Conflicting Impact of Alloreactive NK Cells on Transplantation Outcomes after Haploidentical Transplantation: Do the Reconstitution Kinetics of Natural Killer Cells Create These Differences?

Xiang-Yu Zhao, Ying-Jun Chang, Xiao-Jun Huang

Partially HLA-mismatched related, or HLA-haploidentical, donor stem cell transplantation (SCT) is a feasible therapeutic option for advanced hematologic malignancy patients who lack an HLA-matched related or unrelated donor. Natural killer (NK) cells, a major cell type of the innate immune system, express surface receptors that regulate potent effector functions, such as cytolytic activity and the release of cytokines, and play a central role in the inflammatory response and immunoregulation. Conflicting results have been reported regarding the impact of NK cell alloreactivity on the outcome of haploidentical SCT in leukemic patients. This review summarizes the heterogeneous clinical results and explains the underlying mechanisms with respect to the reconstitution kinetics of NK cells and the interactions between NK cells and T cells.

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INTRODUCTION

Family human leukocyte antigen (HLA)-mismatched/haploidentical transplantation is a feasible therapeutic approach for patients with lethal malignant hematologic diseases who lack an HLA-matched donor [1]. HLA mismatches could trigger donor versus recipient natural killer (NK) cell alloreactivity [2,3]. Clinical observations reveal a potential role for NK cell alloreactivity in reducing the risk of relapse in acute myeloid leukemia (AML) after HLA-haploidentical SCT, especially in the Perugia Bone Marrow Transplant Centre [4-6]. Furthermore, clinical investigations have demonstrated that alloreactive NK cell infusions are helpful in improving transplantation outcomes [7-9]. However, it is notable that the clinical success of this strategy has not been convincingly reproduced in every study. This might be a result of patient selection and different kinetics of NK cell reconstitution, including aspects related to an altered phenotype, increased expression of inhibitory receptors, and delayed cytotoxic function recovery. In recent years, we have successfully established a novel conditioning protocol that includes antithymocyte globulin followed by haploidentical hematopoietic stem cell transplantation (HSCT) without in vitro T cell depletion [10]. We have found that this protocol can achieve outcomes comparable to those obtained with HLA-matched transplantation [11]. We have also investigated the correlations between alloreactive NK cells and the transplantation outcomes of patients undergoing unmanipulated blood and marrow transplantation [12-16]. However, we have not been able to prove the beneficial effect of alloreactive NK cells in haploidentical unmanipulated blood and marrow transplantation without T cell depletion in vitro. Because of the conflicting results for alloreactive NK cells with respect to transplantation outcomes, more research is being focused on the reconstitution kinetics of NK cells to identify the underlying mechanism [12,15,17-24]. Based on currently published data and the heterogeneous clinical results, this review focuses on the underlying mechanisms with respect to the reconstitution kinetics of NK cells.

Conflicting Impact of NK Alloreactivity on Transplantation Outcomes from Different Haploidentical Models

NK cells can discriminate “self” from “nonself” through their inhibitory natural killer receptor
(NKR) expression [25]. The existence of alloreactive NK cells relies on the balance of the active and inhibitory signals between NK cells and their target cells. In biologic study of NK cells, there are at least three models that exist to define NK alloreactivity: a mismatch between the donor and recipient immunoglobulin receptor (KIR) ligands (ligand-ligand model) [4] as defined by Perugia’s group; recipients lacking KIR ligands for donor inhibitory KIR receptors (receptor-ligand model) [26,27]; or a mismatch between the donor and recipient KIR genes (gene-gene model) [28]. The Perugia Bone Marrow Transplant Centre developed transplantation from HLA haplotype-mismatched family donors to provide a cure for more patients [4-6]. Their series study using a KIR-ligand mismatch to define alloreactive NK cells demonstrates that HLA mismatches trigger donor versus recipient NK cell alloreactivity, which improves engraftment, protects from graft-versus-host disease (GVHD), and reduces relapse in AML patients. Following these clinical investigations, the beneficial roles of alloreactive NK cells were demonstrated in a mouse model of transplantation [5], showing that these cells can perform the following functions: (1) ablate AML cells, (2) kill recipient T cells, permitting a reduced toxicity conditioning regimen, and (3) ablate the recipient dendritic cells (DCs) that trigger GVHD, thus protecting the recipient from GVHD. Based on the beneficial roles of alloreactive NK cells, adoptive immunotherapy using NK cells has led to advances in graft engineering. Miller and colleagues [7] used haploidentical, related-donor NK-cell infusions in a nontransplantation setting to prove that haploidentical NK cell infusion is safe, that the cells can persist and expand in vivo, and that this approach may have a role in the treatment of selected malignancies when used alone or as an adjunct to HSCT. Passweg and colleagues [8] further demonstrated that purified donor NK-lymphocyte infusion is technically feasible and can consolidate engraftment after haploidentical stem cell transplantation (SCT). Remarkably, a pilot study conducted to determine the safety, feasibility, and engraftment of haploidentical NK cell infusions after an immunosuppressive regimen in 10 children with AML at first complete remission (CR1) recently showed that all patients had transient engraftment for a median of 10 days with limited nonhematologic toxicity and no evidence of GVHD. At a median follow-up time of 964 days, all the patients remained in remission. The 2-year event-free survival (EFS) estimate was 100% [9]. Taken together, these results suggest that alloreactive NK cells definitely provide favorable transplantation outcomes.

However, various conflicting results still exist between the role of alloreactive NK cells and clinical haploidentical transplantation outcomes from different centers. Nearly all haploidentical transplantation without in vitro T cell depletion failed to show the same result as the Perugia Bone Marrow Transplant Centre. Using the ligand-ligand model, Bishara and colleagues [29] demonstrated that in haploidentical mismatched stem cell allografts with partial T cell depletion in vitro, potential NK alloreactivity in the GVHD direction was associated with an increased incidence of severe GVHD and reduced patient survival but not with nonengraftment or leukemia relapse. Huang and colleagues [13] also demonstrated that KIR ligand mismatch is a strong risk factor for acute GVHD (aGVHD), relapse, and decreases overall survival (OS) under haploidentical unmanipulated blood and marrow transplantation. These results are directly contrary to the findings of Perugia’s group. When using the ligand-ligand model, Symons and colleagues [30] also failed to demonstrate the positive effect of alloreactive NK cells. However, defining alloreactive NK cells with the gene-gene model improved survival with inhibitory KIR gene mismatches. In addition, KIR haplotype B donors were found in patients who underwent nonmyeloablative, HLA-haploidentical bone marrow transplantation [30]. In contrast, Huang and colleagues [16] also failed to find improved survival in alloreactive NK cell donors undergoing haploidentical unmanipulated blood and marrow transplantation when using the ligand-ligand model or even the receptor-ligand model to define the alloreactive NK cells. Differences in GVHD prophylaxis and graft cellularity may explain these varied results. In Perugia’s haploidentical transplant protocol, T cell depletion is vigorous with stem cell inocula containing an average of $3 \times 10^6$ T cells/kg, compared with an average of $1.5 \times 10^8$ T cells/kg in our protocol. Furthermore, the significant adverse effect of the KIR ligand mismatch on the “high” T cell group and the lack of an effect on the “low” T cell group in aGVHD also prove that T cell dose plays an important role in the allograft [13] that might affect NK cell function and KIR expression in vivo, as reported in unrelated HSCT. Therefore, the available data suggest that a benefit of NK cell alloreactivity could be obtained if specific strategies of haploidentical transplantation, including high stem cell doses, extensive T cell depletion, and no postgrafting immune suppression, are used.

**Similar Reconstitution Patterns of NK Cells following Different Haploidentical Models**

Following the above rules, including high stem cell doses, extensive T cell depletion, and no postgrafting immune suppression in haploidentical SCT, Nguyen and colleagues [18] also failed to find the graft-versus-leukemia (GVL) effect. These results were obtained despite the mismatch in the KIR ligand in the GVH direction in 8 of 10 patients. Therefore, as they are the first cells to recover after autologous or
allogeneic BM or peripheral blood stem cell (PBSC) transplantation, the subsequent immune reconstitution of NK cells remains a major concern. In addition, the recovered NK cells would be more important with a sustained effect on GVHD and GVL after the transplantation. In a study by Ruggeri and colleagues [4,6], NK cell activity was correlated with reduced relapse and superior OS for myeloid malignancies. This conclusion was based on the finding of an increased frequency of alloreactive NK cells in patients receiving transplants from donors possessing an inhibitory KIR ligand that was absent in the recipient. These high frequencies of donor NK clones could kill the target cells of the recipient in 8 of the 14 recipients during the first 3 postengraftment months. However, in a study by Nguyen and colleagues [18], NK cells were blocked at an immature state that was characterized by phenotypic features and impaired functioning, which may affect transplantation outcome. Similar to the results of Nguyen et al., nearly all phenotypical studies of NK subsets found an immature phenotype of NK cells after transplantation among the haploidentical transplantations regardless of the presence of in vitro T cell depletion with nonmyeloablative or myeloablative conditioning [6,12,15,17-21,23,24,31,32]. The reconstitution of NK cells was rapid but accompanied by skewing of cell subsets, mainly toward CD56\textsuperscript{bright}. Indeed, the significant deficiency of “cytotoxic” CD56\textsuperscript{dim} NK cells was detectable up to 3 months after transplantation. Despite regulation by the phenotype, the function of NK cells is also regulated by the balance of activating and inhibitory signals transmitted by different cell surface receptors. Therefore, the expression of activating NKRs, such as NKP46, NKP44, NKP30, and NKG2D, as well as inhibiting NKRs, such as CD158a, CD158b, CD158e, and NKG2A, is essential for NK cell activation. Overall expression of inhibitory NKRs and activating NKRs was reduced, whereas CD94/NKG2A expression was increased. NKG2A recovery was inversely correlated with CD158b recovery in the year following transplantation. This altered phenotype, which includes more CD56\textsuperscript{bright} and less CD56\textsuperscript{dim} NK cells, altered CD94/NKG2A expression. Activating or inhibiting NKR expression during early reconstitution showed lower levels of in vitro NK cell cytotoxicity after haploidentical transplantation [6,12,15,17-21,23,24,31,32]. The blockade of CD94/NKG2A restored lysis against the AML blasts expressing HLA-E, which is the ligand for CD94/NKG2A [33]. However, these studies reflect the overall NK cell phenotype and function rather than the phenotype of the individual alloreactive NK cells. In general, the degree of cytolytic activity correlates with the size of the phenotypically defined alloreactive NK cell subsets. For patients undergoing haploidentical HSCT, the size of the “alloreactive” NK cell population present in potential donors (eg, the parents) may be important for optimal donor selection. It is crucial to identify this population in the recipient post-HSCT to assess whether and how it is generated in the allogeneic environment of the recipient and whether it persists over time.

**Does Individual “Alloreactive” NK Cell Reconstitution Govern the Haploidentical Transplantation Outcomes?**

Alloreactive NK cells are characterized by the expression of KIRs specific for the KIR-ligand mismatch and by the lack of other inhibitory receptors specific for the HLA-class I alleles of the patient [23,24]. Thus, to assess NK alloreactivity in haplo-HSCT, it is necessary to analyze donor and recipient HLA-class I and donor KIR genotypes. In addition, the phenotypic analysis of KIR and CD94/NKG2A expressed by donor NK cells can further define the size of the alloreactive NK subset. Finally, functional assays, based on the ability to kill appropriate target cells, provide precise information on the degree of alloreactivity of given NK cell populations.

Using appropriate combinations of monoclonal antibodies (mAb), multicolor flow cytometric analysis could distinguish between certain activating and inhibitory NKRs, making it possible to identify different groups of alloreactive NK cells. KIR2DL1 recognizes HLA-C alleles that have C2 specificity (eg, Cw2, Cw4), whereas it does not react with C1+ cells (eg, Cw1, Cw3). Accordingly, KIR2DL1+ cells kill C1/C1 but not C2+ leukemias. KIR2DL2/3 recognizes C1 alleles, and it can also bind with lower affinity to C2. Therefore, C1+ leukemias are resistant to KIR2DL2/3+ NK cells, whereas C2/C2 leukemias are lysed only partially. KIR3DL1+ recognizes HLA-B and HLA-A alleles carrying the Bw4 supertypic specificity. Thus, Bw4+ leukemic blasts are resistant to KIR3DL1+ NK cells, whereas Bw4− leukemias are susceptible. The KIR2DS1 activating receptor recognizes the C2 specificity.

Thus far, 2 studies have investigated the reconstitution kinetics of alloreactive NK cells after haplo-HSCT. Vago and colleagues [23] analyzed the reconstitution of alloreactive single-KIR NK cells after haploidentical CD34\textsuperscript{+} selected HSCT for high-risk hematologic malignancies. The final graft product contained a median of $11.3 \times 10^6$ CD34\textsuperscript{+} cells/kg, that is, it was extensively T cell-depleted (median, $1.07 \times 10^4$ CD3\textsuperscript{+} cells/kg). Fifty-three patients received a fully myeloablative conditioning regimen, including antithymocyte globulin (ATG) Fresenius at a total dose of 25 mg/kg. Three patients underwent a second salvage HSCT after the rejection of the first transplant; they received immune-modulating conditioning that included thymoglobulin (6 mg/kg total
Impact of Alloreactive NK Cells on Transplantation Outcomes

In consideration of the extensive T cell depletion, patients did not receive any posttransplantation pharmacologic GVHD prophylaxis. Mature receptor reconstitution required at least 3 months. Alloreactive donor NK cells are defined by the expression of a single KIR but not the other KIRs or CD94:NKG2A, whose ligand is missing in the patient. These alloreactive donor NK cells have been cloned from the peripheral blood of patients in the first 3 to 4 months after haploidentical HSCT but are difficult to isolate at later time points. At this time point, the supposedly alloreactive, single-KIR+ NK cells were not yet fully functional. The frequency of these cells was highly variable; it is independent of predicted NK alloreactivity and below 1% in the 3 of 6 alloreactive patients studied. The recovery of functional activity comparable to donor levels in 5 analyses of patients studied more than 2 years after HSCT suggests that acquisition of the effector function is eventually achieved but is a slow process that lags behind the recovery of phenotypic maturity. Therefore, it was easy to postulate that these alloreactive NK cells can hardly have an antileukemia effect during early transplantation. The impact on clinical outcome of NK alloreactivity predicted by the ligand-ligand model was assessed in a retrospective analysis of 56 haploidentical transplantations performed for high-risk malignancies in this study. In line with the delayed reconstitution of alloreactive NK cells after haplo-HSCT, no clinical benefit of predicted NK alloreactivity was observed in the total cohort of 56 patients. Therefore, the kinetics and limits of NK-cell differentiation from purified haploidentical hematopoietic stem cells were evaluated in vivo, and the findings suggest that NK cell antileukemic potential could be best exploited by the infusion of mature single-KIR+ NK cells selected from an alloreactive donor.

Soon afterward, Pende and colleagues [24] analyzed donor-derived alloreactive NK cells in pediatric patients with leukemia who were given haplo-HSCT. The median number of CD34+ cells and of CD3- cells infused/kg of recipient body weight was 23 × 10^6 (range: 10.6-41.2) and 5 × 10^3 (range: 0.5-35), respectively. All patients were given ATG before the allograft to minimize the risk of graft failure. No patient was given posttransplantation pharmacologic immune suppression. This study showed that donor-derived alloreactive NK cells are generated and can persist for years in haplo-HSCT recipients. KIR2DL2/3+ NK cells can barely distinguish between C1+ and C2+ target cells, and their alloreactivity is, in most cases, dependent on the coexpression of KIR2DS1, which can directly recognize C2 alleles on leukemia cells. Remarkably, among the C1-mismatched pairs, all patients given haplo-HSCT from donors expressing KIR2DS1 (ie, 4 of 8) are alive and in complete remission, whereas fatal relapses occurred in 3 of 4 recipients transplanted from donors lacking this activating KIR. This finding suggests the clinical relevance of KIR2DS1-mediated recognition of leukemia. Furthermore, in NK cells derived from C1/C2 or C1/C1 donors, activation via KIR2DS1 may also overcome the KIR2DL2/3-mediated inhibition, resulting in efficient lysis of C2/C2 leukemias. In addition, KIR2DS1 can overcome the CD94/NKG2A-mediated inhibition, again resulting in the killing of C2/C2 leukemias. Thus, the expression of KIR2DS1 may result in NK cells that are endowed with alloreactivity and allow a more precise definition of the size of the alloreactive NK cell subset.

Although both of these haploidentical transplantation models were CD34+ selected and relied on T cell depletion without immune suppression after haplo-HSCT, the phenotype and function reconstitution kinetics of the alloreactive NK cells were absolutely different, and the cells therefore provided different clinical benefits. Quantitative analyses should be performed in other retrospective studies to identify the number of alloreactive NK cells required for a relevant clinical role, especially in haplo-HSCT without T cell depletion in vitro.

Given the alloreactive NK cell phenotype and functional reconstitution after haplo-HSCT, the question arises as to why donor NK cells undergoing maturation in the mismatched recipient can develop into alloreactive NK cells that are capable of killing leukemia cells, as they express KIRs that are not engaged by the HLA-class I alleles of the patient. The solution to this question will involve issues of NK education after transplantation. The process of repertoire shaping may thus be regulated by additional mechanisms to limit the frequency of inappropriate cells by deletion or by induction of inhibitory receptors that recognize self-ligands.

Does NK Cell Education/Licensing after Transplantation Ultimately Occur in the Donor or Recipient?

During maturation, NK cells were shown to require the recognition of self-major histocompatibility complex (MHC) class I to acquire full functionality, a phenomenon referred to as “licensing” or “education” [34]. A few NK cells lacking MHC-specific inhibitory receptors can also be generated, but they would remain virtually anergic or hyporesponsive. Significant debate exists over the proposed mechanisms by which NK receptor expression coordinates with the acquisition of function and titration of responsiveness [35–45]. It is considered that NK cell education must occur to permit the acquisition of function. However, there has been some controversy in the literature as to whether licensing occurs in the donor or the recipient. So far, there is no relative literature about
NK cell education after haploidentical transplantation. The available literature describes experiments that are in the field of basic research or following HLA-matched or unrelated transplantation with T cell depletion in vitro [34-45].

Thus far, 3 studies have investigated the education or licensing of alloreactive NK cells after HLA-matched or unrelated-HSCT with or without T cell depletion [37,40,45]. In T cell-depleted, HLA-matched, KIR-mismatched bone marrow transplants (in which not all donor-derived NK cells are inhibited by the recipient HLA or educated by donor or recipient HLA), the number of inhibitory KIR-HLA mismatches (ie, missing inhibitory ligands in the recipient) correlates with positive outcomes, including fewer leukemic relapses and improved graft acceptance [40]. From 16 T cell-depleted HSCT donor-recipient pairs, Hsu and colleagues [40] show that unlicensed, donor-derived NK cells in the bone marrow recipient (ie, NK cells expressing inhibitory KIR recognizing non-self HLA class I ligands) express high levels of interferon (IFN)-γ ex vivo and are competent to kill target cells, indicating that they are activated effector cells. However, donor-derived NK cells that are licensed (expressing inhibitory KIR for self-HLA class I ligands) are hyperresponsive early post-HSCT. Thus, it was suggested that NK cells early in the posttransplantation phase do not behave strictly according to the tenets of NK licensing, where only NK cells expressing inhibitory KIR for self-HLA class I molecules are functionally competent. Instead, these findings support the possibility that NK cells become activated upon recognition of a lack of class I ligand for any inhibitory KIR (missing ligand) in the first 3 to 6 months after HSCT, restricting themselves gradually to a tolerized state in which they become activated only upon recognition of a lack of self-class I ligands (missing self). However, Malmberg and colleagues [45] found no influence of HLA and KIR genotypes on DFS in the T cell-replete SCT setting. These clinical data were supported by a longitudinal functional evaluation of NK cell repertoires during the first 6 months after transplantation, revealing that educated NK cells expressing inhibitory KIRs for self-HLA class I ligands responded better at all examined time points than uneducated NK cells lacking self-specific receptors. NK cells expressing non-self KIRs remained tolerant at all time points during the first 6 months after transplantation, which was in direct contrast to the findings of Hsu and colleagues [40]. Meanwhile, Dulphy and colleagues [37] investigated NK cell education after KIR-ligand-matched or -mismatched unrelated HSCT. In line with Malmberg and colleagues [45], it was found that after KIR-ligand-matched HSCT, the NK cell subset responsiveness hierarchy was consistent with the HLA genotype. After KIR-ligand-mismatched HSCT, the NK cell education process durably reiterates the responsiveness pattern determined by the HLA ligands of the donor. This finding strongly, albeit indirectly, supports a hematopoietic origin for the cellular partner in NK cell education. In view of these data, the question arises as to how donor NK cell precursors undergoing maturation in the mismatched recipient can give rise to alloreactive NK cells (ie, effector cells capable of killing leukemia cells). A good explanation might be the infusion of “megadoses” of CD34 cells that could provide a bone marrow (BM) microenvironment that is predominantly of the donor type. Under these conditions, the process of NK cell education would be similar to that occurring in the donor and would allow the generation of “licensed” alloreactive NK cells. The reason for the different results in NK licensing between Malmberg et al. [45] and Hsu et al. [40] might be the presence of T cells in the graft and the use of posttransplantation immunosuppressive treatment in the work of Malmberg and colleagues [45]. Further supporting this model is the observation that tolerance is acquired after HSCT in haploidentical transplants with KIR ligand incompatibility.

**Do T Cells in the Allograft Delay NK Cell Reconstitution during Haploidentical Transplantation?**

Recent studies indicate that adaptive immune cells, such as dendritic or T cells, play a role in NK cell differentiation and activation. Considering the diverse reconstitution kinetics of alloreactive NK cells and the different associations with clinical outcomes after haplo-HSCT, some authors focus on the effect of T cells on NK cell reconstitution after transplantation. Cooley and colleagues [46] showed in unrelated bone marrow transplantation with either unmanipulated or T cell-depleted transplants that the presence of T cells in the graft altered the clinical outcome. The presence of T cells was correlated with increased GVHD and decreased KIR expression. However, in the haplo-HSCT without T cell depletion or with partial T cell depletion, the effect of T cells on NK cell reconstitution was different. Nguyen and colleagues [18] found that the NK cells generated after haploidentical SCT were characterized by specific phenotypic features and impaired functioning. Therefore, they observed an absence of the GVL effect in 10 patients with AML who received haplo-mismatched SCT, despite the mismatched KIR ligand in the graft-versus-host (GVH) direction for 8 of 10 patients. By using 2 groups of patients, 1 undergoing partial T cell depletion (pTCD) and the other undergoing extensive T cell depletion (eTCD), Nguyen [19] showed that the persistence of mature donor T cells in the graft seems to enhance NK differentiation after haploidentical SCT. After a pTCD transplant, the newly generated NK cells rapidly acquire phenotypes and functions similar to those found in the donors, in contrast to
the NK cells generated after an eTCD transplant, which remain completely immature. Despite the strong aGVHD reaction, pTCD patients with T cells present during SCT had a better clinical outcome than patients with eTCD transplants. In addition, the frequency of CD3⁺CD56⁺bright and NKG2A⁺ NK cells was much lower in pTCD than in eTCD patients after transplantation. In addition, the level of cytotoxicity against primary haplo-mismatched blasts was significantly more pronounced after pTCD than eTCD transplants. These findings strongly suggest that mature donor T cells in the graft may play a key role in NK cell differentiation in vivo after haplo-HSCT. However, Huang and colleagues [15] found that following unmanipulated HLA-haploidentical/mismatched blood and marrow transplantation, the doses of the T cell subgroups CD4⁺ and CD8⁺ were inversely associated with CD158a and CD158e expression during the 2 months following transplantation. Patients with grades II-IV of aGVHD or who received “high” doses of T cells (>1.37 × 10⁸/kg) showed delayed recovery of KIRs during the 2 months following transplantation. However, the number of NK cells and the reconstitution kinetics of the subsets are similar to those reported by Nguyen and colleagues [12,18]. When comparing these results with the results demonstrated by Nguyen and colleagues, which showed that 7 of 10 patients relapsed and 11 died of 10 died, the clinical outcomes of the study by Huang and colleagues [15] are encouraging. Only 3 patients from a total of 43 relapsed, and 11 died of transplantation-related complications after haploidentical transplantation without in vitro T cell depletion. Moreover, the early rapid recovery of circulating CD56⁺bright NK cells was correlated with better survival in the study by Huang and colleagues [15]. However, the frequency of CD3⁺CD56⁺bright and NKG2A⁺ NK cells was much lower in pTCD than in eTCD patients after transplantation. In addition, the cytotoxicity against primary haplo-mismatched blasts was significantly more pronounced after pTCD than after eTCD transplants in the report of Nguyen et al. Considering the communication among CD56⁺bright NK cells, DCs, and T cells and the rapid T cell reconstitution in unmanipulated HSCT compared with CD3⁺ selected hematopoietic stem cell transplantsations (HSCTs) [47-49], we suggest that CD56⁺bright NK cells might play important immunoregulatory roles after unmanipulated haplo-HSCT if the T cell reconstitution is sufficient. This would help the cytotoxic function recovery of CD56⁺dim after transplantation.

The effect of alloreactive NK cells undergoing different haplo-HSCT varies according to the different effects of the conditioning regimen, different levels of T cell depletion, whether immune suppression is used after transplantation, the actual alloreactive NK cell reconstitution, and the interaction of the NK cells with DCs. Further investigation of the interaction of alloreactive NK cells with immune cells (NK, DC, and T cells) after haplo-HSCT may help to reveal the diverse effects of alloreactive NK cells undergoing different haplo-HSCT.

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