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Review

Natural Killer Cell-Mediated Cellular Therapy of Hematological Malignancies

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ABSTRACT

Our understanding on the mechanisms of graft *versus* tumor/leukemia (GvT/GvL) and graft *versus* host (GvH) effects has tremendously evolved within the past decades. During the search for a mechanism that augments GvT/GvL without increasing GvH effects, natural killer (NK) cells have clearly attracted attention. Current approaches of NK cell immunotherapy for hematological malignancies involve using methods for *in vivo* potentiation of NK cell proliferation and activity; adoptive transfer of NK cells from autologous and allogeneic sources [cord blood mononuclear cells, peripheral blood mononuclear cells, $CD34^+$ stem cells] and NK cell lines; and genetic modification of NK cells. Several cytokines, including interleukin-2 and interleukin-15 take part in the development of NK cells and have been shown to boost NK cell effects both *in vivo* and *ex vivo*. Monoclonal antibodies directed towards certain targets, including stimulating CD16, blockade of NK cell receptors, and redirection of cytotoxicity to tumor cells via bi- or tri-specific engagers may promote NK cell function. Despite the relative disappointment with autologous NK cell infusions, the future holds promise in adoptive transfer of allogeneic NK cells and the development of novel cellular therapeutic strategies, such as chimeric antigen receptor-modified NK cell immunotherapy. In this review, we summarize the current status of NK cell-related mechanisms in the therapy of hematologic malignancies, and discuss the future perspectives on adoptive NK cell transfer and other novel cellular immunotherapeutic strategies.

1. INTRODUCTION

Our understanding on the mechanisms of graft *versus* tumor/leukemia (GvT/GvL) and graft *versus* host (GvH) effects has significantly evolved in the past decades. During the search for a mechanism that augments GvT/GvL without increasing GvH effects, natural killer (NK) cells have clearly attracted attention. These cells, which are activated to kill in the absence of a prior antigen sensitization, were initially identified in 1964 [1,2]. Subsequently, the discovery of killer immunoglobulin-like receptors (KIRs) and the description of the "missing self" hypothesis in the early 1970s enabled us to understand the success behind haploidentical hematopoietic stem cell transplantations (haplo-HSCT) [3–8]. In our era of targeted therapies, natural killer (NK) cells and their receptors are considered as promising targets within the context of pharmaceutical and clinical research. The future holds promise in adoptive transfer of NK cells and the development of novel cellular therapeutic strategies, such as chimeric antigen receptor (CAR)-modified NK cell immunotherapy. In this review, we summarize the current status of NK cell-related mechanisms in the therapy of hematologic malignancies and discuss the future perspectives on adoptive NK cell transfer and other novel cellular immunotherapeutic strategies (Table 1).

2. DEVELOPMENT AND IMMUNOBIOLOGY OF NK CELLS

NK cells originate from a common lymphoid progenitor in the bone marrow (BM), and initially differentiate from a pre-NK precursor into a NK precursor. The receptors for interleukin-15 (IL-15), which stimulates NK cell development and survival, are expressed from the NK precursor stage onwards [9]. Differentiated NK cells express the specific CD56 cell marker. In flow cytometric analysis, immature NK cells are observed as CD56 bright, CD16 (-), and do not express KIRs. These cells are mainly localized in secondary lymphoid tissues and constitute 2%–10% of NK cells. They proliferate in response to interleukin-2 (IL-2) and exert immunomodulatory effects, primarily via interferon gamma (IFN-γ), tumor necrosis factor-α (TNF-α), and granulocyte-macrophage colony-stimulating factor (GMCSF) production [10,11]. Mature NK cells, which are CD56 dim, are predominantly found in the circulating blood and are responsible for cytotoxic effects. These are CD56(+)/16(+), CD3(-) large granular lymphocytes, and constitute only 10%–15% of circulating lymphocytes in healthy individuals [12,13].

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Table 1 | General characteristics of NK cell products.

	Source(s)	Processing Method(s)	Advantage(s)	Disadvantage(s)	Potential Use(s)
Autologous NK cells [9, 42, 58–60]	Recipient's peripheral blood	CD3 depletion Optional: CD56 selection Optional: incubation with cytokines (IL-2, IL-15 or combinations) Optional: expansion in feeder	– Ease of collection – Minimally effective in monotherapy	Difficulty in yielding an adequate cell number (may be overcome with expansion with cytokines; but purity may decrease)	– May be used in combination with other therapies, such as anti-KIR antibodies
Allogeneic NK cells [61–65]	Donor's peripheral blood	CD3 depletion Optional: CD19 depletion Optional: CD56 selection Optional: incubation with cytokines (IL-2, IL-15 or mixture) Optional: expansion in feeder	Better GvL/GvT effect due to alloreactive NK cells	– Risk of GvHD – Risk of passenger lymphocyte syndrome and EBV reactivation (may be reduced via CD19 depletion)	To optimize the results of allogeneic stem cell transplantation (clinical outcomes in AML are superior if given before or within 2 weeks after HSCT)
CB-derived NK cells [35, 67–69]	Umbilical cord blood units	Co-culturing systems and cytokine combinations	Alternative NK cell source	– Difficulty in yielding an adequate cell number – Lower activity due to lower expression of KIRs (may be overcome partially by *ex vivo* expansion)	Various hematologic malignancies and solid tumors; alone or in combination with other immunotherapies
BM-derived NK cells [35, 67–69]	Donor's bone marrow harvest	Co-culturing systems and cytokine combinations	Alternative NK cell source	Difficulty in yielding an adequate cell number	– Various hematologic malignancies and solid tumors; alone or in combination with other immunotherapies – Potential for commercial use
NK cells obtained from hESC or iPSC [35, 70, 71]	hESC or iPSC	Complex systems requiring strict GMP criteria	– May enable to produce large scales of universal NK cells lacking KIR expression – Homogenous product	Requires complex processing	– Various hematologic malignancies and solid tumors; alone or in combination with other immunotherapies – Potential for commercial use
NK cell lines [35, 79, 80]	– Malignant cell clones – Seven established lines: NK-92, YT, NKL,HANK-1, KHYG-1,NK-YS, and NKG	Complex systems requiring strict GMP criteria	– Easy to expand – Uniform and reproducible – Can be used "off-the-shelf"	– Concerns about *in vivo* persistence and the lack of CD16 expression – Limited clinical efficacy	– Generally used in preclinical research – Only NK92 lines are approved for clinical research
CAR-NK cells [9, 58, 81–85]	NK cell lines, PB-derived NK cells, and stem cell-derived NK cells	Genetical engineering of NK cells to express recombinant CARs	– Can be used "off-the-shelf" – Very low risk of GvHD – Intrinsic cytotoxicity may prevent disease escapedue to downregulation ofCAR target antigens. – Long-term side effects and cytokine release syndrome are less likely due to limited *in vivo* persistence	– Questions regarding the optimal NK source, strategies for recruitment, activation, and costimulation need further research	– Potential for commercial use – Preclinical and clinical studies ongoing

NK cells: Natural Killer cells; CD: cluster of differentiation; IL: interleukin; GvL: graft *versus* leukemia; GvT: graft *versus* tumor; GvHD: graft *versus* host disease; EBV: Epstein-Barr virus; AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplantation; CB: cord blood; BM: bone marrow; hESC: Human embryonic stem cells; iPSC: Induced pluripotent stem cells; GMP: good manufacturing practice; KIR: Killer-cell immunoglobulin-like receptor; CAR: Chimeric antigen receptor.

2.1. KIRs and Other NK Cell Receptors

The activity of NK cells is regulated via inhibitory and activating signals mediated through KIRs, which are classified as inhibitory (iKIR) or activating (aKIR) [14–17]. NK-cell self-tolerance is assured by an iKIR signal triggered via the recognition of a specific KIR-ligand, which is a major histocompatibility complex (MHC) class I molecule [18]. According to the "missing self" (KIR-ligand incompatibility or KIR epitope mismatch) hypothesis, NK-cell alloreactivity is defined as the absence of a donor iKIR-ligand in the recipient [6,19]. This alloreactivity has been shown to augment the GvL effect and improve outcomes after haplo-HSCT [8,20]. However, further studies in other allogeneic HSCT settings, including unrelated mismatched, cord blood (CB), and matched sibling transplants yielded conflicting results [21–24]. Although NK cells are known to exert little or no GvH effects, recent evidence suggests that posttransplant residual recipient NK cell activity in the host *versus* graft (HvG) direction may lead to graft destruction, and end up with an increased relapse risk [25,26]. However, these observations strongly depend on the complex interaction of NK cells with

other immune effector cells, mainly T-cell subsets, which are variably modified by graft type, conditioning regimen, and/or immunosuppression method.

The biology of aKIRs is more complex, and their signaling mechanisms and interactions with iKIRs are yet poorly understood [27,28]. In addition to iKIR and KIR ligand mismatch-mediated signals, NK cell activation also requires activatory signals from various receptors including natural cytotoxicity receptors (NCRs), DNAX accessory molecule-1 (DNAM-1), and NK group 2 member D (NKG2D) [29,30]. The binding of NKG2D receptor on the NK cell to the stress-induced ligands on tumor cells, such as MHC class I chain-related gene A and B (MIC A/B) and UL16-binding proteins (ULBP1-6) promotes an activating signal. The recognition of CD112 (Nectin-2) and CD155 (PVR) by DNAM-1 is another important activating pathway. The NCRs including NKp30, NKp44, and NKp46 also provide activating signals via binding of yet undefined ligands. The signals received from NCRs, NKG2D, and DNAM-1 trigger NK cell cytotoxicity and/or cytokine production, whereas signals from NKG2A suppress the stimulatory pathway [31].

2.2. NK Cell Development

The development and the activity of NK cells are dynamically modified by the interaction with their targets (i.e., malignant and virus-infected cells) and other cells of the immune system. NK cell education/licensing process via iKIRs is the most important step, which promotes the maturation of functionally active NK cells and inhibits those lacking appropriate iKIRs [12,18]. Dendritic cells, monocytes, and macrophages contribute to NK cell development by cytokines such as interferons, IL-12, IL-15, and IL-18. IL-2, secreted by CD4+ T cells is also an essential cytokine for NK cell survival and proliferation. In contrast, transforming growth factor-β (TGF-β), secreted by regulatory T cells (Treg), suppresses NK cell proliferation and activity [9]. In addition to aKIRs and iKIRs, various activating signals are transmitted through C-type lectin receptors, NCRs, killer cell C-type lectin-like receptor, Fcγ receptor (CD16), signaling lymphocytic activation molecule (SLAM) family receptors and other co-stimulatory molecules. Some inhibitory signals are transmitted via programmed death-1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and mucin domain containing-3 (TIM-3), and T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (TIGIT) [9]. Upon activation, NK cells exert cytotoxicity via three distinct mechanisms: 1) direct killing of the target cell by release of perforin and granzymes; 2) induction of apoptosis through Fas-FasL or TNF-related apoptosis-inducing ligand (TRAIL)- dependent mechanisms; 3) activation of other inflammatory cells by secretion of several cytokines and chemokines [32]. NK cells may also differentiate into memory cells lacking antigen specificity after *in vitro* incubation with cytokine combinations and in response to some viral infections, including human cytomegalovirus [9].

Current approaches of NK cell immunotherapy for hematological malignancies involve using methods for *in vivo* potentiation of NK cell proliferation and activity; adoptive transfer of NK cells from autologous and allogeneic sources [CB mononuclear cells, peripheral blood (PB) mononuclear cells, $CD34^+$ stem cells] and NK cell lines; and genetic modification of NK cells.

3. *IN VIVO* POTENTIATION OF NK CELL PROLIFERATION AND ACTIVITY

3.1. Haploidentical Hematopoietic Stem Cell Transplantation

Haplo-HSCT should be considered as the first successful attempt of NK cell immunotherapy. Since its success mostly relies on alloreactive NK cells, the first attempts aimed to increase *in vivo* NK cell alloreactivity without increasing GvH effects. The simplest strategy of selecting the best donor has been extensively studied and revealed extensive data with a few consistent findings. Among iKIRs, the mismatches between KIR2DL1, KIR2DL2/3, and KIR3DL1 and their corresponding HLA ligand motifs C1, C2, and Bw4 should be considered for haplo-HSCTs. For matched sibling and unrelated HSCTs donors having aKIRs, especially KIR2DS1 and KIR2DS2 have been reported to yield favorable results [33–35]. Results of studies are also in favor of donors with KIR group B haplotype, which contains more than one aKIR gene, when compared to KIR haplotype A [36–38].

The treatment with high-dose posttransplant cyclophosphamide (PT-Cy) in the haplo-HSCT setting has enabled the use of unmanipulated grafts without inducing GvHD [39]. The exact mechanisms of NK cell alloreactivity and the progress of NK cell recovery in this setting are thought to differ from NK cell alloreactivity models developed in the T cell-depleted transplants. Thus, the kinetics of immune reconstitution after PT-Cy have to be further explained [40].

3.2. *In vivo* Effects of Cytokines

Several cytokines that take part in the development of NK cells have been studied for boosting NK cell effects *in vivo*. IL-2 was the first cytokine approved for this purpose [41]. The competitive activation of nearly all T cells, including Treg and NK cells, by IL-2, and the inhibitory effects of expanded Treg cells on NK cells led to disappointing clinical results. The undesirable side effect profile, especially at high doses, such as capillary leakage and systemic inflammatory response limited its use [42]. However, super-2, which is a modified form of IL-2 developed in mouse models, has an increased affinity to IL-2Rβ and NK cell selectivity, with an acceptable toxicity [43]. Human single-chain recombinant IL-15 also resulted in successful expansion of NK cells without activating Treg cells. However, cytokine release syndrome was prominent, due to structural similarities with IL-2 [44]. IL-12, previously called as “natural killer cell stimulatory factor” stimulates NK cells for IFN-γ production and enhances cytotoxicity. However, toxicity-related deaths observed in early trials limited its use [45]. Consequently, several fusion proteins of recombinant IL-2, IL15, and IL-12 are under investigation in order to get more selective NK cell stimulation, better toxicity profile, and prolonged half-life [9]. Other cytokines, such as IL-7, IL-18, and IL-21 had positive results in preclinical studies [32,41].

3.3. Effects of Specific Monoclonal Antibodies and Immune Checkpoint Inhibitors

Monoclonal antibodies directed towards certain targets may promote NK cell function. NK cell cytotoxicity may be stimulated

via interactions with CD16. An Fc-optimized CD133 antibody has been reported to increase NK cell degranulation without increase in toxicity in a human acute myeloid leukemia (AML) xenograft model [46]. Another problem has been resolved with a highly selective inhibitor of a disintegrin and metalloproteinase-17 (ADAM17), which prevents the decrease in CD16 expression due to NK-cell activation via ADAM17-mediated removal of the CD16 receptor [47]. The blockade of NK cell receptors, particularly immune checkpoints, may eventually lead to immune stimulation. The KIR-blocking antibodies IPH2101 and IPH2102 yielded promising results in preclinical studies. However, IPH2101 showed minimal response in a phase 2 clinical trial for multiple myeloma (MM) treatment [48]. The ongoing preclinical studies target immune checkpoints with the anti-natural killer group-2 member A (anti-NKG2A) blocking antibody monalizumab and anti-TIM-3 blocking antibody MBG453 [49,50]. Although PD-1 antibodies, including pidilizumab, lambrolizumab, and nivolumab mainly target T cells and provide tumor suppression, they also may boost endogenous NK cell functions [51]. NK cell cytotoxicity can also be enhanced and redirected to tumor cells via bi- or tri-specific engagers [52–54]. These monoclonal antibodies may be combined with other treatments, particularly NK-stimulating cytokines, in order to produce synergistic effects. However, they require further research into their safety and efficacy.

3.4. Effects of Immunomodulatory Drugs and Others

Some immunomodulatory drugs, including thalidomide, lenalidomide, and pomalidomide may also promote NK-cell cytotoxicity [55]. They are thought to act through activation of T and dendritic cells to release IL-2 and IFN-γ [56]. Proteasome inhibitors, such as bortezomib and carfilzomib promote apoptosis by sensitizing tumor cells to NK action via the upregulation of TRAILR and natural killer group-2 member D (NKG2D) receptor ligands on tumor cells [57]. Preclinical data have demonstrated similar modes of action with doxorubicin and histone deacetylase inhibitors, such as valproic acid and romidepsin [56].

4. ADOPTIVE TRANSFER OF NK CELLS

4.1. Autologous NK Cells

NK cells have been demonstrated to exert potent cytotoxicity against various hematologic malignancies, especially AML, MM, lymphoma, and many solid tumors as well [9,58]. High efficacy, broad-spectrum, and low toxicity have made NK cells popular for use in adoptive therapy. The initial trials included the use of autologous NK cells. Due to the unacceptable toxicity and minimal benefit obtained from the trials with *in vivo* NK stimulation via high-dose IL-2 administration, *ex vivo* incubation of human PB NK cells with cytokines appeared to be an alternative strategy. However, IL-2 incubated "lymphokine-activated killer" (LAK) cells also failed to produce optimal results [59]. The limitations leading to this failure were identified as the unintended proliferation of Treg cells, eventually leading to NK cell suppression, and the inhibitory effects of self-HLA molecules highly expressed on malignant cells [42,60].

4.2. Allogeneic NK Cells

In order to eliminate these limitations, the use of allogeneic NK cells have been tried. The first attempts in the non-HSCT setting were made by Miller *et al.* in a group of solid tumors, Hodgkin disease, and relapsed/refractory AML. Following a lymphodepleting conditioning regimen, patients were given haploidentical NK cell infusions followed by exogenous IL-2. Among the three conditioning regimens studied, the "Hi-Cy/Flu," which included high-dose cyclophosphamide (60 mg/kg for 1 or 2 doses) and fudarabine (25 mg/m^2 for 5 days), yielded the highest NK cell expansion *in vivo* due to high endogenous IL-15 concentrations related to massive T-cell depletion. Their results were quite promising, with some complete responders and no GvHD [61]. The use of a recombinant IL-2 diphtheria fusion protein (IL2DT) within this scheme achieved further Treg cell depletion and boosted NK cell proliferation [62]. As an alternative strategy, IL-15 was used for NK cell proliferation, in order to overcome the undesired Treg cell expansion problems observed with IL-2 [63]. Results are promising and, currently, many IL-15 products are under development. Using IL-15 complexes is another strategy, and preactivation with IL-12, IL-18 and IL-15 has been shown to differentiate NK cells into memory-like NK cells with enhanced IFN-γ production and cytotoxicity [13,64]. Several different modifications of cytokines are currently being investigated for this purpose.

4.2.1. Sources of allogeneic NK cells

NK cells are frequently derived from PB. Following PB apheresis from a normal donor, CD3 depletion is performed in order to prevent GvHD. Sometimes, the product is also depleted of CD19, aiming to prevent passenger lymphocyte syndrome and Epstein–Barr virus (EBV) reactivation. In another attempt to increase purity, CD3 depletion can be followed by CD56-positive selection, which has a risk of reducing the NK cell yield [61,65]. The final product is either administered immediately, incubated with cytokines, or undergoes *ex vivo* expansion. However, the latter is usually required, since NK cells constitute only 5%–20% of PB mononuclear cells [35]. Autologous feeder cells and/or genetically modified allogeneic feeder cells are used in order to provide the survival, proliferation, and activation signals required for NK cell expansion. For this purpose, irradiated cell populations, such as PB mononuclear cells, T cells, EBV-transformed lymphoblastoid cells, and K562 cells, have been used [56]. Newly developed feeder-free protocols have the potential to reach higher NK cell purity ratios. However, they suffer from donor dependent variabilities in cell yield and purity, which have to be improved [66]. Despite the existence of various protocols for selection and expansion of NK cells, only a few of them are compliant with stringent good manufacturing practice (GMP) requirements, which is a prerequisite for clinical use.

Despite depletion and selection processes, NK cells isolated from PB constitute only 30%–50% of the cells in the end product [67]. Besides PB, NK cells can also be obtained from CB, BM, human embryonic stem cells (hESC), induced pluripotent stem cells (iPSC), or NK cell lines. CB is an important NK cell source, and the challenge of low number of NK cells in CB units and BM harvests has been solved by using co-culturing systems with stromal cell lines and cytokine combinations [35,68]. Another limitation of CB-derived NK cells when compared to PB is their lower activity, due to lower expression of inhibitory KIRs, which can be

partially overcome by *ex vivo* expansion [69]. Obtaining NK cells from hESC or iPSC was recently described, and involves a much more complex process [70]. However, it has the potential for producing a homogenous NK cell product. A recently described GMP-compatible iPSC source and industry-friendly protocol may enable to produce large-scale quantities of universal NK cells without any KIR expression [71].

4.2.2. Donor selection for allogeneic NK cells

Donor selection is also important for allogeneic NK cell therapy. Donor evaluation involves KIR genotyping and identification of KIR haplotype, KIR phenotyping, KIR allelotyping, and typing of FcgR polymorphisms [72]. The principles used for donor selection in haplo-HSCT are overall valid, with few exceptions. However, there is no clear-cut consensus, and the criteria for donor selection have been evolving [9]. "Single-KIR" NK cells harboring particular sets of inhibitory KIRs have been developed and have been reported to be active against human AML cells *in vitro* and *in vivo* [73]. Our institutional experience with autologous PB-derived and allogeneic CB NK cells suggests a higher cytotoxicity of NK cells against human BM myeloma plasma cells and cell lines in the presence of KIR2DS4 positivity [74].

4.3. NK Cell Infusions in the HSCT Setting

HSCT combined with NK cell infusions significantly improve the treatment outcomes in hematopoietic malignancies, especially AML, when compared to HSCT only [75,76]. However, the time of infusion is very important. Superior clinical outcomes are obtained, if infusion is performed before or within 2 weeks, as compared to 4 weeks after HSCT [9,77]. However, the optimal timing, frequency, and dose of NK cell infusion are yet not clear. NK cell infusions are more effective against hematopoietic malignancies than cytokine-induced killer cells, probably due to their increased T cell contents [78].

4.4. NK Cell Lines

NK cell lines are derived from malignant cell clones and seven established NK cells lines exist: NK-92, YT, NKL, HANK-1, KHYG-1, NK-YS, and NKG [35]. Cell lines are easy to expand and appropriate for use as an "off-the-shelf" universal cell product, because they contain a uniform and reproducible NK-like population. Among these, NK-92 is the only FDA-approved cell line for use in clinical trials. It lacks expression of all KIRs (except KIR2DL4) and has been shown to consistently exert high cytotoxicity in preclinical studies [79]. The other cell lines are very similar to NK92 and reported to have *in vitro* cytotoxicity. However, they have never been infused into patients. *In vivo* persistence and the lack of CD16 expression are the major drawbacks of cell lines, and can be improved by irradiation and transgene expression of CD16, respectively [80]. Although promising results have been achieved with NK92 cell lines, the observed limited clinical efficacy brought about the idea of genetic manipulation of these cell lines *ex vivo* in order to increase their cytotoxic capacity.

5. NK CELL-BASED INNOVATIVE CELLULAR THERAPIES AND FUTURE PERSPECTIVES

Adoptive therapy with allogeneic NK cells has proven to be safe, but only moderately efficient, due to problems with *in vivo* persistence, restricted trafficking and homing to tumor sites, inhibitory effects of tumor microenvironment, and lack of antigen specificity. These issues can be substantially solved by means of genetic engineering. NK cell lines, PB-derived, and stem cell-derived NK cells are frequently used for this purpose [81]. The problem of decreased transduction efficiency due to the resistance of NK cells to retroviral infection has been overcome with recent progress in the technique [9]. Arming the NK-92 cell line with CD16a has been reported to augment antibody-dependent cellular cytotoxicity [82]. Modifying NK cells to produce IL-15 and IL-2 can improve their survival, persistence, proliferation, and function *in vivo* [83]. CARs were developed to arm immune effector cells in order to recognize tumor cells via surface antigens and enhance cytotoxicity in an HLA-unrestricted fashion. The success of CAR-T cells has focused research on the development of CAR-NK cells [81]. The intrinsic characteristics of NK cells make CAR-NK more advantageous than CAR-T cells. The risk of cytokine release syndrome is less likely, due to their limited *in vivo* persistence. They offer the opportunity to produce an off-the-shelf allogeneic product, as they do not cause GvHD. Their intrinsic cytotoxic effects mediated through their native receptors make disease escape due to downregulation of the CAR target antigen less likely [58]. Initial preclinical studies targeting B cell malignancies with anti-CD19 and CD20 CAR-NKs had promising results [84]. In addition, several CAR-modified NK-92 cells against various hematologic malignancies have been developed, such as CD19 and CD20 for B cell leukemia/lymphoma, and CD138 and CS-1 for MM [85]. However, the results of clinical studies are pending [86,87].

6. CONCLUSION

The understanding of NK cell immunobiology, together with the development of *ex vivo* manipulation techniques and genetic engineering have made it possible to develop NK cell-based immunotherapies, which has the potential to maximize the curative capabilities of personalized cancer treatments. The products of ongoing research not only diversify the present choices of therapy, but also minimize therapy-related side effects and increase convenient and effective use. The future of NK cell immunotherapy foresees personalized combination therapies.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest.

AUTHORS' CONTRIBUTIONS

Ugur Sahin and Meral Beksac wrote, reviewed, and approved the manuscript.

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