCT. Fludarabine containing conditioning is recommended for adults or those with a high risk of graft failure. All patients receiving MUD-HCT, CBT or haplo-HCT should receive fludarabine containing conditioning	⊕⊕◯◯ Low	Strong	93%

(*continued*)

Table 1 (*Continued*)

Guideline Question and Recommendation	Quality of Evidence	Strength of Recommendation	Level of Agreement
Question 10: Should bone marrow be prioritized over peripheral blood as stem cell source in patients with SAA ? For SAA patients undergoing MRD, MUD or Haplo-HCT, our panel recommends using bone marrow as the preferred stem cell source.	⊕⊕⊕◯ Moderate	Strong	93%
Question 11: What Should be the preferred regimen for GVHD prophylaxis? i. The panel suggests either Calcineurin inhibitor (CNI)+ Methotrexate or Post Transplant Cyclophosphamide (PTCy) as GVHD prophylaxis for patients undergoing MRD or MUD HCT ii. For patients undergoing Haplo-HCT, our panel recommends PTCy based prophylaxis	⊕⊕◯◯ low ⊕⊕⊕◯ Moderate	Conditional Strong	86%
Question 12: How should graft failure and poor graft function be managed post HCT in SAA patients? Chimerism assessment should be done by testing split chimerism (CD3 for T cells and most commonly CD33 for myeloid). Stable Mixed T-cell chimerism can be seen post-transplant in patients receiving ATG containing conditioning regimens and do not require intervention if accompanied with normal blood counts. For patients with poor graft function not responding to immunosuppression escalation, a stem cell boost may be beneficial. Patients with graft failure usually require conditioning to eradicate residual recipient T-cells and generally do not respond to boost alone.	Good practice statement	Good practice statement	93%

HCT, Allogeneic hematopoietic cell transplant; SAA, severe aplastic anemia; GVHD, graft versus host disease; BMF, bone marrow failure; MRD, matched related donor; MUD, matched unrelated donor; Haplo-HCT, haploidentical cell transplant; IST, immunosuppressive therapy; PTCy, post transplant cyclophosphamide; CNI, calcineurin inhibitors.

DISEASE AND PATIENT ASSESSMENT PRIOR TO HCT

Question 1: How Should Patients With Suspicion of SAA Be Assessed Prior to HCT?

Recommendation

The panel recommends that all patients undergo evaluation to confirm the SAA diagnosis and exclude an underlying inherited bone marrow failure (BMF) syndrome. All newly diagnosed patients should be assessed for HCT and early donor search initiated *(Good practice statement).*

Implementation Considerations

As the diagnosis of SAA is based on exclusion, a thorough history, focused clinical examination and necessary investigations are required for all patients to evaluate the possibility of inherited BMF or other alternate secondary etiologies [9–11]. Assessment of bone marrow cellularity, cytogenetics, peripheral blood flow cytometry for CD55, CD59, fluorescent aerolysin (FLAER) for paroxysmal nocturnal hemoglobinuria (PNH) and exclusion of hypoplastic myelodysplastic syndrome (MDS) is essential. Patients less than 50 yr proceeding to HCT as initial therapy should also have peripheral blood lymphocyte telomere length and chromosome breakage analysis to rule out short telomere syndromes and Fanconi Anemia, respectively. If available, more detailed genetic testing for inherited BMF and myeloid neoplasm should be performed in those with higher suspicion or positive family history.

In any patient for whom HCT is a consideration, it is crucial to initiate human leukocyte antigen (HLA) typing early to identify a family or volunteer donor [12]. If haploidentical HCT (Haplo-HCT) is being considered, testing to detect presence of donor specific antibodies (DSAs) should be performed, as their presence is strongly associated with graft failure and requires desensitization or a search for an alternative donor [13]. Time from diagnosis to transplant is a crucial determinant of transplant outcomes. More waiting times (> 3 mo) and heavy transfusion burden pr-HCT are associated with inferior outcomes [14–16]. Every effort should be made to expedite donor availability and transplant workup with aim to minimize time to transplant.

Question 2: Should An Age Cutoff of 40 yr Be Used for Adult Patients Receiving HCT for SAA?

Recommendation

The guideline panel recommends against using age 40 yr as the cutoff. Due to improvement in supportive care and tolerability of current conditioning regimens, our panel suggests that upfront HCT may be considered selectively in biologically fit patients up to 50 yr or even beyond. This is an especially important consideration in older adults with a low likelihood of response to immunosuppressive therapy (absence of PNH clone, very severe aplastic anemia, presence of myeloid mutations). (Strength of recommendation, Conditional; Certainty of evidence, Moderate ⊕⊕⊕◯).

Summary of Evidence

Age has been a key determinant of eligibility for HCT in SAA patients, with priority given to younger patients because in that context HCT has been associated with less mortality and better survival compared to IST. Traditionally, upfront HCT was recommended for age ≤40 yr with a MRD, while IST was reserved for age >40 yr without a MRD [17–19]. In a CIBMTR analysis of 1364 patients who underwent marrow transplantation between 2000-2014, age > 30 yr versus ≤ 30 yr was associated with higher mortality risk after HLA matched sibling (HR=2.7) or HLA matched unrelated donor (MUD) (HR = 1.98) [20]. Another study by Giammarco et al. [21] documented similar HCT outcomes for patients younger and older than 40 yr over last 2 decades.

With improvements in supportive care and conditioning regimens, patients > 40 yr may be considered for upfront MRD HCT. Recently, comparable overall survival (OS) was documented for patients ≤50 and >50 yr of age using a MUD or MRD. Studies by Sheth et al. [22] and Shin et al. [23] documented comparable OS for patients up to 50 yr of age using a MUD or MSD. Rice et al [24] documented similar OS in patients younger and more than 50 yr of age undergoing MRD HCT [22,25, 26].

GVHD remains an important consideration when selecting HCT for older adults with SAA. Meta-analysis done as part of this guideline showed similar rates of acute GVHD (aGVHD), p = .18 (supplemental figure 1A) [22,27–30] and significantly higher (p < .004) chronic GVHD (cGVHD) (Supplemental Figure 1B) in older as compared to younger adults [23,22,27,31]. However, GVHD free survival (GRFS) has significantly improved by incorporating PTCy based GVHD prophylaxis [32]. Certainty of the evidence according to GRADE pro-GDT is tabulated in supplementary files Table 2.

Implementation Considerations

Upfront HCT should be considered for patients age >40 yr who have a life-expectancy that fits with the HCT goal of providing long-term benefits of disease control plus mitigation of clonal evolution, while outweighing HCT risks by selecting patients with adequate performance status and suitable organ function.

DECISION FOR HCT

Question 3: Should MRD or IST Be Used for Newly Diagnosed Children and Young Adult Patients With SAA?

Recommendation

We recommend upfront MRD-HCT for children and young adults with SAA as it offers high cure rates with a lower risk of disease transformation (Strength of recommendation, Strong; Certainty of evidence; moderate ⊕⊕⊕◯).

Summary of Evidence

HCT is potentially curative demonstrating >90% OS and failure free survival (FFS) [33–35] in children with minimal long-term effects on growth, development, and fertility, and risk of

Table 2
GRADE summary of finding table comparing outcomes between pediatric patients receiving IST or ADT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with IST	Risk with Alternate donor			
OS ADT vs IST in Pediatrics	Study population		RR 0.56 (0.34 to 0.90)	371 (6 non-randomized studies) (53,58,91-94)	⊕⊕◯◯ Low
	192 per 1,000	108 per 1,000 (65 to 173)			
FFS ADT vs IST	Study population		RR 0.25 (0.14 to 0.43)	230 (4 non-randomized studies) (19,58,92,95)	⊕⊕⊕◯ Moderate
	492 per 1,000	123 per 1,000 (69 to 212)			

progression to MDS or AML is reduced significantly [36,37]. The European Group for Blood and Marrow Transplantation (EBMT) reported lower 3-year event-free survival (EFS) when IST was compared to MRD-HCT in younger children (33% IST vs. 87% HCT) as well as adolescents (64% IST vs. 83% HCT) [16]. Another study examined outcomes for 1488 patients and reported that age <20 yr was among the best predictors of survival [38].

The guideline panel conducted a 1374 patient meta-analysis comparing MRD-HCT to IST and showed significantly better FFS with HCT in comparison to IST; RR 0.30 (95% CI 0.18 to 0.50), I^2 83%. OS was assessed for 1973 patients and was similar in both arms; RR 0.91 (95% CI 0.62 to 1.34). (supplemental figures 2A and 2B). In contrast to adults where addition of eltrombopag to IST improved ORR [39], similar improvements were not reported (p = .836) in children [40].

Implementation Considerations

MRD-HCT is the recommended first-line therapy for children and young adults as it offers high OS and FFS with minimal risk of GVHD [34,35]. Despite improvement in IST with the incorporation of eltrombopag, complete responses remain low, relapses are common and risk of progression to MDS and AML persists, especially in children with potentially more decades of life ahead.

Question 4: Should MRD-HCT Be Prioritized Over IST for Newly Diagnosed Adults With SAA?

Recommendation

We recommend HCT as a preferred first-line treatment for patients with a MRD (Strength of recommendation, Strong; Certainty of evidence, Moderate ⊕⊕⊕◯).

Summary of Evidence

A Meta-analysis of 15 studies by Zhu et al. [41] showed a superior OS and FFS for patients receiving first line HCT. Superiority of HCT is retained in the era of triple IST, as shown by a recently published prospective study comparing triple IST with MRD-HCT [42]. A systematic review and meta-analysis comparing MRD-HCT with IST subsequent to 2000 showed superior OS [42–47] and FFS [42,46] with HCT (Supplemental Figure 3A and 3B). Conversely, patients receiving IST are at increased risk of relapse and clonal evolution usually within 2 to 4 yr of IST [48]. Certainty in the evidence was judged moderate because randomized controlled trials were lacking and data from studies examining OS and FFS were heterozygous.

Implementation Considerations

MRD HCT is a preferred treatment for adults with SAA (Figure 2) and is available at most centers specializing in the treatment of SAA. Centers not offering HCT should refer their patients to centers with expertise [49].

DONOR SELECTION

Question 5: Should HCT be prioritized over IST for children and young adults who lack a MRD?

Recommendation

The panel suggests upfront HCT (either MUD or Haplo-HCT) for children and young adults lacking a MRD (Strength of recommendation, Weak; Certainty of evidence very Low ⊕◯◯◯).

For patients failing the first course of IST, the panel recommends HCT (either MUD or Haplo-HCT) over the second course of IST (Strength of recommendation, Strong; Certainty of evidence; low ⊕⊕◯◯).

Summary of Evidence

Around 70-80% of children and young adults with SAA will lack a MRD and will require IST or alternate donor transplant (ADT); either MUD or haplo-HCT [50,51]. For children and young adults lacking a MRD, IST is historically used upfront due to low toxicity and overall response rates of 60-70% [40,49], However complete response (CR) rates are low, life-threatening infections remain a risk and outcomes are also limited by relapse rates of 30% as well as 10% to 15% risk of clonal evolution to myeloid malignancy.

Survival after upfront MUD-HCT in children and young adults has improved and is now similar to MRD-HCT and superior to IST and MUD-HCT following-IST failure [52], prompting UK guidelines to recommend upfront MUD HCT for SAA [53].

A retrospective EBMT study reported similar 2-year OS and EFS after upfront MUD compared to matched historical controls who had undergone upfront MRD [52]. The prospective US BMT CTN 2202 (TransIT) study seeks to compare MUD HCT versus IST for newly diagnosed pediatric and young adult patients with SAA; feasibility of randomization to upfront MUD BMT has so far been demonstrated without major delay in identifying a suitable MUD [54]. Similarly, outcomes of Haplo-HCT have improved significantly over past decade resulting in high OS and EFS when used upfront [51,55]. DeZern et al. showed efficacy and

feasibility of haplo-HCT in upfront and relapsed refractory setting with high OS, disease free survival (DFS) and acute and chronic GVHD rates both <10% [51,55]. Studies comparing haplo-HCT with IST have all reported OS and FFS that favors haplo-HCT, resulting in increasing use of upfront haplo-HCT [51,55–57]. Alternative donor transplant (ADT), either MUD or haplo-HCT, is an option for patients with recurrent or life-threatening infections, significant bleeding, transfusion dependence and the presence of cytogenetic abnormalities associated with MDS (monosomy 7, others). For patients initially treated with IST and who failed to respond, or relapsed, HCT is superior to additional courses of IST.

As per GRADE evidence synthesis, overall certainty of evidence was low for OS and moderate (large effect observed) for FFS. Both OS (RR 0.56, 95% CI 0.34 to 0.90) and FFS (RR 0.25, 95% CI 0.14 to 0.43) were better in the ADT group (Table 2)

Implementation Considerations

Despite the absence of randomized data, retrospective and prospective data have shown superior survival, fewer relapses and lower risk of clonal evolution in children and young adults receiving ADT. If a donor can be identified early and patients are treated in centers with expertise in ADT, it is suggested to proceed with upfront MUD or Haplo-HCT. For children and young adults with only a highly mismatched unrelated donor or CBT available, upfront IST is preferred. The panel acknowledges that long term data on fertility using fludarabine, 4 Gy TBI for children and young adults is lacking.

Question 6: Should HCT Remain a Priority for Adults With SAA Who Lack a MRD?

Recommendation

The panel suggests either MUD or haplo-HCT for patients without a MRD (Strength of recommendation, Conditional; Certainty of evidence, low ⊕⊕◯◯)

Summary of Evidence

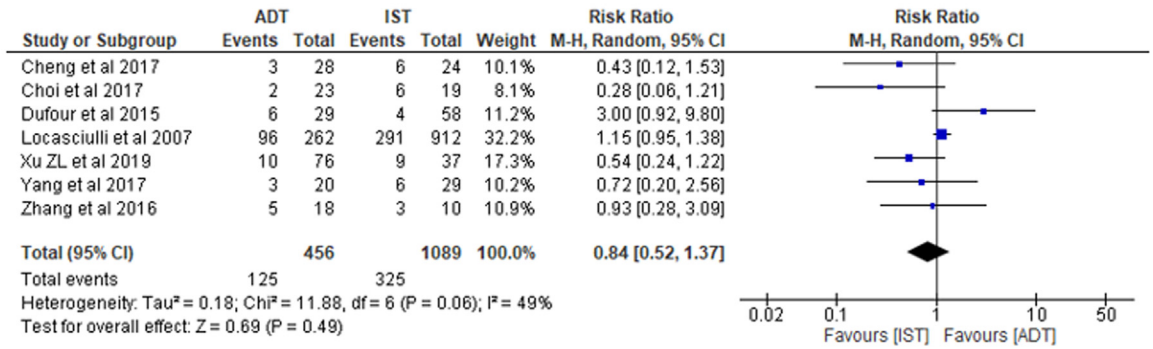
The probability of finding a MRD in US is 30% for older adults but 1.5 times lower for patients aged 18 to 44 yr [58]. Recent prospective and retrospective data have shown improved outcomes using MUD or Haplo-HCT [51,55,59]. A meta-analysis of 5 studies (343 patients) showed a 5-year pooled OS in favor of upfront ADT compared with IST (OR,0.44); upfront ADT was also superior to salvage ADT (OR,0.31) [59]. An EBMT study reported MUD to be non-inferior to MRD HCT [38]. Haploidentical donors are used increasingly in SAA and have moved into the upfront settings in multi-center studies and at some centers [51,55]. The BMT CTN trial of Haplo-HCT for children and adults with relapsed or refractory SAA showed a 1-year OS of 81% (95% CI 62 to 91) [55]. Meta-analysis by Zhao et al [60] including 25 studies and 2252 patients demonstrated no difference in OS, FFS or engraftment outcomes between haploidentical and MRD-HCT. Comparison of haplo-HCT with IST showed a higher 3-year FFS with haplo-HCT while OS was same [60].

Long-term durability with IST remains relatively low [48,61,39] and FFS remains <40% in most series [61–66]. A recent meta-analysis found a pooled 5-year OS in favor of up-front ADT over IST [67]. However, GVHD, graft rejection, treatment-related mortality (TRM), and infertility remain areas for study. Further development of alternative donor options is under evaluation. GVHD and graft failure remain concerns with ADT, particularly with haplo-HCT. A recent prospective study of upfront haplo-HCT from Johns Hopkins University showed 92% OS and a low risk of severe acute and chronic GVHD [51]. OS increased to 100% when 400 cGy TBI was used. A meta-analysis of 7 studies by the guideline panel compared survival outcomes with ADT (MUD or Haplo) versus IST. There was no difference in OS; RR 1.05 (95% CI 0.96 to 1.15), I^2 37% and p = .19 (Figure 1A) but FFS was significantly better in the ADT arm; RR 2.02 (95% CI 1.60 to 2.55, I^2 0%, p < .00001 (Figure 1B). The certainty in the evidence was judged to be low because the studies were non-randomized and there was data heterogeneity in studies looking at OS. For FFS, the evidence was rated moderate because of imprecision.

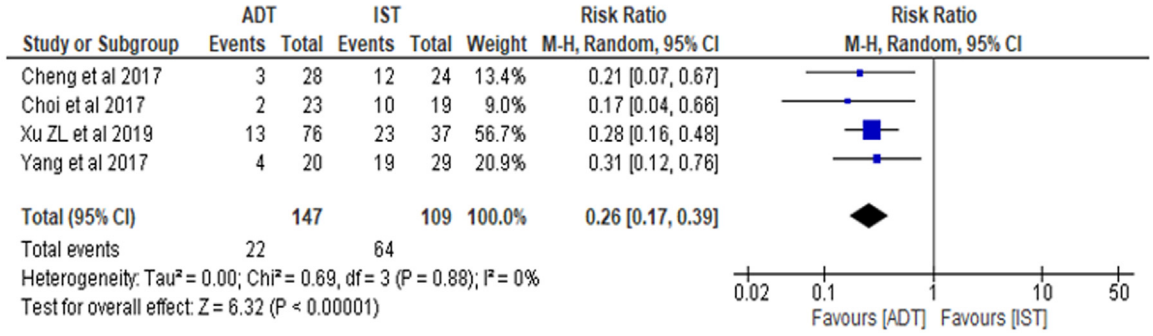
The number of cord blood transplants (CBT) for SAA has declined in the last decade due to rising use of haplo-HCT and the availability of more effective IST. In 2024, use of CBT outside of a research study for SAA is discouraged due to high rates of graft rejection; only 50% achieving neutrophil engraftment in a retrospective analysis from EBMT and Eurocord [68]. However, a recent prospective phase II study using the APCORD protocol (Flu-Cy-ATG-2GyTBI) reported impressive 1 year OS of 88.5% in refractory SAA patients [5,69].

Implementation Considerations

Our panel recommends the use of ADT (MUD or Haplo) over IST in SAA because of the long-term risk for disease relapse and secondary MDS/AML after IST. Implementation of ADT as a first-line



1a: Overall Survival for adult patients undergoing ADT vs IST



b: Failure free Survival for adult patients undergoing ADT vs IST

Figure 1. (A) Overall Survival for adult patients undergoing ADT vs IST. (B) Failure free Survival for adult patients undergoing ADT vs IST.

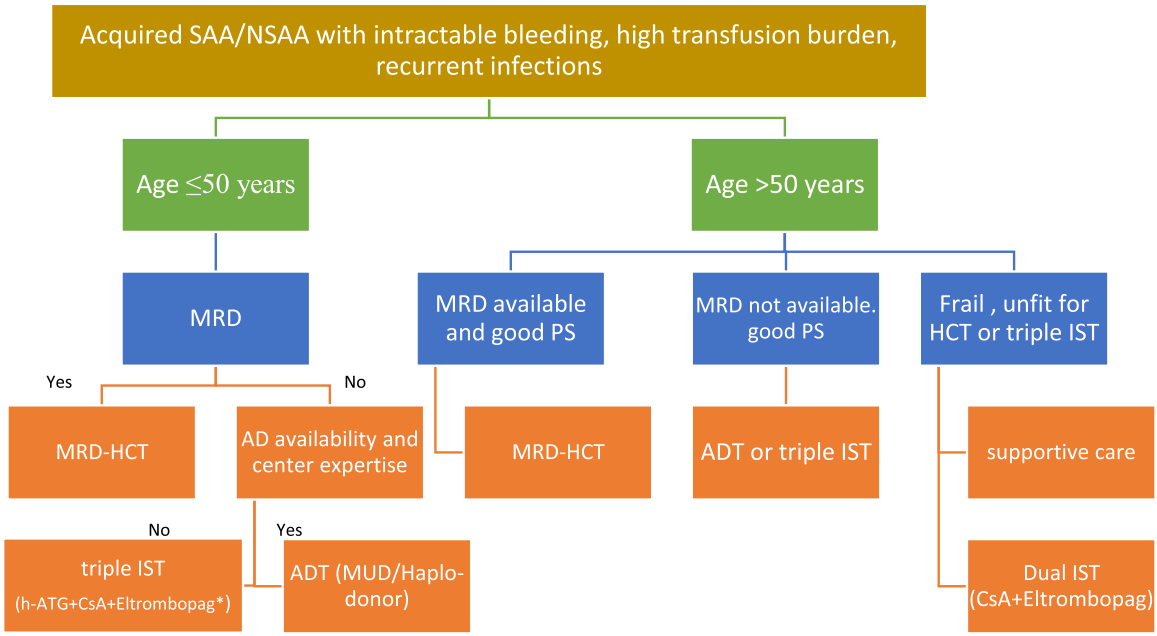


Figure 2. Treatment Algorithm of SAA patients. SAA severe aplastic anemia, NSAA non-severe aplastic anemia, MRD (matched related donor), MUD (matched unrelated donor) IST (immunosuppressive treatment), Haplo (Haploidentical), PS performance status, HCT hematopoietic cell transplant, AD alternate donors, CSA ciclosporine, h-ATG horse anti-thymocyte globulin. *Currently there is lack of clear evidence indicating benefit to give eltrombopag in children less than 18 yr of age.

treatment strategy provides the best chance of long-term disease-free survival.

Question 7: Should MUD-HCT Be Prioritized Over Haplo-HCT for Patients Lacking a MRD?

Recommendation

The panel suggests either a MUD or haplo-HCT for patients lacking a MRD (Strength of recommendation, conditional; Certainty of evidence, low ⊕⊕◯◯) with insufficient evidence for prioritization.

Summary of Evidence

Outcomes of MUD and Haplo-HCT have improved over last decade and are comparable to MRD while superior to IST [70,71]. A recent meta-analysis reported similar OS, FFS and engraftment between haplo-HCT and MRD [60].

Implementation Considerations

For patients lacking a MRD, either MUD or haplo-HCT may be used, but there is insufficient evidence to prioritize one approach over the other. Practical considerations include the presence of donor specific antibodies (DSA) to the related donor or timing of available donors.

HCT PROCEDURES

Question 8: Should Rabbit ATG or Horse ATG Be Used in Conditioning Regimens for SAA Patients?

Recommendation

The guideline panel recommends rabbit ATG over horse ATG as part of the HCT conditioning regimen for SAA patients receiving HCT (Strength of recommendation, Strong; Certainty of evidence, low; ⊕⊕◯◯).

Summary of evidence

For the initial IST treatment of SAA, horse ATG (h-ATG) is superior to rabbit ATG (r-ATG) [61]. However, for HCT conditioning, r-ATG is preferred based on the results of an 833-patient CIBMTR study where acute and chronic GVHD rates were lower ($p < .001$) after MRD-HCT for patients who received r-ATG versus h-ATG [72]. Following MUD-HCT there was no difference in cGVHD between the two groups, however, aGVHD was higher ($p < .001$) in the h-ATG group while OS was lower ($p = .02$) [72]. Rabbit ATG is associated with more effective lymphocyte depletion [73] and enhances the number and function of regulatory T cells likely facilitating tolerance induction and reduction in GVHD [74]. An EBMT study [38] reported improvement in survival and reduction in GVHD with use of ATG regardless of the source of stem cells. The survival benefit of ATG extended to URD as well; 5 year survival of unrelated donor grafts with ATG was 70% vs 52% without ATG [38].

Implementation Considerations

Allo-HCT conditioning for SAA should include ATG regardless of donor type, stem cell source, patient age and gender. When used for HCT preparative regimens, the rabbit ATG formulation is preferred over the horse formulation. Some centers have successfully replaced ATG with alemtuzumab in both MRD and MUD-HCT [75–77].

Question 9: Should Fludarabine Containing HCT Conditioning be Prioritized Over Other Regimens for Aplastic Anemia?

Recommendation

The panel recommends cyclophosphamide-ATG conditioning for children and young adults receiving MRD-HCT. Fludarabine containing conditioning is recommended for adults or those with a high-risk of graft failure (Strength of recommendation, Strong; Certainty of evidence, low ⊕⊕◯◯).

All patients receiving MUD-HCT, CBT or haplo-HCT should receive fludarabine-containing conditioning (Strength of recommendation, Strong; Certainty of evidence: low ⊕⊕◯◯)

Summary of Evidence

There are no randomized controlled trials available comparing conditioning regimens in aplastic anemia. CIBMTR analysis by Bejanyan et al reported similar survival with Cy-ATG and Flu-Cy-ATG [20]. In patients receiving MUD-HCT in the same study, the optimal regimens for HCT were Flu-Cy-ATG and Flu-Cy-ATG+TBI.

Retrospective single-center and multicenter studies have shown the superiority of fludarabine (FLU)-containing conditioning in patients undergoing MRD HCT with 1 or more high-risk factors [20,78,79]. A pooled analysis of 3 studies [20,78,80] including 1189 patients reported the superiority of fludarabine-containing regimens (OR 0.62; 95% CI 0.41 to 0.92). Overall certainty of evidence was rated as low due to the absence of randomized trials and no large effect. British guidelines [2] recommend fludarabine-containing conditioning for patients >30 yr of age undergoing MRD HCT and for all patients undergoing MUD HCT. Table 4 enlists the preferred conditioning regimens for SAA.

Implementation Considerations

Choice of conditioning regimen depends on factors such as recipient and donor age, donor

type, risk factors of graft rejection, comorbidities, center expertise and resource availability [27,38]. Fludarabine-containing conditioning is suggested for adults >30 yr undergoing MRD-HCT and for any patient receiving MUD or haplo-HCT irrespective of age.

Question 10: Should Bone Marrow Be Prioritized Over Peripheral Blood as Stem Cell Source in Patients With SAA?

Recommendation

For SAA patients undergoing MRD, MUD or Haplo-HCT, our panel recommend using bone marrow as the preferred stem cell source. (Strength of recommendation, Strong; Certainty of evidence, moderate ⊕⊕⊕◯)

Summary of evidence

Recently published meta-analysis [81] and studies published over last 2 decades have reported lower cumulative incidence of GVHD and better survival outcomes using bone marrow (BM) stem cells. If we consider effects on quality of life (QoL), the peripheral blood (PB) graft source can have large undesirable effects on target population.

For selected patients with serious ongoing infections before HCT, those where the donor only consents for PB collection, or when there are clinical concerns about large donor-recipient weight disparity and the ability to harvest adequate TNC/kg, clinicians may use PB as graft source while accepting a higher risk of GVHD. Use of post-transplant cyclophosphamide may be considered in this situation to lower rates of cGVHD. Using the GRADE evidence table, there is low-moderate quality evidence for undesirable effects with the PB graft source. OS was better for BM compared with PB (p = .0004), similarly aGVHD (p = .0004) and chronic GVHD (p = .0010) were higher among PB recipients (Table 3)

Implementation Considerations

BM is the preferred stem cell source for HCT in SAA irrespective of donor type and results in superior OS, FFS and lower cumulative incidence of GVHD. PB stem cells may be used in selected scenarios and will require enhanced GVHD prophylaxis (i.e., PTCy).

Question 11: What Should be the Preferred Regimen for GVHD Prophylaxis?

Recommendation

The panel suggests either calcineurin inhibitor (CNI) plus methotrexate (MTX) or PTCy based prophylaxis for patients undergoing MRD or MUD HCT (Strength of recommendation, weak; Certainty of evidence: low ⊕⊕◯◯).

For patients undergoing Haploidentical HCT, our panel recommends PTCy-based prophylaxis (Strength of recommendation; Strong, Certainty of evidence: Moderate ⊕⊕ ⊕◯).

Best Practice Statement

- *MRD and MUD:* For CY-ATG/Flu-Cy-ATG conditioning, CNI+MTX has been the standard GVHD prophylaxis. Cyclosporine (CSA) trough levels are recommended to be maintained 200 to 300 ng/mL and tacrolimus (Tac) levels 8 to 12 ng/mL. CSA/Tac should be continued for 6 to 9 mo followed by a linear taper over 3 to 6 mo.

Table 3
GRADE Summary of Finding Table Comparing Effect of Stem Cell Source on GVHD and HCT Outcomes

Outcomes	No. of Participants (Studies) Follow-Up	Certainty of The Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects* (95% CI)	
				Risk With Bone Marrow	Risk Difference With Peripheral Blood
aGVHD	3230 (5 non-randomized studies) [82–86]	⊕⊕◯◯ Low	OR 1.53 (1.25 to 1.86)	Study population	
				158 per 1,000	65 more per 1,000 (32 more to 101 more)
cGVHD	3283 (5 non-randomized studies) [82–86]	⊕⊕⊕◯ Moderate	RR 2.06 (1.74 to 2.43)	Study population	
				112 per 1,000	119 more per 1,000 (83 more to 160 more)
Overall Survival	2874 (3 non-randomized studies) [83,84,87]	⊕⊕◯◯ Low	RR 0.82 (0.78 to 0.86)	Study population	
				833 per 1000	150 fewer per 1,000 (183 fewer to 117 fewer)

Table 4
Preferred Conditioning Regimens in Acquired Aplastic Anemia

Donor Type	Conditioning Regimen
Matched related donor	Age < 30 yr: CY200 mg/kg + r-ATG [20,88,89] or CY200 mg/kg + Alemtuzumab [75] Age >30 yr: FLU 30 mg/m2 × 4-5 d, CY 300 mg/m2 × 4 d and r-ATG (FCA regimen) [20] High risk of Graft failure: Flu 120-150 mg/m^2 + CY 120 mg/kg + r-ATG [15]
Matched unrelated donor	Adults: 1. FCA-TBI: fludarabine 30 mg/m^2 x 4, cyclophosphamide 300 mg/m^2 x 4 and ATG 3.75 mg/kg x 2, TBI 2 Gy [1] 2. FCC: fludarabine 30 mg/m^2 x 4, cyclophosphamide 300 mg/m^2 x 4, alemtuzumab 0.2 mg/kg x 5 d (total dose 40-100mg) [76] 3. For 9/10 MMUD: FCC plus 2G TBI [1] 4. Alternative for 8/8 or 7/8−BMT CTN 0301: fludarabine 30 mg/m^2 x 4, cyclophosphamide 50mg/kg x 1 (older patients) or x 2 (pediatric/young adult patients), rATG 3 mg/kg x 3, TBI 2 Gy [90] Pediatric 5. Flu 30mg/m^2 x 5 d, CY 60 mg/kg x 2 d with r-ATG (5-20 mg/kg) or alemtuzumab 0.3 mg/kg for 3 d and CSA± MTX for GVHD prophylaxis [91] 6. 8/8 or 7/8−BMT CTN 0301: fludarabine 30 mg/m^2 x 4, cyclophosphamide 50mg/kg x 2, rATG 3 mg/kg x 3, TBI 2 Gy [90]
Haplo-HCT	PTCy based: r-ATG 4.5 mg/kg total dose, FLU 30 mg/m2 × 4-5 d, CY 14.5 mg/kg x 2 d and TBI 2-4 Gy (D-1) with PTCy 50 mg /kg x 2 d [92,93]
Cord blood	1. FLU 30 mg/m2 × 4, CY 30 mg/kg x 4, ATG 2.5 mg/kg x 2 and TBI 2 Gy The French protocol (called APCORD) [94] 2. FLU 40 mg/m^2 per day (d -6 to d -2),CY 30 mg/kg per day (d -5 to d -2), and TBI or total marrow irradiation [95]
Syngeneic HCT	Although there is paucity of data, studies recommend use of Cy-ATG conditioning and PB as stem cell source to avoid graft failure [96].

CY, Cyclophosphamide; r-ATG, rabbit anti thymocyte globulin; Flu, fludarabine; FCA, fludarabine cyclophosphamide antithyomcyte globulin; FCC, fludarabine cyclophosphamide campath; TBI, total body irradiation; MMUD, mismatch unrelated donor; GVHD, graft versus host disease; PTCy, post-transplant cyclophosphamide; haplo-HCT, haploidentical hematopoietic cell transplant.

CNI-alone GVHD prophylaxis is recommended for protocols incorporating alemtuzumab [2]. Recently uniform conditioning has been proposed employing PTCy regardless of donor type [32].

- *Haploidentical:* PTCy 50 mg/kg on d +3 and +4, mycophenolate mofetil 15 mg/kg 3 times a day (max dose 3000 mg daily) from d 5 to d 35 and CNI given orally or IV from d 5 to 9 mo, maintaining a trough serum level 8 to 12 ng/mL for Tac and 200 to 300 ng/mL for CSA until a linear taper over 3 to 6 mo may begin in the absence of chronic GVHD [50,97].
- *Cord blood:* CSA alone if APCORD regimen used targeting trough concentrations 200 to 400 ng/mL for 3 mo before progressive tapering to stop at 1 year [94].

Implementation Considerations

CNI + MTX remains the standard regimen for GVHD prophylaxis in MRD and MUD-HCT. For Haplo-HCT, PTCy based prophylaxis is preferred. In recent years, PTCy based GVHD prophylaxis for MRD and MUD-HCT has been employed successfully; prospective studies will be needed to determine whether a uniform conditioning and GVHD prophylaxis is efficacious for all SAA patients receiving HCT.

Question 12: How Should Graft Failure and Poor Graft Function Be Managed Post HCT in SAA Patients?

Recommendation

Chimerism assessment should be done by testing split chimerism on flow-sorted peripheral blood leukocytes (CD3 for T cells and most commonly CD33 for myeloid); this is favored over whole blood chimerism. Mixed T-cell chimerism can be seen post-transplant in patients receiving ATG-containing conditioning regimens and does not require intervention if accompanied by normal blood counts and full donor myeloid

engraftment. For patients with poor graft function (reviewed elsewhere) [98] not responding to immunosuppression escalation, stem cell boost may be needed. Patients with graft failure usually require conditioning to eradicate residual recipient T-cells and may not respond to boost alone.

Good Practice Statement

Split chimerism is preferred for post-transplant monitoring and any donor chimerism below 95% in the myeloid or the T cell compartment should be considered mixed chimerism. In aplastic anemia, a graft is considered functional if it results in correction of the underlying marrow failure, even in the setting of mixed chimerism. Transient mixed chimerism in the T cell fraction is frequently seen after ATG-based conditioning and reverts to full chimerism in most cases. Patients with stable mixed T-cell chimerism and normal counts require monitoring alone [99].

Decreasing blood counts with full donor chimerism suggests poor graft function; either due to low viability or low numbers of stem cells in the graft. It is possible that this is due to incomplete clearance of the T cells that initially caused the AA and can be corrected in some cases by increasing immunosuppression. Erythropoietin and eltrombopag can potentially aid hemoglobin and platelet recovery [100]. For patients not responding to escalation in immunosuppression, a stem cell boost may be beneficial [98]. If counts stabilize after augmented immunosuppression, a slow taper is generally required with close and more frequent monitoring of blood counts and chimerism.

Decreasing counts and very low donor chimerism indicates graft failure/rejection. Patients with graft failure usually require conditioning to eradicate residual recipient T-cells and will generally not respond to stem cell boost.

For early rejection with continued cytopenias, a second HCT is required. A different donor (haplo or MUD) and a repeat testing for DSA is recommended before proceeding to salvage Haplo-HCT [101].

LIMITATIONS OF THE GUIDELINES

A significant limitation of these guidelines is the absence of randomized trials for many of the questions addressed. The evidence primarily comes from non-randomized prospective or retrospective studies, and for some questions, the certainty of the evidence is low or very low due to imprecision, indirectness, and biases, as evaluated by the Risk of Bias in Non-interventional Studies (ROBINS-I) tool. The panel's suggestions and recommendations are based on the current evidence but may change in the future with new findings. Result of two ongoing trials; A phase III randomized trial comparing unrelated donor bone marrow transplantation with IST for newly diagnosed pediatric and young adult patients with SAA (TransIT, BMT CTN 2202) and CUREAA (BMT CTN 2207) utilizing upfront haploidentical or unrelated HCT in adults with SAA are likely to add further evidence regarding choice of upfront treatment in patients lacking MRD.

GRADE ADOLOPMENT OF ASTCT GUIDELINES

The ASTCT guidelines are followed globally by transplant physicians; however, disease demographics, HCT expertise, donor and drug availability, financial support varies across different regions. These guidelines can serve as a source for adolopment (allowing adoption, adaptation and as needed, de novo development of recommendation), resulting in development of local guidelines as per available evidence which can be regularly updated.

CONCLUSION

Improvement in multiple aspects of HCT care have expanded applicability of the procedure to older fit patients with superior outcomes compared to IST. Since the results of MUD and Haplo-HCT have improved over the last decade and outcomes at experienced centers are now comparable to MRD-HCT, alternative donor HCT may be offered in preference to IST for patients lacking a MRD. With attempts to improve outcomes utilizing uniform and novel conditioning and optimal GVHD prophylaxis, along with better understanding of approaches to treat and prevent graft failure, transplant outcomes are likely to improve in patients with SAA. Ongoing prospective trials are likely to further clarify treatment algorithms for pediatric and adult patients when a MRD is not available.

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SUPPLEMENTARY MATERIALS

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