Cytotherapy 24 (2022) 385–392

Contents lists available at ScienceDirect

CYTOTHERAPY

journal homepage: www.isct-cytotherapy.org

ISCT Committee Paper

An ISCT Stem Cell Engineering Committee Position Statement on Immune Reconstitution: the importance of predictable and modifiable milestones of immune reconstitution to transplant outcomes

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ARTICLE INFO

Article History:
Received 21 June 2021
Accepted 18 September 2021

Keywords:
Hematopoietic Stem Cell Transplant
Immune Reconstitution
T cells

ABSTRACT

Allogeneic stem cell transplantation is a potentially curative therapy for some malignant and non-malignant disease. There have been substantial advances since the approaches first introduced in the 1970s, and the development of approaches to transplant with HLA incompatible or alternative donors has improved access to transplant for those without a fully matched donor. However, success is still limited by morbidity and mortality from toxicity and imperfect disease control. Here we review our emerging understanding of how reconstitution of effective immunity after allogeneic transplant can protect from these events and improve outcomes. We provide perspective on milestones of immune reconstitution that are easily measured and modifiable.

Introduction

Integral to the process of allogeneic hematopoietic stem cell transplant (HCT) is a period of profound immune compromise with defects in both innate and adaptive immunity. While restoration of innate immunity typically occurs in the first month after transplant, defects in adaptive immunity persist for longer. These defects arise from the need to both eradicate the recipient immune system to prevent rejection of the non-self HSCs, and to suppress the donor immune system to avoid overwhelming hyper-acute Graft versus Host Disease (GvHD). Critical to successful HCT is re-establishing T cell immunity – especially CD4+ T cell immunity - in the post-transplant period [1]. The reconstitution of T cell immunity occurs by both homeostatic expansion of populations infused at the time of transplant as well as by de novo thymic dependent T cell production. For over two decades we have understood that the pace of this process is controlled by recipient age, donor/host HLA disparity, intensity of the conditioning regimen, method of GvHD prophylaxis, incidence of GvHD, and graft composition. Reconstitution can take up to 1-2 years, with a significant number of both pediatric and adult patients experiencing even longer lasting deficits [2–5].

While some of the factors controlling immune reconstitution are not modifiable – e.g. recipient age – others are. Approaches to limit the incidence of GvHD have profound impacts on both the incidence of GvHD and the pace of post-transplant immune reconstitution. Standard approaches for prevention of GvHD employ serotherapy [anti-thymocyte globulin (ATG) and Alemtuzumab] to eliminate T

Abbreviations: ADCC, Antibody dependent cellular cytotoxicity; CBT, Umbilical cord blood transplant; CLPs, Common lymphoid progenitors; CRFS, Chronic GvHD Relapse Free Survival; DFS, Disease Free Survival; GvHD, Graft versus Host Disease; HCT, Allogeneic hematopoietic stem cell transplant; HPCSs, Hematopoietic progenitor cells; IR, Immune Reconstitution; NRM, Non-relapse mortality; OS, Overall Survival; PTCy, Post-Transplant Cyclophosphamide; TRM, Treatment related mortality; TCD, T cell depleted

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https://doi.org/10.1016/j.jcyt.2021.09.011
1465-3249/

cells by Antibody-dependent Cellular Cytotoxicity (ADCC), calcineurin inhibitors to limit T cell activation [6], and methotrexate and mycophenolate mofetil to limit proliferation [7]. These approaches are effective in limiting the incidence of GvHD in the setting of fully HLA matched HCT and in Cord Blood transplant; but are insufficient to control GvHD arising in the HLA disparate transplant setting. In addition to serotherapy, approaches to limit the incidence of GvHD by eliminating donor T cells either before or after infusion have included in vivo and ex vivo depletion of T cells (reviewed in [8]). There are currently three primary methods for accomplishing T cell depletion: ex vivo positive selection of CD34+ HSCs, ex vivo negative selection of α/β T cells, and in vivo depletion with post-transplant cyclophosphamide (PTCy). At present, all three approaches are in clinical use [9]. However, any technique to limit the number and function of T cells in the post-transplant period also risks delaying immune reconstitution and, depending on the indication for transplant, increasing the risk of rejection and relapse. Several factors influence the incidence of GvHD and the pace of immune reconstitution with these approaches to HCT including the type of cells depleted [i.e., T cells only versus other populations such as B cells and natural killer (NK) cells]. The few multicenter trials comparing T cell depletion (TCD) with conventional approaches to GvHD prophylaxis have predictably demonstrated a decreased incidence of acute and chronic GvHD, but also an increased incidence of infections in the TCD setting such that this has not translated into improved overall survival [10, 11]. Most recently, a multi-center BMT CTN trial compared standard calcineurin-inhibitor based GvHD prophylaxis to two different platforms for T cell depletion with preliminary results presented in abstract form (LBA1, TCT 2021) reporting superior chronic GvHD relapse free survival (CRFS) but inferior overall survival (OS) driven by increased treatment related mortality (TRM) in the ex vivo CD34+ selected HCT arm. Across platforms, the post-HCT immune reconstitution has demonstrated a key role in improving non-relapse and in some settings, relapse related outcomes [12–14].

STATEMENT: Successful HCT requires balancing the need for immune suppression to achieve engraftment and control of GvHD while limiting the deleterious effects of delaying immune reconstitution. There is now sufficient support to use established milestones of immune reconstitution as primary endpoints in prospective trials. In addition, milestones or biomarkers of immune reconstitution can be used for risk-based stratification of the management of complications of transplant such as viral reactivations and GvHD and to initiate revaccination.

Milestones of Immune Reconstitution

The best demonstration of complete restoration of the adaptive immune system after HCT is response to vaccination with specific antibody production. It has been demonstrated that revaccination based on acquisition of immune milestones is associated with higher rates of vaccine mediated immunity [15, 16]. However, most current recommendations are to initiate revaccination post-transplant based on time rather than acquisition of immune milestones, [17–19] and response to vaccination is not uniformly assessed. The COVID-19 pandemic has provided a new opportunity to evaluate response to vaccination after HCT with to date 233 HCT recipients reported in single center assessments of the efficacy of mRNA COVID-19 directed vaccination, Response was demonstrated in 75% [20] 38.2% [21] and 83% [22] of vaccinated HCT recipients. In two studies, recipients were vaccinated a median of 32 [20] and 21.8 [22] months post-HCT and in one 47/55 [21] were vaccinated after 6 months, despite which all three identified a longer time from HCT as predictive of response. Other identified factors predictive of a poor response included being on immune suppression [21, 22] and lymphopenia [22]. Short of response to vaccination, other milestones of immune reconstitution evaluated at least 6 months after HCT have been demonstrated to be associated with both response to vaccination and improved overall survival, [15, 23-25] but have not been assessed prospectively as primary outcomes. Other investigators have evaluated immune reconstitution as a continuous variable [24, 26]. The advantage of using specified milestones of immune reconstitution includes that if validated they can 1) be predictors of outcomes 2) be applied across studies and 3) identify individuals at increased risk of mortality in whom alternative either pre-emptive or adoptive approaches to foster better immune reconstitution may be appropriate.

STATEMENT: Simple validated milestones of immune reconstitution are needed and should be prospectively evaluated as primary outcomes in HCT.

Absolute Lymphocyte Count as a Milestone of Immune Reconstitution

The absolute lymphocyte count (ALC) has been evaluated as a simple surrogate for rapid NK recovery by several groups [27–30]. A study evaluating ALC at Day 21 found that an ALC $\geq$ 350/uL was associated with late events including lower incidence of relapse and fungal infections at 1 year and better 3 year OS and Disease Free Survival (DFFS) [27]. This effect was subsequently evaluated in the setting of TCD HCT from matched sibling donors in which multivariable analysis identified that at Day 30 an ALC above the median of 450/uL in patients transplanted for AML (but not ALL) was associated with improved survival and less relapse, and for all patients was associated with less NRM [28]. While potentially the simplest of milestones to measure, these studies did not identify a specific threshold ALC that would apply across transplant platforms and need to be confirmed in modern era multicenter trials.

NK cell Reconstitution

NK cells are the first lymphocytes to recover and typically recover by several weeks to a month after HCT, though recovery of their effector function takes longer. In both HLA disparate TCD and HLA matched T replete HCT early NK cell reconstitution is associated with both better NRM and OS [31–34].

Milestones Extrapolated from HIV

In early studies of individuals infected with HIV, CD4+ lymphopenia was identified as a predictor of opportunistic infections. It was demonstrated that a progressive decline in CD4+ T cell numbers was associated with progression to AIDS and an increasing spectrum of infections. Salient from this work was the initial identification of the risk of pneumocystis pneumonia at a CD4+ count of less than 200 cells/uL [35]. The use of this threshold for initiation of prophylaxis has persisted and has been extrapolated beyond the realm of HIV. This early work also identified the modifiable risk of other opportunistic infections including candidiasis, cryptococcus, cytomegalovirus (CMV), herpes zoster and M. tuberculosis such that the incidence of each of these infections decreased as the level of CD4+ deficiency decreased [reviewed in [36].

In 1999, Small et al [37] linked the kinetics of T cell reconstitution after TCD HCT to outcomes and demonstrated that life-threatening and fatal opportunistic infections occurred exclusively in patients whose CD4 count was less than 200 cells/uL. The delayed recovery of total and naïve $CD4^+$ T cells is associated with prolonged inversion of the $CD4^+/CD8^+$ ratio and delayed recovery of T cell mitogen responses, which places patients at increased risk of opportunistic infections, including CMV, Epstein-Barr virus (EBV), adenovirus, and human herpesvirus-6, as well as poorer OS [24, 38, 39].

A subsequent study using this CD4+ cutoff of 200 cells/uL at 3 months confirmed a strong correlation with OS, NRM, opportunistic infections and T-cell recovery at 12 months [40]. In a multivariate analysis, together with a higher CD34+ cell transplant dose, rapid recovery of CD4+ T cells at 3 months was a favorable prognostic factor for OS and NRM [41].

Milestones of CD4+ Immune Reconstitution Identified in Retrospective HCT Studies

Two small retrospective studies [40,42] identified thresholds for early CD4+ reconstitution that correlated with subsequent outcomes of interest. Berger and colleagues demonstrated that even as early as Day +35 differences in CD4+ T cell number were associated with subsequent outcomes of interest. A CD4+ count above versus below a median of 86/uL was associated with superior TRM due to a lower risk of lethal infections and GvHD. In multivariate analysis MSD and recipient age less than 16 years were significantly associated with a better CD4+ cell recovery. Fedele et al [42] used a receiver operating characteristic curve to find the cut-off value of early (approximately Day +20) CD4+ cell count to differentiate groups. They found a CD4 threshold of 114/uL associated with improved TRM at 2 years and OS at 5 years. In multivariate analysis stem cell source and donor type were associated with CD4+ reconstitution.

More recently, in single center and multi-center retrospective studies initially exclusively in recipients of bone marrow or cord blood transplant and now validated in recipients of *ex vivo* TCD transplant, we have shown that another milestone of early CD4+ T-cell reconstitution predicts survival after HCT [43, 44]. We show that a threshold of CD4+ IR of 50 CD4+ T-cells/uL within 100 days after transplantation is associated with decreased NRM, improved EFS and improved OS. A retrospective analysis of a large cohort of adult and pediatric recipients of CD34+ HCT has been performed with similar findings (manuscript under review [45]).In addition, this same measure of early CD4+ T cell reconstitution can overcome the risk associated with GvHD [46] and viral reactivation [47]. This simple, easily replicated milestone is informative regardless of age, indication for transplant and transplant platform and is feasibly applied even in small centers and those with limited resources.

Other tools for measuring immune reconstitution can add to our understanding of how a diverse T cell repertoire is reestablished post-HCT and is associated with outcomes including infections, GvHD and relapse. Early studies by complementarity determining region 3 (CDR3) spectra-typing demonstrated that skewed T-cell repertoires emerging early after TCD HCT could persist for years [48]. T cell repertoire diversity can now be measured by next generation sequencing of V-gene and CDR3 composition and has again demonstrated restricted diversity early post-HCT with more rapid normalization seen after CBT compared to TCD transplant [49] and can link characteristics of donor and recipient repertoire to the repertoire that emerges post-HCT [50–52]. This type of analysis has shown lower T cell diversity in patients not only with GvHD [50] but preceding the development of GvHD [50, 53]

Measuring thymic output by identifying recent thymic emigrants (RTEs) or T cell receptor excision circles (TREC) can also quantify de novo lymphocyte reconstitution which is associated with reduced TRM and improved OS (recently reviewed by Velardi et al [54]). Measurements of RTEs and TREC have also been used to compare different GvHD prophylaxis regimens [55] as well as finding similar modifiers of de novo IR of older age and ATG exposure, but are not yet easily performed on all recipients of HCT and may have limitations in measuring thymic function after HCT [56–58]. Alternatively, thymic function has been measured by evaluation for early thymic emigrants by flow cytometry for eg CD31 [59, 60]. These approaches will likely be important in future studies of immune reconstitution after HCT as well as assessing thymic dysfunction in both autoimmune and alloimmune reactions post-HCT.

Despite the promise of sophisticated measures of thymic activity to aide our assessment of immune reconstitution, they remain expensive and difficult to perform prospectively. One advantage of simple measures off IR such as ALC and early CD4 IR of 50/uL is that they are simple assessments that can be performed as part of standard of care, in real time, prospectively and are predictive of outcomes. Unlike other milestones of immune reconstitution that have not been demonstrated to predict outcomes across different transplant platforms (Table 1), early CD4 IR of 50/uL has been show to predict outcomes including NRM and OS in both pediatric and adult recipients of conventional, cord blood and TCD HCT regardless of the indication for transplant or conditioning regimen. Importantly these simple measures can be used even in regions with limited resources to identify patients at risk of inferior outcome.

STATEMENT The milestone of early minimal CD4+ IR of 50 CD4 T cells/uL by day 100 is powerful, simple and predictive of outcomes of interest in pediatric and adult recipients of transplant for malignant and non-malignant disease and across transplant platforms. This milestone is currently being evaluated prospectively as a primary outcome in both single and multi-center trials.

Predictors of Immune Reconstitution

Precision dosing

Across transplant platforms, the precise dosing of Busulfan based on levels and adjustments to achieve targeted exposure has been the standard for more than two decades. This approach has been demonstrated to improve outcomes by reducing the risk of relapse or incomplete stem cell chimerism with underdosing and toxicity with overdosing [61, 62]. More recent work has demonstrated that the model used for these calculations has profound effects on outcomes of interest including freedom from infectious complications and emphasizes the importance of personalized dosing [63]. Targeted dosing of other agents used in cytoreduction including melphalan [64] and fludarabine [65] can also improve HCT outcomes with evidence that over-exposure to fludarabine also impairs post-HCT IR [65]. Current studies are assessing the role of targeted peri-HCT exposure to fludarabine and subsequent immune reconstitution.

A major factor hampering CD4+ IR is exposure to residual antithymocyte globulin (ATG) at the time of infusion of the stem cell graft [43, 66]. This residual exposure is related to the dose and timing of ATG administration [43] as clearance is dependent on the size of the target pool at the time of administration. As a result, the effect of lymphodepleting serotherapy can vary by the specific cytoreductive regimen as was demonstrated in a randomized control trial where the ALC at the time of ATG administration varied by conditioning regimen [67] Exposure to ATG can be controlled by using prospective modeling to individualize ATG dose and timing such that host immune cells are exposed to appropriate ATG levels prior to transplant to minimize the risk of rejection while donor immune cells in the post-HCT period are not over-exposed [43]. Furthermore, pharmacodynamics of ATG may be altered by exposure to growth factors early post transplantation, and recent pre-clinical and clinical studies suggest administration of filgrastim after ATG administration may be detrimental to immune reconstitution [68]. Similar studies have demonstrated that alemtuzumab can impair post-HCT immune reconstitution [69] and prospective studies are needed to determine whether dosing nomograms can be developed to improve the predictable exposure to this agent.

Table 1

Author (reference)	N	Age Range	HCT Types	Disease	Milestone	How Milestone Identified	Outcomes Predicted
Kim DH (24)	82	16-54	PBSC, BM MA + NMA	Malignant + AA	ALC 350 Day 21	not described	Higher OS, DFS, and infections Lower Relapse and CI of CMV
Savani (25)	157	10-56	TCD MA	Malignant + AA	ALC > 450 Day 30	Median	Higher OS Lower NRM, Relapse (myeloid), GvHD and graft failure
LeBlanc (26)	102	0.5–58	PBSC, BM MA	Malignant (Myeloid)	ALC Day 30	Continuous no threshold	Higher OS and RFS Lower TRM
Tedeschi (27)	40	0.6-64	CBT MA + NMA	Malignant Non-Malig	ALC 150 & 100 Day 30	Continuous & Dichotomous	Higher OS (150) Lower NRM, graft failure, no association with relapse (100)
Savani (28)	54	10-58	TCD MA	Malignant	NK > 150 Day 30	Median	Higher OS Lower Relapse, NRM and aGvHD
Minculescu (30)	298	16-74	PBSC, BM MA + NMA	Malignant	NK > 150 CD4 >200	Validation Study	Higher OS (NK) Lower TRM, and infections including CMV (CD4 & NK) No association w/ relapse or GvHD
Hattori (31)	81	18-71	PBSC, BM, CBT MA, NMA	Malignant	BM NK Day 21	Median	Higher OS and RFS Lower NRM and Infections
Small (34)	62	2-69	TCD MA	Malignant Non-Malig	CD4 >200 PHA	No specified time	Lower infections/Lethal infections
Fedele (39)	99	11-67	PBSC, BM MA, RIC	Malignant +AA	CD4> 115 Day 20	ROC curve of CD4+	Higher OS Lower TRM, Disease Related Mortality No association with GvHD
Goldberg (21)	375	2-68	TCD MA	Malignant	CD4 & PHA Day 180	Landmark analysis	Higher OS and EFS (PHA) Univariate Higher OS and EFS (CD4) No assoc.w/relapse
Novitzky (36)	42	15-54	TCD MA	Malignant	CD45RA Day 180	Median	Higher Relapse Free Survival
Berger (37)	758	4-72	BM MA, RIC	Malignant + AA	CD4 >84 Day 35	Median	Lower TRM and lethal infections
Kim (38)	69	16-58	PBSC, BM MA	Malignant	CD4>200 Day 100	Prior studies	Multivariate Higher OS, Lower NRM Univariate Higher infection & relapse, lower cGvHD
Admiraal (40)	251	0.2-23	PBSC, BM, CBT MA, RIC	Malignant Non-Malig	CD4 >50 Day 100	Prior studies	Higher OS and EFS Lower NRM and relapse (myeloid)
Van Roessel (41)	315	0.2–26	BM, PBSC, CBT, TCD MA, RIC	Malignant Non-malig	CD4 >50 Day 100	Validation Study	Higher OS and EFS Lower NRM No impact on relapse or aGVHD
Lakkaraja (42)	554	0.2-73	TCD	Malignant Non-malig	CD4 >50 Day 100	Validation Study	Lower NRM

Transplant Platform

The stem cell source and approach to GvHD prophylaxis have significant impact on the quality of post-HCT immune reconstitution. Historically, when compared with conventional peripheral blood stem cell (PBSCT) or bone marrow (BMT) transplant, cord blood transplant (CBT) has been associated with rapid NK and B cell IR, but increased infection risk due to delayed T cell IR [70–72]. However, this difference in IR and infectious complications has not been consistently associated with increased infectious related mortality [73]. More recent studies have demonstrated that this delay in T cell IR is strongly influenced by exposure to ATG [74], and thus modifiable. In pediatric and adult CBT recipients no or low exposure to ATG is associated with improved early CD4+ IR [75, 76]. In addition, the exact composition of individual grafts can be associated with outcomes including IR in both conventional and TCD PBSCT/BMT and in CBT (reviewed in [77]). Examples include improved early CD4+ IR in recipients of CB units with higher CD3+ composition [78] and higher PBSC graft composition of NK cells [79]. While graft engineering to achieve these beneficial characteristics is not uniformly possible, in the setting of conventional PBSCT the CD34 dose is frequently capped as a result of a retrospective analysis demonstrating inferior outcome in recipients of PBSCT grafts containing high doses of CD3 and CD34 cells [80]. Importantly, this cannot be extrapolated to in vivo or ex vivo TCD HCT platforms [81–83]. In fact, new approaches to ex vivo graft engineering such as α/β T cell and CD3/CD19 depletion allow optimization of the T cell and CD34 graft composition for recipients of ex vivo TCD HCT [84, 85] resulting in reports of improved T cell IR compared to historical approaches to ex vivo TCD relying on CD34+ selection [86, 87].

Post-transplant cyclophosphamide (PTCy) as a method of in vivo TCD is also reported to foster improved IR over historical methods for TCD. The early NK cell reconstitution seen after other TCD and conventional transplants is blunted by the administration of cyclophosphamide [88]. However, while cyclophosphamide eliminates rapidly dividing cells interfering with early homeostatic expansion, transferred regulatory T cells preferentially survive cyclophosphamide leading to an increased Treg/Tcon ratio [89, 90]. The cessation of mycophenolate at 6 weeks after PTCy HCT has been identified as a factor allowing for CD8 T cell reconstitution comparable to that after standard conventional BMT [77]. In this setting it was also demonstrated that naïve T cells can differentiate directly into memory stem T cells (Tscm) such that the expanded population of Tscm after PTCy HCT originate from naive precursors and contribute to early peripheral reconstitution by differentiating into effectors.[91, 92]. Current efforts to improve IR after PTCy HCT include modifying the post-HCT

immune suppression [93, 94] and the dose and timing of serotherapy to achieve predictable exposure. One can imagine that an improved understanding of the pharmacokinetics of cyclophosphamide and its metabolites could allow targeted dosing based on the number of specific populations of T cells infused with the graft. While the use of PTCy based transplantation is easily applied in countries or regions with limited resources, it is these same areas that do not have the capacity to treat the consequences of poor IR. Simultaneously, it is important that centers with the resources to do so continue to perform in depth monitoring of immune reconstitution and explore ways to improve immune reconstitution in patients treated with this platform.

STATEMENT: Milestones of immune reconstitution, including CD4+ IR, are modifiable by transplant regimens that include personalized exposure.

Future perspectives

Improving the probability of achieving early CD4+ IR after HCT is an important strategy to enhance HCT success. individualizing the conditioning regimens to allow for better and more predictable IR is one approach that could improve both thymic dependent and thymic independent IR across transplant platforms. In addition to already established approaches to individualized dosing of Busulfan and ATG, a similar approach to dosing of other serotherapies and fludarabine has the potential to further improve immune reconstitution.

The absence of post-transplant immune suppressive medications makes the TCD platforms with CD3/CD19, α/β depletion and CD34+ selection ideal for the study of preemptive strategies such as adoptive transfer of T regs, human T cell progenitors or cytotoxic lymphocytes directed against herpes viruses. Strategies to enhance immune recovery post-transplant represent a critical unmet need in the TCD setting.

Strategies to Enhance Thymic Dependent post-HCT Immune Reconstitution

The thymus is the principal lymphoid organ responsible for generating and supplying naïve T cells. After allo-HCT, T-cell differentiation of donor progenitors within the recipient thymus is required in order to generate the naïve RTEs that provide a diverse TCR repertoire with robust response to pathogens. Insufficient recovery in thymopoiesis translates into a predisposition to severe infections. Approaches to enhance thymic regeneration after HCT are being adapted from preclinical models including sex-steroid ablation [95], infusion of prethymic precursors [96–98], growth hormone (GH) [99], keratinocyte growth factor (KGF) [100], insulin-like growth factor (IGF-1) [101] and interleukin-7 (IL-7) [102] (reviewed by [54].

Strategies to Enhance Thymic Independent post-HCT Immune Reconstitution

Thymic independent T cell immune reconstitution is largely dependent on graft composition and homeostatic expansion of T cells infused at the time of transplant. As a result, targeted exposure of the graft to immune ablating therapies is critical to effective immune reconstitution.

Similarly, a better understanding of the role that graft composition plays in outcomes of interest will likely contribute to an improved ability to identify patients at risk of poor post-HCT IR. Correlations between outcomes and graft composition will depend on better identification of the frequency of pluripotent CD34+CD90+ hematopoietic stem cells (HSC) within the population of hematopoietic progenitor cells (HPSCs) identified by CD34+ and by improved enumeration of common lymphoid progenitors (CLPs). The different graft composition of these populations will likely explain some of the differences in IR between transplant platforms. Such analyses will be instrumental not only for prediction of clinical outcome, but also for optimization of novel graft engineering strategies.

Finally, T cell reconstitution can be mediated by infusion of well characterized populations of donor derived cell products. These cell products can be defined doses of bulk T cells (DLI) [103–108] but the risk of provoking GvHD is high and it is increased by the presence of HLA disparity between the donor and the recipient. Adoptive cell therapies with donor-derived alloreactive-depleted (eg CD45RA-(naïve) or CD4 depleted) T cells [109–112], T cells transduced with a suicide gene [113–115], T-cell clones or lines directed against life-threatening pathogens [116–121], and regulatory or conventional T cell [122–127] infusions after -HCT (including after haploidentical HCT) can reduce transplantation-related mortality due to infectious complications. The results reported so far are encouraging, but they have been obtained primarily in single center trials in a limited number of patients. In addition, while donor derived viral specific T cells have been demonstrated to persist long term [128] this approach may not contribute to broad protection or overall immune reconstitution [129]. A comparison of the efficacy of these different cell therapy approaches requires confirmation in larger cohorts of patients, homogeneous in terms of disease and treatment. Most importantly, future efforts focused on standardizing and simplifying the manufacture of these cell-therapy products are needed to make them accessible to a broad number of patients including those in resource poor regions.

Statement

Understanding the role of graft composition and control of peri-transplant exposure to immune-ablating therapies will improve the ability to minimize the number of patients at risk for poor post-HCT immune reconstitution. For those at risk, adoptive T-cell therapies can accelerate reconstitution of cellular immunity with enhanced antitumor effects following HCT.

OVERALL STATEMENT

Milestones of immune reconstitution that are predictable and modifiable are associated with improved HCT outcomes. A simple, early milestone of CD4+IR (50/uL) by day 100 that is validated across transplant platforms and can be used in regions with limited resources, should be validated prospectively, and used to stratify transplant recipients for interventions to improve CD+4IR or compensate for its absence.

Conflicts of Interest

Allistair Abraham: Served on the safety monitoring committee for Sangamo Therapeutics and has no financial interest in the development of gene therapies

Jaap Jan Boelens: Consulting: Avrobio, BlueRock, Race Oncology, Advanced Clinical, Omeros, Sanofi, Medexus

Carmem Bonfim: Consulting: Zodiac, Amgen, Novartis

Sandra Cohen: ExCellThera: royalties, consulting, shares

Susan Prockop: Receives support for the conduct of clinical trials through MSK from AlloVir, Atara, and Jasper. Inventor of IP related to development of third party viral specific T cells program with all rights assigned to MSK

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