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Standardizing Definitions of Hematopoietic Recovery, Graft

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Rejection, Graft Failure, and Donor Chimerism

In Allogeneic Hematopoietic Cell Transplantation: A Report on

Behalf of the American Society for Transplantation and Cellular

Therapy

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Guideline

Standardizing Definitions of Hematopoietic Recovery, Graft Rejection, Graft Failure, Poor Graft Function, and Donor Chimerism in Allogeneic Hematopoietic Cell Transplantation: A Report on Behalf of the American Society for Transplantation and Cellular Therapy



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A B S T R A C T

Allogeneic hematopoietic cell transplantation (allo-HCT) is potentially curative for certain hematologic malignancies and nonmalignant diseases. The field of allo-HCT has witnessed significant advances, including broadening indications for transplantation, availability of alternative donor sources, less toxic preparative regimens, new cell manipulation techniques, and novel GVHD prevention methods, all of which have expanded the applicability of the procedure. These advances have led to clinical practice conundrums when applying traditional definitions of hematopoietic recovery, graft rejection, graft failure, poor graft function, and donor chimerism, because these may vary based on donor type, cell source, cell dose, primary disease, graft-versus-host disease (GVHD) prophylaxis, and conditioning intensity, among other variables. To address these contemporary challenges, we surveyed a panel of allo-HCT experts in an attempt to standardize these definitions. We analyzed survey responses from adult and pediatric transplantation physicians separately. Consensus was achieved for definitions of neutrophil and platelet recovery, graft rejection, graft failure, poor graft function, and donor chimerism, but not for delayed engraftment. Here we highlight the complexities associated with the management of mixed donor chimerism in malignant and nonmalignant hematologic diseases, which remains an area for future research. We recognize that there are multiple other specific, and at times complex, clinical scenarios for which clinical management must be individualized.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is potentially curative for certain hematologic malignancies and nonmalignant diseases [1,2] and is now more broadly applicable owing to improved outcomes using not just HLA-matched sibling or unrelated donors, but also umbilical cord blood and haploidentical related donors. Increased options of reduced-intensity (RIC) or nonmyeloablative (NMA) conditioning can mitigate transplantation-related mortality in high-risk allo-HCT and further expand feasibility [3–7]. More than 95% of patients needing an allo-HCT now have access to a suitable donor. These advances have led to clinical practice conundrums when applying traditional definitions of hematopoietic recovery, graft rejection, and graft failure, because hematopoietic recovery and engraftment kinetics may vary based on donor type, cell source, cell manipulation and dose, primary disease, graft-versus-host disease (GVHD) prophylaxis, and conditioning intensity, among other factors [8–12]. In daily clinical practice definitions have been used interchangeably, albeit inconsistently or incorrectly. For instance, recovery of neutrophils, operationally defined as achievement of an absolute neutrophil count (ANC) of ≥ 500 cells/ μL , is at times also used to define hematopoietic engraftment. The latter implies that donor neutrophils have reached 500 cells/ μL , which might

not be true in the case of primary graft failure with autologous neutrophil recovery. Moreover, in NMA conditioning, especially for nonmalignant diseases, engraftment definitions based only on neutrophil recovery but agnostic of chimerism are insufficient to address late graft failure, because neutrophil recovery might occur with complete loss of donor chimerism.

Contemporary allo-HCT practice measures the level of donor chimerism by quantifying the percentage of unsorted marrow and/or microfluorimetrically sorted peripheral blood leukocytes. Leukocyte compartments most commonly evaluated include granulocytes (via CD33 surface expression) and T cells (CD3), sometimes extending to B cells (CD19) and natural killer cells (CD56), depending on the disease indication for allo-HCT. Full donor chimerism is most commonly defined empirically using a cutoff of $>90\%$, $>95\%$, or $>97.5\%$. Partial, more commonly known as mixed, donor chimerism has been defined empirically using lower-end cutoffs such as $>2.5\%$ up to $>10\%$ and upper-end cutoffs such as 90% up to 97.5% . Absence of donor chimerism has been empirically defined by cutoffs of $<2.5\%$, $<5\%$, and $<10\%$ [13]. RIC or NMA conditioning regimens are more likely to result in mixed donor chimerism compared with myeloablative conditioning (MAC) regimens [14]. In the 2001 workshop, the authors recommended avoiding using a specific threshold to define mixed chimerism,

owing to multiple factors that may potentially affect results, including assay sensitivity, underlying disease, and cellular compartment(s) involved; accordingly, mixed chimerism was simply defined as any reliable detection of host hematopoietic cells, hence the wide range still used in current practice [15]. Although this is conceptually factual, certain levels of mixed chimerism within this wide range might be considered clinically acceptable or not, depending on the underlying allo-HCT indication. For instance, in patients who undergo allo-HCT for sickle cell disease, a certain level of stable mixed donor myeloid chimerism is considered an acceptable endpoint for disease correction because it tracks with donor erythrocyte chimerism. Similarly, marrow failure syndromes, like Fanconi anemia or Diamond Blackfan anemia, are correctable with stable mixed chimerism, but anything less than full donor myeloid chimerism does not erase concerns about future (host) myelodysplasia or acute myelogenous leukemia. After allo-HCT for hematologic malignancies, it is intuitive that early, durable full donor chimerism is desirable, because a low level of donor chimerism is associated with an elevated risk for disease relapse [16,17].

To address these contemporary challenges, we organized a panel of pediatric and adult allo-HCT experts to attempt to standardize definitions of hematopoietic (neutrophil and platelet) recovery, graft rejection, primary and secondary graft failure, poor graft function, and donor chimerism. We conducted a survey of adult and pediatric transplantation physicians separately. Whenever applicable, we provide clinical scenarios to highlight the application of these consensus definitions in clinical practice.

METHODS

Panel Composition

We assembled a steering committee of 14 physicians with expertise in allo-HCT and 1 independent methodology expert with expertise in evidence synthesis and the RAND-modified Delphi methods to develop the survey questions. The steering committee drafted the protocol and consensus statements based on systematic review of the literature and clinical practice considerations, and set up the expert panel. The first round of the survey comprised 3 questions on panel demographics, 4 questions on practice setting, and 26 questions on definitions and clinical management. Considering the differences in transplantation practices across age groups, we assembled separate final panels for adult (n = 25) and pediatric (n = 23) HCT physicians with steering committee representative(s) from either panel. Panel physicians included diverse geographical representation and expertise in the field, as demonstrated by a track record of peer-reviewed publications, leadership of clinical trials, and involvement in national and international transplantation societies. The methodology expert assisted with designing, developing, and administering the surveys along with data collection and analysis, but did not participate in the voting process at any stage.

Methodology

Before voting on recommendations, a formal guidance document on the RAND-modified Delphi method was shared with all participants; a statement with $\geq 70\%$ vote in favor/against was considered a consensus. A formal evaluation of patient values and preferences and cost was not conducted; however, an overall assumption was made that recommendations would be feasible in the setting across panel member practices and would not add any additional burden on existing resources. The questions covered the broad domains of definitions and clinical practice recommendations. Consistent with the RAND-modified Delphi methodology, participants rated all statements anonymously for all rounds of voting. Furthermore, all but one rounds of voting were administered online via Qualtrics survey management software (Qualtrics, Provo, UT). One round of the survey was administered anonymously online via Poll Everywhere (polllev.com) during the virtual meeting aimed at reaching consensus, in lieu of an in-person meeting, owing to the COVID-19 pandemic. Descriptive statistics was used to analyze the results of the survey, which are summarized as proportions.

Table 1
Panel Member Demographics

Characteristic	Adult Transplantation Physicians (n = 20)	Pediatric Transplantation Physicians (n = 19)
Age, yr, n (%)		
5-45	6 (30)	4 (21)
46-55	10 (50)	8 (42)
56-65	3 (15)	6 (32)
>65	1 (5)	1 (5)
Sex, n (%)		
Female	3 (15)	10 (53)
Male	17 (85)	9 (47)
Years in practice, n (%)		
<5	1 (5)	1 (5)
5-10	3 (15)	2 (11)
11-15	7 (35)	2 (11)
16-20	5 (25)	6 (32)
>20	4 (20)	8 (42)

RESULTS

Demographics

During the initial round, 20 of the 25 invited identified themselves as adult-treating and 19 of 23 invited identified themselves as pediatric-treating transplantation physicians. In the adult-treating group, the majority were male (85%), and 80% of participants had more than 10 years of experience. In the pediatric-treating group, female physicians composed 53% of the total participants, and 85% had more than 10 years of experience (Table 1).

Practice Characteristics

The majority (55%) in the adult-treating group reported practicing in transplant centers that perform >100 allo-HCT procedures annually, mostly from HLA-matched unrelated donors (MUDs) using peripheral blood stem cells as the preferred cell source. On the other hand, the majority in the pediatric-treating group (63%) reported practicing in centers that perform >50 allo-HCT procedures annually, mostly from HLA-MUDs using bone marrow (BM) as the preferred cell source (Table 2).

Definitions and Management Recommendations

Neutrophil and Platelet Recovery

As summarized in Table 3, both the adult and pediatric transplantation panels endorsed existing working definitions of neutrophil and platelet recovery set forth by the Center for International Blood and Marrow Transplant Research (CIBMTR).

Delayed Engraftment, Graft Rejection, Graft Failure, Poor Graft Function, and Secondary Graft Failure

Neither panel could reach consensus on the definition of delayed engraftment (Table 3). However, there was consensus on differentiating graft rejection from graft failure, defining poor graft function, and secondary graft failure. Both panels defined graft rejection as an immune-mediated process, whereas graft failure was considered to represent a wider array of possibilities, including cell dosing, disease, infections, drugs, and an immune-mediated event.

There was consensus on defining primary graft failure based on different cell sources. For instance, both panels defined graft failure when using peripheral blood stem cells or unstimulated BM as lack of achievement of an ANC $\geq 500/\mu\text{L}$

Table 2
Transplant Center and Practice Characteristics

Center Characteristics	Adult Transplantation Physicians	Pediatric Transplantation Physicians
Number of allo-HCTs/yr, n (%)		
<50	2 (10)	7 (37)
51–100	7 (35)	9 (47)
101–200	6 (30)	1 (5)
>200	5 (25)	2 (11)
Cell source, n (%)[*]		
PBSCs	20 (74)	5 (21)
Unstimulated BM	6 (22)	13 (54)
G-CSF-stimulated BM	1 (4)	0
UCB	0	4 (17)
Other	0	2 (8) [†]
Donor type, n (%)[*]		
MRD	10 (29)	7 (17)
MUD	16 (47)	15 (36)
MMRD/haploidentical	7 (21)	7 (17)
MMUD	0	6 (14)
UCB	1 (3)	7 (17)

PBSCs indicates peripheral blood stem cells; UCB, umbilical cord blood; MRD, HLA-matched related donor; MUD, HLA-matched unrelated donor; MMRD: HLA-mismatched related donor; MMUD: HLA-mismatched unrelated donor.

^{*} More than one option may apply/the number of responses may exceed the number of participants.

[†] Alpha-beta-depleted haploidentical transplantation (n = 1), ex vivo T cell-depleted PBSCs (n = 1).

by day +30 with associated pancytopenia. When using cord blood, both panels defined graft failure as lack of achievement of an ANC $\geq 500/\mu\text{L}$ by day +42 with associated pancytopenia. This assumes that donor chimerism testing is also done to confirm the suspicion of graft failure. There was no consensus by either panel to define graft failure when using G-CSF-stimulated BM (Table 3).

Poor graft function was defined as frequent dependence on blood and/or platelet transfusions and/or growth factor support in the absence of other explanations, such as disease relapse, drugs, or infection (Table 3).

Secondary graft failure was defined as a decline in hematopoietic function (possibly involving hemoglobin and/or platelets and/or neutrophils) necessitating blood products or growth factor support, after having met the standard definition of hematopoietic (neutrophil and platelet) recovery (Table 3). Both panels recommended assessing secondary graft failure by evaluating hematopoietic function (based on peripheral blood counts), BM cellularity, and donor chimerism (Table 4).

Donor Chimerism

Both panels endorsed current definitions of full donor chimerism as >95%, mixed donor chimerism as 5% to 95%, and absent donor chimerism as <5%, for both myeloid and lymphoid lineages (Table 3).

Measuring Donor Chimerism

Both panels recommended routine measurement of donor chimerism using CD3 or similar for lymphoid cells and CD33 or similar for myeloid cells. During the first year after allo-HCT, both panels recommended routine measurement of donor chimerism on approximately days +30, +90, and +180 and at 1 year regardless of the intensity of the preparative

regimen or whether T cell-replete or T cell-depleted grafts were prescribed (Table 4).

Managing Mixed Donor Chimerism in Allo-HCT

Although both panels endorsed the current definition of mixed donor chimerism as 5% to 95% for both myeloid and lymphoid lineages, they also recognized the practical importance of using the actual percentage of donor cells for clinical management. In this case, the panels recommended that individual patient management be based on a consideration of the actual (downward or upward) trajectories of percent donor myeloid and lymphoid chimerism, together with complete blood counts and clinical status. Because trajectories can help inform medical decision making, the panel recommends measuring donor chimerism at specific time points during the first year post-allo-HCT (eg, days +30, +90, +180, and +365).

Pertaining to specific management of downward trajectories in donor CD3 and CD33 chimerism in the malignant disease setting, Figure 1 highlights the complex decision-making in real-world clinical practice. Although withdrawal (or tapering) of immune suppression appeared to be the most frequently chosen approach for declining donor chimerism, the median response was to select 2 possible therapeutic options (range, 1 to 5). Decision making is further complicated by other variables, for example, did the downward donor chimerism trajectory occur in the setting of disease relapse/progression or during a continuous remission? Was GVHD present or not? What was the ablative intensity of the conditioning regimen? Was T cell depletion part of conditioning? These are just a few examples.

Figure 2 also highlights the complex clinical decision process associated with managing similar downtrends in donor chimerism in the context of nonmalignant disease. Interestingly, fewer adult transplantation physicians responded to this question relative to pediatric transplantation physicians (n = 15 versus n = 17; Figure 2) compared with responses to the same questions for malignant disease context (n = 19 versus n = 16; Figure 1). This may highlight the broader experience with allo-HCT for nonmalignant diseases in the pediatric transplantation group. Both panels recognized that the level of donor chimerism required for nonmalignant disease correction depends on the specific underlying disease indication for transplantation; however, specific levels of donor chimerism were not discussed for particular disease indications.

Finally, the panel could not identify a single best approach to the management of down-trending donor chimerism in either the malignant or the nonmalignant disease setting.

DISCUSSION

This work represents an effort to standardize definitions of hematopoietic recovery, graft rejection, primary and secondary graft failure, poor graft function, and donor chimerism in the setting of allo-HCT, and also to provide broad guidance on the clinical management of mixed donor chimerism. We recognize that there are multiple other specific and at times complex clinical scenarios for which clinical management must be individualized.

Pertaining to neutrophil and platelet recovery, both adult and pediatric transplantation physician panels endorsed the existing CIBMTR working definitions. Here, using the word “recovery” instead of “engraftment” is more appropriate, because confirmation of donor source ideally requires also proof of at least mixed/partial donor chimerism, which generally occurs later in the course of transplantation. Neither panel reached a consensus in defining a specific time point for

Table 3
Consensus Definitions from the Adult and Pediatric Transplantation Physician Panels

Term	Definition
Neutrophil recovery	Both panels endorsed the existing definition of neutrophil recovery as the first of 3 successive days with an absolute neutrophil count of $\geq 500/\mu\text{L}$ after post-transplantation nadir.
Platelet recovery	Both panels endorsed the definition of platelet recovery as the first of 3 consecutive days with a platelet count of 20,000/ μL or higher in the absence of platelet transfusion for 7 consecutive days.
Delayed engraftment	No consensus was reached by either panel.
Graft rejection versus graft failure	Both panels defined graft rejection as an immune-mediated process, whereas graft failure represents a wider array of possibilities, including cell dosing, disease, infection, drugs, and an immune-mediated event.
Graft failure (primary)* (according to cell source)	PBSCs: Both panels defined graft failure as lack of achievement of an ANC $\geq 500/\mu\text{L}$ by day +30 with associated pancytopenia.
	Unstimulated BM: Both panels defined graft failure as lack of achievement of an ANC $\geq 500/\mu\text{L}$ by day +30 with associated pancytopenia.
	G-CSF-stimulated BM: No consensus was reached by either panel.
	UCB: Both panels defined graft failure as lack of achievement of an ANC $\geq 500/\mu\text{L}$ by day +42 with associated pancytopenia.
Poor graft function**	Both panels defined poor graft function as frequent dependence on blood and/or platelet transfusions and/or growth factor support in the absence of other explanations, such as disease relapse, drugs, or infections.
Secondary graft failure†	Both panels defined secondary graft failure as a decline in hematopoietic function (may involve hemoglobin and/or platelets and/or neutrophils) necessitating blood products or growth factor support, after having met the standard definition of hematopoietic (neutrophils and platelets) recovery.
Donor chimerism	Full: Both panels endorsed the existing definition of full donor chimerism as >95% for both myeloid and lymphoid lineages.
	Mixed or partial: Both panels endorsed the existing definition of mixed donor chimerism as 5% to 95% for both myeloid and lymphoid lineages.
	Absent: Both panels endorsed the existing definition of absent donor chimerism as <5% for both myeloid and lymphoid lineages.

PBSC, peripheral blood stem cells; ANC, absolute neutrophil count; BM, bone marrow cells; G-CSF, granulocyte colony stimulating factor.

* Donor chimerism testing is also done to confirm the suspicion of graft failure.

** Assumes that donor myeloid and lymphoid chimerism are within a desirable target level.

Table 4
Recommendations of the Adult and Pediatric Transplantation Physician Panels

Category	Recommendations
Assessment of secondary graft failure	Evaluating hematopoietic function (based on peripheral blood counts), bone marrow cellularity, and donor chimerism(s) when assessing secondary graft failure
Measuring donor chimerism	Routine practice includes measurement of donor chimerism using CD3 or similar for lymphoid cells and CD33 or similar for myeloid cells.
	During the first year after allo-HCT, measure donor chimerism routinely on days +30, +90, and +180 and at 1 year during the first year post- allo-HCT.
	Measure sorted (CD3 and/or CD33) donor chimerism routinely in patients receiving MAC, RIC, or NMA conditioning.
	Measure sorted (CD3 and/or CD33) donor chimerism routinely when using T cell-depleted grafts (in vivo or ex vivo).
Managing mixed donor chimerism (malignant diseases)	The panel recognizes the impact of the actual percentage of donor cells for clinical management.
	Consider using the actual percentages of donor myeloid cells and lymphoid cells, blood counts and the clinical status of the patient for a change in management.
	Use the actual percentage of mixed donor chimerism at specific time points post-allografting (ie, days +30, +90, +180, and +365) for a change in management.
	Consider the decline from a prior chimerism level to inform clinical management.
Managing mixed donor chimerism (nonmalignant diseases/bone marrow failure syndromes)	The panel recognizes that the level of donor chimerism required for disease correction depends on the disease.
	Consider the decline from a prior chimerism level to inform clinical management.

delayed engraftment. This is not surprising, because in theory, delayed engraftment represents a continuum from the time of absence of hematopoietic recovery until objective confirmation of graft failure. Moreover, from a treatment standpoint, these patients generally continue to receive supportive interventions while cytopenic, such as antimicrobial prophylaxis, blood products, and growth factors, among others.

Guidelines differentiate between graft rejection and graft failure because they have different therapeutic implications. For graft rejection, interventions concentrate primarily on overcoming the HLA disparity barrier. However, interventions for graft failure are more varied based on specific situations and might include

administering a CD34-selected cell boost to address poor graft function with or without mixed/absent chimerism in the myeloid compartment and prescribing donor lymphocyte infusion(s) to treat low mixed chimerism, but do require at least 5% donor lymphoid chimerism. Other interventions to treat graft failure include considering a second allo-HCT, treatment of infections, and withholding suspected myelotoxic drugs, among others, as clinically indicated.

Different from graft failure, poor graft function assumes that donor myeloid and lymphoid chimerism are within a desirable target level and that there are other causes that explain the continuous need for blood products or growth

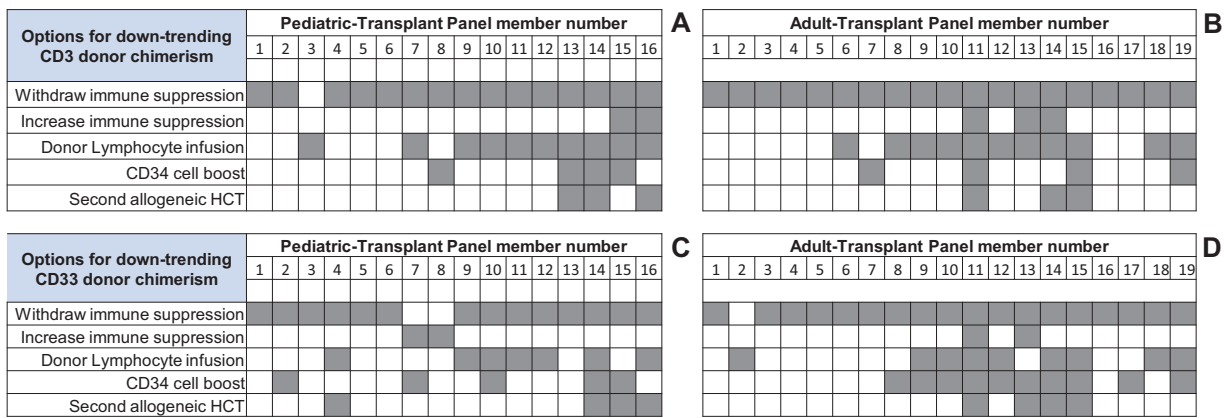


Figure 1. Transplantation physician responses to options for managing down-trending chimerism in malignant diseases. Management responses are shown for pediatric transplantation panel members to declines in CD3 (A) and CD33 donor chimerism (C). Similar responses are shown for adult transplant panel members in (B) and (D), respectively.

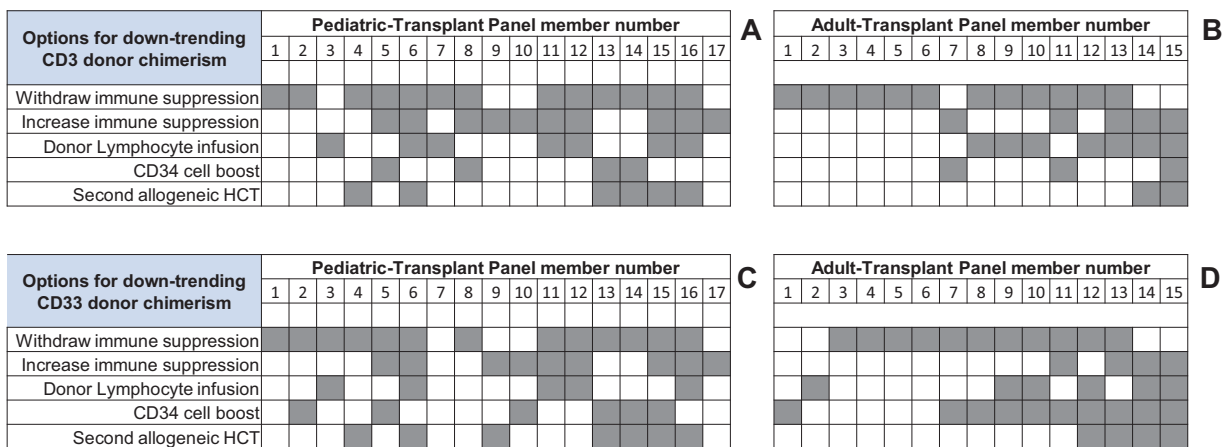


Figure 2. Transplantation physician responses to options for managing down-trending chimerism in nonmalignant diseases. Management responses are shown for pediatric transplantation panel members to declines in CD3 (A) and CD33 donor chimerism (C). Similar responses are shown for adult transplantation panel members in (B) and (D), respectively.

factor support. For instance, diseases such as myelofibrosis could cause poor graft function post-transplantation, requiring frequent transfusion of blood products during the first few months, even in the presence of full donor myeloid chimerism.

For primary graft failure, both panels endorsed using a practical definition based on lack of recovery of ANC to $\geq 500/\mu\text{L}$ in the presence of associated cytopenias at a particular time point based on the prescribed stem cell source (Table 3). We acknowledge that additional workup is certainly required, which should include assessing marrow cellularity and quantifying donor chimerism levels to confirm graft failure (Table 3), and that future interventions could vary depending on several factors, such as patient functional status and disease-specific reasons, among others. In cases of secondary graft failure, patients have a decline in hematopoietic function and confirmation of absent donor chimerism levels after previously documented full or mixed donor chimerism levels.

Notwithstanding the different sensitivities of donor chimerism methodologies, both panels endorsed current working definitions of full donor chimerism in myeloid and lymphoid lineages as $>95\%$, mixed or partial donor chimerism as 5% to 95%, and absence of donor chimerism as $<5\%$ (Table 3). Although both panels endorsed the definition of mixed donor chimerism as 5% to 95%, they acknowledged several clinical

practice limitations related to this definition. Intuitively, patients with lower levels of mixed donor chimerism are likely to be treated differently than those with higher levels. Moreover, mixed chimerism is a dynamic state in which a progressive decline in donor chimerism might portend or confirm graft loss or disease recurrence, depending on the cell compartment analyzed. For instance, a 10% level of CD3 donor chimerism might prompt consideration for donor lymphocyte infusion or even prescription of antineoplastic therapy in the case of a T cell malignancy. On the other hand, an 80% donor CD3 level, which still meets the definition of mixed donor chimerism, is more likely to be followed closely until a clearer trend is established. Furthermore, management could be different if mixed donor chimerism is observed in only one lineage versus both lineages. We acknowledge that in the setting of T cell depletion, ex vivo or in vivo, CD3 chimerism might be low or absent for many months after transplantation.

When managing declining donor chimerism levels, approaches tend to consider not only the specific lineage(s) involved, but also the percentage decline (trajectory) over time from a known peak level. Repeating donor chimerism levels should be considered to confirm the results. When both panels were asked about the immediate next step in managing declines in donor CD3 and CD33 chimerism in the setting of

allo-HCT for malignant diseases, the most frequent response was to withdraw (or taper) immune suppression (Figure 1). In addition, more than one-half of respondents chose more than one possible option, underscoring the complexities associated with managing such clinical situations. Caveats must certainly be applied, because in certain scenarios, such as the presence of active GVHD, withdrawing (or tapering) immune suppression might be inappropriate.

In the case of declining CD3 and CD33 donor chimerism in the setting of nonmalignant disorders, both panels also chose withdrawing immune suppression as the next immediate step in managing a downward trend in CD3 and CD33 chimerism. Again, more than one-half of the participants chose more than one option. Such decisions need to consider several factors, including but not limited to the patient's underlying disease indication for allo-HCT, whether the downtrend occurred in the context of minimal versus heavy pretransfusion, whether the decreases in chimerism and blood counts were observed during steady-state versus tapered immune suppression, and the intensity of the preparative regimen (MAC versus RIC). We acknowledge that optimal management of declining donor chimerism, particularly in patients with nonmalignant disorders, remains an area in which future research is definitely needed.

The main goal in developing these consensus definitions and recommendations is to harmonize allo-HCT clinical practice. These guidelines are not intended to replace clinical judgment, as there are several situations where decisions need to be individualized.

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