HSPC The Open Access Publisher

JSCTT JOURNAL OF STEM CELL THERAPY AND TRANSPLANTATION
ISSN 2577-1469

Editorial

The rising role of natural killer cells in patients with malignant hematological disorders and in recipients of hematopoietic stem cell transplantation

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Submitted: 23 September 2019
Approved: 30 September 2019
Published: 01 October 2019

How to cite this article: Al-Anazi KA. The rising role of natural killer cells in patients with malignant hematological disorders and in recipients of hematopoietic stem cell transplantation. J Stem Cell Ther Transplant. 2019; 3: 023-027.

DOI: dx.doi.org/10.29328/journal.jsctt.1001015

Introduction

Natural killer (NK) cells, the third population of lymphoid cells, comprise 5%-25% of peripheral blood (PB) lymphocytes and represent the first line of defense against infections and tumors [1-7]. They can be derived from: bone marrow, PB, cryopreserved umbilical cord blood (UCB), human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and various cell lines such as NK-92 and KHYG-1 [1]. NK cells; which have been divided into cytotoxic, tolerant, and regulatory subsets; are classified into: (1) naïve CD56 ^{bright} CD 16 ^{dim} CD 3 ^{dim} cells, (2) mature CD56 ^{dim} CD16 ^{bright} CD3 ^{dim} cells, and (3) lymphoid tissue-resident CD69+/CXCR6+ NK cells [1,2,8-11]. Although NK cells have been traditionally considered as part of the innate immune system, they have recently been shown to exhibit many of the features associated with adaptive immunity [8,12]. The functions of NK cells which are influenced by several cytokines include: elimination of infected cells, destruction of cancer cells, reducing the incidence of graft versus host disease (GVHD) following hematopoietic stem cell transplantation (HSCT), and regulation of pregnancy outcome [10,11,13]. NK cell function is finely tuned by activating and inhibitory receptors that recognize both foreign and self-antigens expressed by NK cell-susceptible targets [7,14]. Activated NK cells interact with dendritic cells (DCs) and mesenchymal stem cells (MSCs) and the complicated crosstalks between NK cells, MSCs, and DCs may alter the functions of any of the 3 cell types [15-27].

NK cells are attractive candidates for adoptive cellular therapy in patients with hematologic malignancies (HMs) and solid tumors, as well as in recipients of allogeneic HSCT by enhancing graft versus leukemia (GVL) effect without causing GVHD [1,28-34]. Approximately 10%-20% of NK cells remain unlicenced and functionally hyporesponsive due to lack of receptors for self-major histocompatibility complex (MHC). However, unlicenced NK cells become alloreactive after adoptive transfer into recipients of HSCT [7]. NK cells express inhibitory inhibitory killer cell immunoglobulin-like receptors (KIRs) to recognize self - HLA (human leukocyte antigen) class I molecules and provide inhibitory signals to preclude killing of the target cells [8].

Multiple myeloma (MM) is characterized by gradual immune dysregulation and myeloma cells exhibit specific immunoevasive strategies to circumvent and attenuate NK cell function [32,35]. Transformed plasma cells in MM are susceptible to NK cell-mediated killing by engagement of tumor ligands for activating receptors or missing self recognition [32,33,35]. Despite the advancements in novel therapies and autologous HSCT, MM remains an incurable and difficult-to-treat HM due to drug resistance predisposed to by the immunosuppressive microenvironment and clonal evolution thus making allogeneic HSCT the only potentially curative therapeutic modality due to its potent graft versus myeloma effect [31,35]. In patients with MM, NK cells have been used in several trials in the setting of autologous as well as allogeneic HSCT as NK cells elicit cytotoxic effects against MM cells and as KIR-ligand mismatch may improve the outcome of allogeneic HSCT [31,32,36-38]. NK cell killing of tumor cells in MM can

be augmented by: check point inhibitors (CPIs), therapeutic antibodies such as daratumumab, immunomodulatory agents such as lenalidomide, indoleamine 2,3 dioxygenase inhibitors, and adoptive transfer of unmanipulated or chimeric antigen receptor (CAR)-engineered NK cells [30,35].

Allogeneic HSCT has revolutionized the treatment of HMs, but the use of this potentially curative therapy is limited by: GVHD, infections and relapse of the primary disease [29,39-41]. NK cells are the first subset of donor-derived lymphocytes to reconstitute after HSCT thus they may protect against relapse in the early months following HSCT by providing GVL effect without causing GVHD [1,39,42]. Although the initial studies on the use of autologous NK cells were disappointing, the use of allogeneic NK cells has resulted in favorable outcomes in both transplant and non-transplant settings and this led to the advancement of NK immunotherapy over the last decade [1].

Donor NK cells play significant roles in: promotion of hematopoietic engraftment in recipients of HSCT, preventing relapse of HM post-allogeneic HSCT by mediating GVL effects, and regulation of GVHD by suppressing alloreactive T-cell responses [39]. Enhancement of GVL without increasing the incidence of GVHD can be achieved by: optimal donor selection, optimal conditioning therapy, administration of GVHD prophylaxis, and administration of T-cells and donor-derived NK cells which are amenable to ex vivo manipulation and clinical manufacture [40]. Separating GVL effects from GVHD is of special interest in non-specific cell-based immunotherapy which may eradicate molecular disease and prevent relapse following allogeneic HSCT particularly when leukemia burden is low [28,43]. The recognition of missing-self on target cells is crucial for promoting NK cell-mediated GVL effects [8]. NK cells have a central role in tumor-cell surveillance but leukemic cells have great capacity to escape NK cell recognition and killing thus limiting the use of NK cells in immunotherapy [44]. Augmentation of T-cell alloreactivity may be influenced by NK cells in recipients of T-cell deleted allografts, while immunosuppression with sirolimus and expansion of T-regulatory cells may decrease the incidence of acute GVHD by suppressing the development of T-cell mediated alloreactivity [29,45,46]. NK cell infusions derived from PB and UCB contain contaminating T-cells whose stimulation by cytokines that are produced by NK cells may trigger GVHD in vivo thus limiting the safety and efficacy of NK cell infusions in allogeneic HSCT. However, NK cells obtained from iPSCs, hESCs, and NK cell lines are free of contamination with T and B cells thus offering alternative sources of NK cells that can be used in adoptive immunotherapy [47]. Unfortunately, non-specific immunotherapy is dependent on repeat administrations [28].

Invariant NK T (iNKT) cells that are derived from HSCs protect against GVHD and cancer, while cytokine-induced killer (CIK) cells have demonstrated cytotoxicity against a variety of malignant or leukemic cells with no or only minor effects on normal hematopoietic progenitor cells [28,41,48,49]. Allogeneic CIK cells retain the ability to produce GVL effect while generating minimal GVHD [41]. CIK cell infusion comprises a safe and a feasible novel immunotherapeutic approach that targets relapse or minimal residual diseasae following HSCT for HMs [41,50]. In a recently published study that included 91 patients with various HMs relapsing after allogeneic HSCT; conventional donor lymphocyte infusion (DLI) given to 55 patients was compared to CIK given to 36 patients, the outcome of CIK therapy was superior to that of DLI with higher overall survival, less relapses, and less acute GVHD [28]. However, optimal timing and dosage of NK cells need to be determined [50].

The use of post-transplant cyclophosphamide (PTC) as GVHD prophylaxis has revolutionized haploidentical HSCT although PTC eliminates most mature donor NK cells infused in the graft including alloreactive NK cells [51]. NK cell recovery after haploidentical HSCT is greatly influenced by other subsets of immune cells and by drugs used in the post-transplant period [51]. NK cell immunotherapies have the potential to significantly enhace the ability of conventional therapies to eliminate acute myeloid leukemia (AML) after HSCT [43]. Initial reports of haploidentical HSCT in AML patients showed that alloreactive NK cells had favorable effects on relapse and survival by promoting engraftment, enhancing GVL effect and reducing the incidence of GVHD. However, subsequent studies have shown either no defference in the incidence of GVHD or adverse outcomes related to GVHD, infections and disease relapse. Therefore, selecting the most appropriate alloreactive NK cell model and selective expansion of a particular NK cell subset may become vital in restoring NK cell function in the post-HSCT period [52]. Fortunately, acquisition of large numbers of mature and functional NK cells that can be derived and differentiated from UCB-$CD3^+$ HSCs is easily accessible, but optimal clinical protocols for NK cell therapies in leukemia and other cancers are still lacking [53]. Strategies that can be employed to improve NK cell immunotherapies include: optimal donor selection; combination with cytokine stimulation or immune CPIs; drugs that enhance NK cell antitumor activity or sensitize malignant cells to NK cells; bispecific or trispecific killer engagers; adoptively infused allogeneic NK cells in haploidentical transplantation; advancing the field of ex vivo manipulation and genetic engineering; priming of NK cells; and using extracellular vesicles derived from NK cells [1,8,44,45,54-56].

HMs such as: acute lymphoblastic leukemia, chronic lymphocytic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma are associated with immune deficiencies including NK cell dysfunction. Consequently, therapeutic strategies aimed at restoring NK cell function in these HMs are evolving [57-61]. Although the majority of clinical trials involving NK cells have initially focused on AML and MM, trials on the use of NK cell immunotherapies to treat other HMs as well

as solid tumors are rapidly expanding. However, certain limitations have to be resolved, quality and safety measures should be taken into consideration, and preparatory as well as therapeutic protocols for specific subsets of NK cells need to be implemented.

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