Biol Blood Marrow Transplant 21 (2015) 1744–1750

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

# Haploidentical Hematopoietic Stem Cell Transplantation as a Platform for Post-Transplantation Cellular Therapy

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*Article history:*
Received 16 May 2015
Accepted 7 July 2015

*Key Words:*
Haploidentical transplantation
Post-transplantation cyclophosphamide
Alpha-beta T cell depletion
Cellular therapy
Donor lymphocyte infusion
Natural killer cells
Chimeric antigen receptor T cells

A B S T R A C T

Haploidentical transplantation can extend the opportunity for transplantation to almost all patients who lack an HLA-matched donor. Advances in the field of haploidentical transplantation have led to a marked decrease in treatment-related mortality, allowing investigators to focus on developing rationale pre- and peri-remission therapies aimed at preventing disease relapse after transplantation. Because of widespread availability, low treatment-related mortality, and cost, haploidentical donors may become the preferred "alternative" donors for allogeneic hematopoietic stem cell transplantation. One of the major advantages of using a related donor is the possibility of collecting or generating additional cellular products from the same immediately available donor, which will not be rejected. Infusion of these cells in the peri-transplantation period, derived from the same immune system, is opening the possibility of markedly enhancing the anti-tumor effects of the graft and hastening immunologic reconstitution after transplantation.



## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (AHSCT) is a potential curative treatment for patients with advanced hematologic malignancies. However, donor availability remains one of the major limitations to extending this treatment modality to all patients in need. Although an HLA-matched sibling is the preferred donor, only a minority of patients will have such a donor available [1]. An HLA-matched unrelated donor has been considered the next best option; however, identification of a matched unrelated donor is challenging [2]. Also, the unrelated donor search and procurement of stem cell product take much longer than when using a related donor. Many patients urgently need transplantation to prevent disease relapse, and a prolonged unrelated donor search is not feasible. One HLA haplotype–matched first-degree relative, as a related transplantation, is the most accessible stem cell source that is also widely available, as most patients will have a haplotype-matched related donor in the immediate family, typically a parent, child, or sibling. In addition, an important advantage that has recently come to the forefront is the immediate availability of the same donor to collect or generate additional cells, such as T cells or T cell subsets, such as natural killer (NK) cells, to enhance antitumor effects of the graft [3]. This may provide a significant advantage to haploidentical stem cell transplantation (HaploSCT), which, in addition to low nonrelapse mortality (NRM), lower cost compared with unrelated donor transplantation, and widespread availability, may be an ideal setup for cellular therapy with cells collected from the same donor that may not be rejected, as they are part of the same immune system, and, when infused early after transplantation, could enhance the antitumor effects of the graft and improve immunologic reconstitution.

Here, we review the use of HaploSCT as a platform to apply post-transplantation cellular therapy with cells collected or generated from the same donor to enhance the graft-versus-tumor (GVT) effect and we discuss current and anticipated developments using cellular therapy in this setting.

## METHODS OF HAPLOIDENTICAL TRANSPLANTATION

HaploSCT, initially performed in late 1970s using unmanipulated T cell–replete (TCR) stem cell grafts and conventional graft-versus-host

*Financial disclosure:* See Acknowledgments on page 1718.

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http://dx.doi.org/10.1016/j.bbmt.2015.07.002
1083-8791/

disease (GVHD) prophylaxis, led to severe acute GVHD (aGVHD) and graft rejection in most patients [4,5]. Early evidence suggested that the T cells in the graft are responsible for causing aGVHD [6,7]. In an early attempt to minimize T cell alloreactive reactions across the HLA barrier and decrease the risk of GVHD, complete ex vivo T cell depletion (TCD) of the graft was developed. Unfortunately, extensive T cell depletion was associated with an increased risk of graft failure [8-11] and a significant delay in immunologic reconstitution was observed, associated with a higher risk of opportunistic infections after transplantation [12,13].

Several novel approaches have been subsequently developed to partially deplete T cells from the graft with the goal of preserving immunity and GVT effects while selectively eliminating the cells mostly responsible for GVHD (Table 1). Some, if not all, of these methods may become a platform for post-transplantation cellular therapy.

### *Co-infusion of Regulatory T Cells and Conventional T Cells*

*Regulatory T cells* (Tregs) defined by $CD4^+CD25^+$ and the transcription FOXP3 expression, suppress autoreactive lymphocytes and control innate and adaptive immune responses. In preclinical models, Tregs suppressed the early expansion of alloreactive donor T cells and their capacity to induce GVHD without abrogating their GVT effect [14,15] and when coinfused with $CD4^+CD25^-$ conventional T cells (Tcons), immune recovery was accelerated [16]. Given these observations, immunotherapy with Tregs and Tcons has been explored for clinical applications. The Perugia group treated 28 patients with high-risk hematologic malignancies conditioned with fludarabine, cyclophosphamide (CY), total body irradiation (TBI), and thiotepa before haploidentical donor–derived Tregs infusion, followed by the TCD stem cell graft combined with Tcons infusion, with a ratio of Tcons to Tregs about 1:2. No GVHD prophylaxis was administered. Twenty-six of the 28 patients achieved primary engraftment and only 2 patients developed aGVHD. No patient had chronic GVHD (cGVHD). Even though immune recovery appeared rapid, NRM occurred in 13 of the 26 evaluable patients, including 8 from infection. Long-term results of this study have confirmed low GVHD and relapse incidences; however, NRM remains a concern [17].

### *Photodepletion of Alloreactive T Cells*

This approach aims to selectively deplete T cells that react against recipient alloantigens to prevent GVHD, yet preserve tumor-specific and pathogen-reactive T cells. It requires the alloactivation of donor T cells by patient-derived antigen-presenting cells. Alloreactive donor T cells are then targeted by their expression of surface activation markers, proliferation in a mixed leukocyte reaction, or the preferential retention of photoactive dyes. One of the methods to eliminate these alloreactive donor T cells is ex vivo photodepletion. This strategy's principle is that alloreactive T cells uptake and accumulate the TH9402 compound. Then, these cells are lysed after exposure to a specific wavelength of visible light. This approach would spare resting T cells to fight infections. This method also has been found to transform non-Tregs to Treg cells and can help prevent GVHD in HaploSCT patients [18]. This approach is now being studied in a multi-institutional phase II setting.

### *Depletion of Alpha-beta and $CD19^+$ T Cells*

The αβ T cell receptor–positive T cells are a major content of the T cell population and responsible for the occurrence of GVHD as they recognize alloantigens in MHC dependent manner [19]. On the other hand, innate like γδ T cells are capable of directly recognizing their targets in an MHC-independent manner, thereby allowing them to respond to malignancy cells without recognition of alloantigens that could result in GVHD. Several studies have shown that patients who develop increased numbers of donor-derived circulating γδ T cells after HaploSCT or partially mismatched AHSCT experience prolonged survival [20,21]. These findings have led to the rationale of selective elimination of αβ T cells while preserving γδ T cells with the aim of reducing GVHD without abrogating GVT effect. Early results in a pediatric population with nonmalignant diseases are very encouraging. Twenty-three children received HaploSCT after ex vivo elimination of αβ T cells without post-transplantation GVHD prophylaxis. Sustained engraftment in the great majority of patients, rapid immune reconstitution, and low incidence of NRM were observed in this study. With the median follow-up of 18 months, disease-free survival was 90% [30]. These patients did not receive additional post-transplantation immune suppression and had a low incidence of aGVHD. Studies evaluating this approach in adult patients are ongoing. The biggest advantage of this approach appears to be the possibility of avoiding post-transplantation immunosuppression.

### *Post-transplantation CY for GVHD Prevention*

CY is a highly immunosuppressive alkylating agent, which has been incorporated in various conditioning regimens for AHSCT. High-dose post-transplantation CY (PTCY) has been used to selectively deplete alloreactive T cells after TCR HaploSCT. This approach is based on an observation that CY can promote tolerance to allogeneic MHC-mismatched skin grafts in mice [31]. In animal models of AHSCT, CY administered on day +3 allowed stable engraftment of MCH-incompatible cells and attenuated lethal and nonlethal GVHD [32]. Moreover, Ross et al. demonstrated that alloreactive or stimulated T cells, which are responsible for causing graft rejection and GVHD, are more susceptible to the cytotoxic effect of CY than resting or memory T cells [33]. However, concerns about its myelotoxicity have deterred clinical application of high-dose PTCY. Kastan et al. have shown that human hematopoietic progenitor cells express high levels of cytoplasmic aldehyde dehydrogenase, which makes them resistant to the cytotoxic effect of CY [34]. Moreover, both preclinical and clinical studies have demonstrated the resistance of Tregs to CY through expression of aldehyde dehydrogenase, which may contribute to GVHD prevention in this setting [22,35]. Based on its ability to induce maximal immunosuppression without myeloablation, several clinical trials have been performed at multiple transplantation centers to assess the efficacy of PTCY administration to prevent GVHD. An initial phase 1 clinical trial showed safety and efficacy of PTCY in preventing graft rejection and GVHD after nonmyeloablative, TCR bone marrow transplantation from haploidentical donors. This protocol used a conditioning regimen of fludarabine, CY, and 2 Gy TBI, initially with only 1 dose of PTCY of 50 mg/kg on day +3 [23]. The regimen was subsequently modified by adding 1 more dose on day +4. A remarkably low incidence of aGVHD, cGVHD, and NRM were observed in this study. However, more than one half of the patients relapsed after 1 year after transplantation [24]. A recent study by McCurdy et al. has shown that disease aggressiveness is the main factor for relapse and survival after nonmyeloablative HaploSCT with PTCY [25]. To reduce the risk of relapse, especially for patients with high-risk malignancies, a more intense conditioning has been investigated by several groups. In a recent study by Solomon et al., 30 patients with advanced hematologic malignancies were treated with a conditioning regimen using fludarabine and fractionated TBI (total dose 1200 cGy) and a peripheral blood graft. Donor engraftment occurred in all patients; the cumulative incidence of grade II to IV and III and IV aGVHD was 43% and 23%, respectively; and NRM at 2 years was only 3%. With a median follow-up of 24 months, disease-free survival was 73% at 2 years [26]. Our group recently reported the outcomes of the first 100 patients treated at MD Anderson Cancer Center using a fludarabine, melphalan, thiotepa conditioning regimen. The 3-year progression-free survival rates for patients with myeloid and lymphoid malignancies were 56% and 62%, respectively, with 1-year NRM rates of 12% and 22%, respectively [27]. Other groups reported alternative conditioning regimens with similar outcomes [28]. Collectively, these clinical data suggest that the use of PTCY with tacrolimus and mycophenolate mofetil is very effective in controlling GVHD in HaploSCT, can be used with many conditioning regimens, and because of the low NRM, could serve as a platform for cellular therapy after transplantation. These improved outcomes were found to be significantly better compared with complete ex vivo TCD HaploSCT because of more rapid immune reconstitution and lower incidences of severe aGVHD, cGVHD, and NRM [29]. Nonetheless, it remains unclear how TCR HaploSCT with PTCY will compare with other in vivo and ex vivo methods of partial TCD [36].

A number of other methods to control alloreactivity in haploSCT have been developed by other investigators from different institutions, but are not discussed in this review.

**Table 1**
Current Selective Approaches to Haploidentical Transplantation

| Approach | Rationale and Advantages |
|---|---|
| Tregs and Tcons coinfusion [14-17] | Prevent GVHD by Tregs while promoting immune reconstitution by addition of Tcons |
| Photodepletion of alloreactive T cells [18] | Ex vivo depletion of alloreactive T cells with TH9402 that accumulates in activated T cells |
| Selective αβ T cell depletion [19-21] | Removing αβ T cells that are most responsive for aGVHD; remaining γδ T cells are thought to have an innate immune-like response capability without inducing GVHD. |
| High-dose PTCY [22-29] | Eliminates early alloreactive T cells; rapid immune recovery with low rate of infectious complications; acceptable rates of GVHD; lower cost |

## POST-TRANSPLANTATION CELLULAR THERAPY

With significant improvement in NRM, disease relapse has become the most important cause of treatment failure in patients undergoing HaploSCT, similar to matched transplantation. Several strategies have been used and novel approaches are being explored to prevent and treat disease relapse after transplantation (Table 2). This may offer a unique opportunity, probably for the first time since the beginning of allogeneic transplantation, to greatly enhance the antitumor effects of the graft when administered early after transplantation. Current and foreseeable cell therapy approaches that could be applied after HaploSCT are outlined below.

### *Unmodified Donor Lymphocyte Infusion (DLI)*

Donor lymphocyte infusion (DLI) has been used primarily as a therapeutic option to treat disease relapse after HLA-matched sibling or unrelated donor AHSCT. Considering the ready availability of haploidentical donors, donor lymphocytes can be easily obtained and infused to the recipients to prevent or treat early disease relapse. A higher risk of severe aGVHD when using haploidentical DLI (haploDLI) is the most important concern. However, several studies did not show an increase risk of aGVHD after haploDLI compared with DLI from HLA-matched donors, probably because the tolerizing effect on donor cells had already occurred. An early study by Huang et al. used granulocyte colony–stimulating factor–primed therapeutic haploDLI in 20 patients with relapse after transplantation, with the median cell dose of $61 \times 10^6$ $CD3^+$ T cells/kg. The incidences of grade III and IV aGVHD and cGVHD were 30% and 64%, respectively [37]. A more recent report from the same group described the experience with haploDLI administered to 124 patients after TCR HaploSCT. The cumulative incidence of aGVHD (53.2% for grade II to IV and 28.4% for grade III to IV) was reduced with post-DLI GVHD prophylaxis [38]. However, with a dose-escalated approach using a lower starting DLI dose, the incidence aGVHD appears to be lower and well tolerated. The Johns Hopkins group administered 52 doses of haploDLI to 40 patients with hematologic malignancies treated with PTCY who relapsed after HaploSCT. Using dose escalation, they started with $1 \times 10^5$ $CD3^+$ T cells/kg of recipient's ideal body weight. The majority of patients (72.5%) received $1 \times 10^6$ $CD3^+$/kg DLI dose. Overall, 12 (30%) patients responded to haploDLI and all achieved a complete remission, with a median response duration of 12 months. aGVHD occurred in only 25% and grade III and IV aGVHD occurred in 15% [39]. This group recommended $1 \times 10^6$ $CD3^+$/kg as starting dose. This was the first study to confirm the feasibility of DLI in patients receiving PTCY as GVHD prevention. In a similar study by Ghiso et al. using DLI from haploidentical sibling donors for treatment of 108 patients who relapsed after HaploSCT, the starting DLI dose was $1 \times 10^4$ or $1 \times 10^5$ $CD3^+$ T cells/kg. The cumulative incidence of aGVHD grade II to IV was only 14% and none of the patients developed cGVHD. The response rates were 45%, 33%, and 70% in patients with molecular relapse and hematologic relapse of leukemia and Hodgkin's disease, respectively [40]. Results from these studies suggest that dose-escalated DLI can be safely administered in patients who relapse after HaploSCT, as no significant increase GVHD was observed in these patients compared with DLI administered for HLA-matched transplantations. The use of unmodified DLI with a "safety switch," as described below, to prevent disease relapse in patients with advanced hematological malignancies is being tested in clinical trials.

### *Unmodified DLI with a "Safety Switch"*

A higher risk of aGVHD is the main limitation of early administration of an unmodified DLI. To control the development of severe aGVHD after transplantation, infused T cells can be genetically modified ex vivo to express a specific suicide gene, which may be turned on to induce cell apoptosis if GVHD occurs. The administration of donor T cells with a "safety switch" can help prevent relapse when administered earlier after transplantation and may accelerate immune reconstitution. The safety and efficacy of this approach have been investigated in several preclinical and early clinical studies [41-44]. In a phase 1/phase 2 clinical trial by Ciceri et al., donor T lymphocytes engineered to express herpes simplex thymidine-kinase suicide gene (TK cells) were infused in patients with high-risk leukemia who underwent HaploSCT with TCD peripheral blood grafts. T cell apoptosis can be triggered by the use of gancyclovir if the patients developed GVHD. No GVHD prophylaxis was used after transplantation. Of 28 patients, 22 successfully engrafted with TK cells. Improvement of immune response against cytomegalovirus and Epstein-Barr virus was seen after TK cell infusions. Ten patients developed aGVHD, which was abrogated by using gancyclovir. No acute or chronic adverse events were related to the gene-transfer procedure [45]. Correspondingly, a study by Vago et al. has confirmed that TK cell infusion can drive the recovery of thymic activity in adults patients treated with TCD haploSCT, leading to immune reconstitution. In this study, 11 patients developed GVHD after TK cell infusion and all of them achieved complete resolution of all signs and symptoms by the activation of the suicide gene in TK cells through intravenous administration of gancyclovir [46]. However, gancyclovir is a drug commonly used to treat cytomegalovirus reactivation in AHSCT; thus, using this drug might not be optimal. Although the expression of the gene-encoding herpes simplex virus TK has shown promise as a safety switch, its mechanism of action requires interference with DNA synthesis. Therefore, the cell killing may take several days and be incomplete, resulting in a delayed clinical benefit. The Baylor group developed an alternative approach by using T cells engineered to express caspase 9, which can be induced by using a dimerizing agent, AP1903. These inducible caspase 9 T cells

**Table 2**
Post-transplantation Cellular Therapy Approaches Aimed at Decreasing Disease Relapse after Haploidentical Transplantation

| Approach | Advantages and Limitations |
|---|---|
| Unmodified DLI [37-40] | Increase graft-versus-malignancy effect; nonselective |
| Unmodified DLI with a "safety switch" [41-46] | Increase graft-versus-malignancy effect; control of GVHD, if develops; nonselective |
| γδ donor T cell infusion [47-55] | Infusion of selected gamma-delta T cells; no GVHD potential; unclear efficacy |
| T cells with CARs [56-58] | T cells engineered to recognize specific antigens (eg, CD19) provides graft-versus-malignancy effect for B cell lymphoid malignancies (ALL, NHL); efficacy demonstrated in small series; no GVHD potential |
| Infusion of ex vivo–expanded NK cells [59-64] | Potential graft-versus-malignancy for myeloid malignancies; no GVHD; efficacy unclear |

NHL indicates non-Hodgkin lymphoma.

provided rapid immune recovery in 10 pediatric patients who received AHSCT with TCD. AP1903 administration rapidly resolved GVHD without a significant effect on antiviral immune reconstitution [44,65]. Ongoing and future studies are investigating the efficacy of this approach in preventing disease relapse after HaploSCT.

### *Gamma-delta Donor T Cell Infusion*

The γδ T cells are a subset of T cells, accounting for 1% to 10% of circulating human T lymphocytes, largely outnumbered by T cell receptor αβ $CD4^+$ and $CD8^+$ T cells [66]. Unlike αβ T cells, γδ T cells have a directed cytotoxic effect on target cells, independent from antigen presentation via HLA molecules, which allows them to target and kill tumor cells without causing GVHD. Preclinical studies have shown that donor γδ T cells are able to promote alloengraftment and the GVT effect, yet they did not cause lethal GVHD in mice that underwent transplantation with MHC-incompatible TCD marrow grafts [47-49]. However, in a clinical setting, immunotherapy with γδ T cells requires their activation and expansion, as they constitute only a small percentage of circulating T cells. Aminobisphosphonates, eg, zoledronic acid, or synthetic phosphoantigens, eg, bromohydrin pyrophosphate and 2-methyl-3-butenyl-1-pyrophosphate, have been used with promising results for γδ T cells expansion in clinical settings [50-52].

Also, many clinical studies have demonstrated that γδ T cells as immune therapy for hematologic malignancies is a well-tolerated and feasible method, with objective tumor responses in patients with various hematologic malignancies [21,52,53,67,68]. In the HaploSCT setting, Airoldi et al. assessed functional and phenotypic characteristics of γδ T cells after HaploSCT using αβ T cells and $CD19^+$ B cell–depleted graft in 27 children with either malignant or nonmalignant disorders. This group demonstrated that selective depletion of αβ T cells from haploidentical peripheral blood stem cells enhances the functional and phenotypic reconstitution of γδ T cells. Further, the Vδ2 subset of γδ T cells are expanded in vitro after exposure to zoledronic acid and efficiently lyse primary lymphoid and myeloid blasts [54]. These new insights may have important implications for the use of γδ T cell infusion after transplantation for preventing or treating disease relapse, especially after partially TCD–haploidentical grafts, where donor γδ T cells can easily be obtained using the same immunomagnetic procedure as the αβ TCD grafts.

### *Infusion of T Cells with Chimeric Antigen Receptors (CARs)*

This approach offers a targeted antitumor effect without added risk of developing GVHD by using T cells that are engineered to express a chimeric receptor with an extracellular domain that can recognize a specific antigen on the tumor cells and an intracellular domain that can activate the cytotoxic T cells [69]. CARs have been used successfully in tumors that express the CD19 antigen, such as B cell acute lymphoblastic leukemia (ALL) or B cell non-Hodgkin lymphomas. Kochenderfer et al. reported outcomes of 10 patients who received anti-CD19 CARs for post-transplantation relapsed B cell malignancies. Three patients had regression of their malignancies and none of the patients developed GVHD after CARs infusion [56]. Maude et al. conducted a pilot clinical trial using autologous T cells transduced with a CD19-directed CAR (CTL019) lentiviral vector in 30 patients with relapsed or refractory ALL. Twenty-seven of 30 patients (90%) were in a morphologic remission 1 month after the infusion of CTL019. Of those who had a morphologic remission, 22 patients had negative minimal residual disease. These investigators also demonstrated that CTL019 cells proliferated in vivo and were detectable in the blood, bone marrow, and cerebrospinal fluid of patients who responded [57]. We are exploring the use of haploidentical donor–derived CAR T cells generated using the "Sleeping Beauty" system and administered early after HaploSCT to prevent disease relapse, as a part of a multiarm clinical trial [58]. Four HaploSCT recipients received CAR T cells in escalating doses up to $1 \times 10^7/m^2$ so far; 3 with ALL and 1 with primary induction failure large B cell lymphoma who never achieved remission after multiple different courses of chemotherapy. CAR T cells were administered 6 to 12 weeks after stem cell infusion. CAR T cells were detected in all patients 2 to 4 weeks after the infusion. All patients received mycophenolate mofetil until day +90 and tacrolimus until 6 months after transplantation. Overall, 3 of 4 patients remain in remission at last follow-up. These results are very promising and show that allogeneic CAR T cell therapy can be safely administered early after HaploSCT without significant GVHD in the presence of nonsteroid-based immunosuppression.

### *Infusion of Ex Vivo–Expanded NK Cells*

NK cells are part of the innate immune system involved in identifying and killing tumor cells or virally infected cells. NK receptors specific for HLA class I molecules, called killer immunoglobulin-like receptors (KIRs), play a major role in the antitumor effect in AHSCT. NK cells express KIRs, which mediate inhibition by recognizing specific HLA class I alleles. Missing expression of the KIR ligand on mismatched allogeneic cells can, therefore, enhance NK cell alloreactivity [70-73]. In HaploSCT, HLA mismatches can trigger donor-versus-recipient NK cell alloreactivity without causing GVHD, as they target hematopoietic cells sparing other body organs, making them ideal in the HaploSCT setting [74]. This concept was first observed in the TCD HaploSCT setting, where patients with a KIR mismatch had a lower incidence of relapse [72]. In both animal and clinical studies, it has been demonstrated that donor NK cells inhibit donor T cell proliferation and increase apoptosis, resulting in reduced severity and delayed progression of GVHD [75-77].

Several studies suggested a lower risk of relapse with donors who possess specific activating KIR genes, such as KIR2DS1, KIR2DS2, or the KIR "B" haplotype [76,78-80]. There is currently great interest in identifying HaploSCT donors with a KIR mismatch to possibly maximize the GVT effects and in exploring the potential benefit of using NK cells for adoptive cellular immunotherapy to prevent disease relapse, which has been used successfully in children with acute myeloid leukemia [81]. However, the major obstacle for NK cell therapy, especially in adult patients, is the relatively low number of NK cells that can be obtained from the donor, and much like with T cell therapy, in which a higher cell number proportional to the estimated number of tumor cells is needed, it is likely that higher numbers of NK cells are needed for effective NK cell therapy [82]. In addition, multiple studies have shown that NK cells generated early after transplantation have an immature phenotype and a relative lack of function [83-86]. To address these problems and increase the cytotoxic effect of NK cells, various ex vivo expansion methods have been developed and tested in preclinical and early clinical studies [59-63]. Choi et al. generated donor NK cells from the $CD3^+$ cell–depleted portion of

the mobilized leukapheresis product and expanded them using human IL-15 and -21. Expanded doses of NK cells up to $2 \times 10^8$/kg were then infused into 41 patients with hematologic malignancies who underwent HaploSCT after reduced-intensity conditioning containing busulfan, fludarabine, and antithymocyte globulin. The researchers observed no significant difference in the cumulative incidences of major transplantation outcomes when comparing them with 31 historical control patients who had undergone HaploSCT using the same conditioning regimen without high-dose NK cell infusion. However, a reduction in leukemia progression was seen in patients who received a high NK cell dose and the authors found that post-transplantation NK cell infusion was an independent predictor for less leukemia progression [63]. Although these results are encouraging, they are not conclusive of a beneficial effect in reducing relapse or improving survival; further studies are needed.

We are currently exploring infusion of ex vivo–expanded NK cells using the mb-IL21 method developed at MD Anderson Cancer Center in patients treated with a HaploSCT in a phase 1/phase 2 clinical trial that is evaluating the safety and efficacy of these NK cells to prevent disease relapse in patients with advanced myeloid malignancies when administered early after transplantation. Six patients were treated on study with escalating doses between $1 \times 10^5$ to $1 \times 10^7$/kg. All engrafted and no adverse effects of aGVHD were observed, compared with a recent published report in which aGVHD was a major complication after NK cell infusion, especially in unrelated donors [64].

## CONCLUSIONS

The field of HaploSCT has grown substantially over the past several years. A significant advantage of using haploidentical donors is the possibility of using cells obtained from the same donor and immune system, which represents a major opportunity of greatly enhancing the antitumor effects of the graft and potentially improving immunologic reconstitution, key components of a successful allogeneic hematopoietic stem cell transplantation.

## ACKNOWLEDGMENTS

*Financial disclosure:* All authors have no relevant financial relationships to disclose.

*Conflict of interest statement:* Some of technology described was advanced through research conducted at the MD Anderson Cancer Center by L.J.N.C. Both MD Anderson Cancer Center and L.J.N.C have a financial interest in ZIOPHARM Oncology, Inc. and Intrexon Corporation. On May 7, 2015, L.J.N.C was appointed the chief executive officer at ZIOPHARM. L.J.N.C is now a visiting scientist at MD Anderson, where he will continue to supervise the development of this technology. The rest of authors have no potential conflict of interest to declare.

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