Natural Killer Cells in Immunotherapy

Subjects: Immunology

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Here, the last pre-clinical and clinical studies published in the last five years where natural killer (NK) cells have been administered as an immunotherapy option for the treatment of cancer patients. Author describe studies administering NK cells alone and in combination with monoclonal antibodies that either promote antibody-dependent cell cytotoxicity or block immune checkpoint receptors. They review the use of genetically modified NK cells including chimeric antigen receptor (CAR)-modified NK cells and other modifications that can enhance the anti-tumor activity of NK cells. Moreover, author describe studies related to the antimicrobial activity of NK cells as we believe they demonstrate important lessons that we can learn and apply to improve the anti-tumor activity of NK cells. All these studies are described with the aim to find tips to improve the success of NK cells as an immunotherapy option in cancer patients.

Keywords: NK cells, cell immunotherapy, cancer, infections

1. The Potential of Natural Killer Cells

Natural killer (NK) cells have been recognized as potent anti-tumor and anti-microbial cells of the innate immune system. In peripheral blood, there are two main populations of NK cells, where 90% of them are $CD56^{low}$ and $CD16^{high}$, and are considered the mature and cytotoxic subpopulation [1], and which also express T-bet^{high} and $Eomes^{low}$. In contrast, the remaining 10% are $CD56^{high}$, CD25+, and $CD16^{low}$, exhibit robust cytokine production, are less mature, less cytotoxic, and express T-bet^{high}, $Eomes^{high}$ [2].

The anti-tumor properties of NK cells have attracted a high level of interest in biomedicine. In the 1980s, several studies reported a higher incidence of cancers in individuals with defective NK cell function caused by genetic disorders, such as Chédiak–Higashi syndrome and X-linked lymphoproliferative syndrome [3][4]. During the same period, increased tumor growth and metastasis were described in mutant mice with impaired NK cell activity [5]. Impaired NK cells or NK cell deficiency were associated, not only with recurrent virus infections, but also with an increased incidence of various types of cancer [6].

As opposed to immune T cells that require a considerable length of time to acquire cytolytic activity, NK cells are “ready to kill”, and their activity is observed at earlier time points (within one hour) than in T cells. Moreover, the vast array of activating and inhibitory receptors on their surface equips NK cells with the capacity to recognize and kill a high variety of targets. These important features of NK cells made them the focus of attention in hemato-oncology, and led to the first evidence of their clinical benefit by Velardi and colleagues in 2002 [7]. They observed that acute myeloid leukemia (AML) patients who received T cell-depleted haploidentical allogeneic stem cell transplantation (allo-SCT), with a mismatch between the inhibitory killer-cell immunoglobulin-like (KIR) receptor in NK cells and the human leukocyte antigen (HLA)-I of the patient, experienced lower rates of relapse, suggesting that donor-derived NK cells were mediating an alloantigen-specific response against AML blasts, without causing graft versus host disease (GVHD). Importantly, this KIR-HLA mismatch, which can also occur when there is HLA-I down-regulation in tumor cells, activates NK cells after allo-SCT, leading to lysis of leukemia blasts, recipient dendritic cells, and recipient T cells, which translates into a reduction of relapse, prevention of GVHD, and avoidance of graft rejection, respectively [8][9]. These findings led to the adoptive cell transfer of in vitro-activated haploidentical KIR-mismatched NK cells into patients with AML. In these initial studies, two different conditioning regimens were tested, demonstrating that the more intense, high cyclophosphamide/fludarabine regimen resulted in a marked rise in endogenous IL-15, expansion of donor NK cells, and induction of complete hematologic remission in 26% of poor-prognosis patients with AML [10]. Since then, a high number of clinical trials have started to administer NK cells in patients, not only with AML, but also with other hematological malignancies and solid tumors.

2. NK Cells as a Single Immunotherapy Option

The allogeneic origin of NK cells in immunotherapy strengthens the idea of an “off-the-shelf” product, because they can be available at any time. This is one of the main benefits of NK cells above the use of autologous T lymphocytes. In the last five years, many clinical trials administering NK cells have been started. However, many of them are either still recruiting patients or the results are not available yet. The most relevant studies are mentioned here and summarized in Table 1.

Clinical studies have used different NK cell sources, which include cord blood-derived NK cells (CB-NK) [11][12], peripheral blood NK cells (PB-NK) [10], NK cells derived from human induced pluripotent stem cells (iPSC-NK) [13], or NK cells derived from clonal cell lines, such as NK-92. Although NK-92 is dependent on IL-2, and cells die within 72 h if they lack the cytokine [14], in terms of safety, it has to be irradiated prior to infusion in patients, which can limit its therapeutic efficacy [15]. Regarding activation and expansion of NK cells, most protocols use cytokines such as IL-2, IL-12, IL-15, IL-18, and IL-21. Each cytokine impacts NK cell maturation, proliferation, survival, and distribution differently (reviewed in [16]). IL-15 has appeared as an important cytokine that increases the anti-tumor response of $CD56^{bright}$ NK cells [17]. However, a disparity of opinions have emerged, as recently it was demonstrated that continuous in vitro exposure of NK cells to IL-15 leads to NK cell exhaustion [18]. Moreover, a clinical study in patients reported severe GVHD in cancer patients receiving allogeneic NK cells pre-activated in vitro with IL-15 and 4-1BBL and given HLA-matched T cell-depleted allogeneic hematopoietic stem cell transplants. GVHD was associated with higher donor CD3 chimerism, suggesting that NK cells might not be responsible for the GVHD development [19]. Bachanova et al. performed a phase II clinical trial in patients with refractory non-Hodgkin lymphoma (NHL), who received haploidentical NK cells with anti-CD20 antibody rituximab and IL-2 (NCT01181258) [20]. This study demonstrated safety without GVHD, cytokine release syndrome (CRS), or neurotoxicity, and the responding patients had lower levels of regulatory T (T-reg) cells and myeloid-derived suppressor cells (MDSCs) at baseline than non-responding patients. Importantly, endogenous IL-15 levels were higher in responders than non-responding patients at the day of NK cell infusion [20]. Moreover, although cytokine therapy can augment in vitro NK cell anti-tumor activity, the same approach in vivo may be limited by the systemic toxicity of cytokines [21]. In this regard, there is an ongoing clinical study evaluating the administration of haploidentical NK cells with the addition of subcutaneous IL-15 in AML patients (NCT03050216). Of interest, novel studies with CAR-NK cells include the addition of IL-15 secretion in the CAR construct [22], which avoids the administration of cytokines and the associated toxicities.

The addition of exogenous cytokines for NK in vitro expansion can be complemented or substituted by the use of artificial feeder cells, which provide a continuous source of cytokines for NK cells [11], obtaining a high number of NK cells to treat patients [11][12]. To take advantage of this approach in vivo, Chen et al. designed a chimeric protein with NKG2D and IL-15 that would bind to MICA on tumor cells and would trans-present IL-15 to NK cells. This strategy enhanced NK cell recruitment to tumor sites in mouse models of gastric cancer and melanoma, resulting in slowed tumor growth [23].

In recent years, some novelties introduced in the clinical protocols to expand NK cells have included the use of a combination of cytokines to obtain “memory-like” NK cells. Thus, NK cells expanded with IL-12, IL-15, and IL-18 induce a memory-like phenotype, with increased IFNγ production, expression of the high affinity IL-2 receptor, and cytotoxicity against AML blasts [24][25]. In mouse models of AML and melanoma, it was demonstrated that memory-like NK cells proliferate in vivo and exhibit increased effector function, resulting in enhanced tumor clearance and improved survival [24][25]. Moreover, in a phase I clinical trial, adoptively transferred memory-like NK cells proliferated and expanded in AML patients during the first week and demonstrated ex vivo responses against leukemia targets. In nine evaluable patients, an objective response (OR) of 55% and a complete remission (CR) rate of 45% was observed [24]. Even though the number of patients was small, results were suggested to be better than those obtained by Bachanova et al. in 57 AML patients treated with haploidentical NK cells and IL-2 administration, where they obtained 21% of CR. However, in the same study by Bachanova et al., they included a cohort who received IL-2-diphtheria fusion protein (IL-2DT) that depletes T-reg cells, and which significantly improved CR to 53% [26].

Khatua et al. [27] performed a phase I clinical trial of 12 pediatric patients with brain tumors who received intraventricular infusion of autologous NK cells expanded with feeder cells. Nine evaluable patients were treated, receiving up to three infusions weekly. Safety of 112 intraventricular infusions of NK cells was achieved in all nine patients. There were no dose-limiting toxicities. However, despite the high amount of NK cells administered, all patients showed progressive disease (PD), except one patient who showed stable disease (SD) for one month. Of note, frequent infusions of NK cells resulted in cerebrospinal fluid pleocytosis, with the presence of NK cells.

Björklund et al. evaluated the administration of IL-2-activated haploidentical NK cells in primary relapsed/refractory (R/R) high-risk myelodysplastic syndrome (MDS), secondary AML (MDS/AML), and de novo AML patients. A total of 16 patients were treated and NK cells were well tolerated. Six patients (37.5%) achieved ORs with CR, marrow CR, or partial response (PR). However, five patients proceeded to allo-SCT afterwards. Three patients were still free from disease three

years after treatment. All evaluable patients with OR had detectable donor NK cells at days 7/14 following infusion. Responding patients displayed less pronounced activation of CD8+ T cells and lower levels of inflammatory cytokines following NK cell infusion. All patients displayed increased frequencies of activated T-reg cells of recipient origin following NK cell therapy [28]. These findings suggest some type of immunoregulatory activity performed between both T cells and NK cells, as has been observed for the microbial infections that we will discuss in Section 5.

Another phase II study in relapsed or progressive AML or MDS was performed, in which patients were treated with haploidentical NK cells after cyclophosphamide-based lymphodepletion following allo-SCT. A total of eight patients were treated with a median of 10.6×10^6 NK cells/kg and six doses of IL-2 every other day. Safety was demonstrated without incidence of GVHD [29]. As in the study by Björklund et al. [28], 37.5% of patients achieved OR. Two patients achieved CR (one patient with AML and one patient with MDS); however, they relapsed at 1.7 and 1.8 months. The median overall survival (OS) was 12.9 months. Of note, in this study, NK cells were not detected after infusion [29].

Yang et al. performed a phase I study (NCT01212341) evaluating repetitive administrations of allogeneic expanded NK cells from random unrelated healthy donors (MG4101) into patients with lymphoma or refractory solid tumors. Safety was demonstrated for the maximum dose (3×10^7 cells/kg, triple infusion). Of 17 evaluable patients, 47.1% showed SD and 52.9% showed PD. Of interest, it was observed that MG4101 reduced T-reg cells and MDSCs, increased NKG2D expression on CD8+ T cells, and upregulated the chemokines that recruit T cells [30].

In solid tumors, there are ongoing studies evaluating intraperitoneal administration of CB-NK to treat recurrent ovarian carcinoma (NCT03539406) or oral cavity carcinoma in pediatric patients (NCT03420963). However, results are not available yet.

Table 1. Clinical results in the last 5 years administrating natural killer (NK) cells.

NCT Number. Phase. Investigator. Reference	Source of NK and Method of Expansion	Stage of Disease and Number of Patients	Clinical Outcome
NCT01181258. Phase II. Bachanova, V. et al. [20]	Allogeneic PB-NK + IL-2 (1000 IU/mL)	R/R NHL or CLL $CD20^+$. 14 evaluable patients.	4/14 OR at 2 months (28%). 2/24 CR for 9 months (14%)
NCT01898793. Phase I/II. Romee, R. et al. [24]	Haploidentical PB-NK + 12–16h: IL-15, IL-12 and IL-18. 3 doses: 0.5, 1 and 10^6 NK/Kg	R/R AML (*n* = 13, 9 evaluable).	Well tolerated, no GvHD. OR: 55% CR: 45%
NCT02271711. Phase I. Khatua, S. et al. [27]	Autologous PB-NK + K562-mbIL-21	R/R brain tumor: medulloblastoma (*n* = 5) and ependymoma (*n* = 4) in pediatric patients	SD: 11.1% PD: 88.9%
NCT00526292. Phase II. Shaffer, B. C. et al. [29]	Haploidentical PB-NK. 6 doses of IL-2 in patients every other day.	AML (*n* = 6) and MDS (*n* = 2)	No GvHD PR: 37.5% CR: 25% Median OS = 12.9 months

EudraCT number 2011-003181-32. Bjorklund, A. T. et al. [28]	Allogeneic PBNK + IL-2 (1000 IU/mL)	R/R or high-risk MDS (*n* = 5), MDS-AML (*n* = 9) or de novo AML (*n* = 3). 16 evaluable.	OR: 37.5% and SD: 12.5% 5/16 underwent allo-SCT. Of these in 3/16, DFS > 3 years
NCT01212341. Phase I. Tae Min Kim [30]	Allogeneic PB-NK. 14 days of expansion with irradiated auto-PBMCs, OKT3 +IL-2 (500 IU/mL) every other day	Lymphoma (*n* = 2) and solid tumor (*n* = 19). 17 evaluable	No GvHD, no severe toxicities. 47.1% SD, 52.9% PD, median PFS in SD patients of 4 months

R/R: relapsed/refractory; OR: objective response; SD: stable disease; PR: partial response; PD: progressive disease; CR: complete response; GvHD: graft-versus-host disease; NE: not evaluable; MLFS: morphologic leukemia-free state; allo-SCT: allogeneic stem cell transplantation; OS: overall survival; PFS: progression free survival.

3. Use of NK Cells in Combination with Monoclonal Antibodies

The little success observed administering NK cells as a single therapy has led to their combination with other immunotherapeutic tools to improve their efficacy. Monoclonal antibodies bind to surface targeted molecules expressed on cancer cells, and owe their mechanism of action partially to NK cell-mediated antibody-dependent cell cytotoxicity (ADCC). NK cells express CD16 (FcRIII receptor), which is key to ADCC. Thus, among the studies being performed, there is a phase I clinical trial (NCT02030561) administering NK cells after trastuzumab (anti-HER2) treatment [31]. Autologous NK cells were expanded with K562-mb15-41BBL artificial antigen presenting cells for 10 days. Prior to infusion, NK cells expressed high levels of CD16, which was down-regulated once infused in the patient. Nine patients with HER2+ breast or gastric cancer received trastuzumab and subcutaneous IL-2 the day before NK cell infusion. Subsequently, patients received IL-2 three times a week and three more cycles of trastuzumab. The combination treatment was well tolerated but no OR was observed. In total, 66.6% of patients achieved SD for >6 months and 11% accomplished PR. The results obtained set the basis for a future phase II trial with 20 patients [31]. Another clinical study, analyzed the combination of NK cells with cetuximab (anti-EGFR) in 54 patients with advanced non-small cell lung cancer. Patients were randomized to receive either cetuximab plus NK cells or cetuximab alone. Safety was demonstrated in both groups, and the group receiving NK cells presented lower levels of carcinoembryonic antigen, neuron specific enolase, and circulating tumor cells than before treatment. Moreover, in comparison to cetuximab alone, they had a significant improvement in immune function and quality of life, and survived longer (median PFS: 6 months vs. 4.5 months; median OS: 9.5 months vs. 7.5 months) demonstrating a beneficial effect of combining NK cells with antibodies that promote ADCC of NK cells [32].

The use of immune checkpoint inhibitors is another area of interest for NK cell combination therapies. NK cells express a wide variety of inhibitory receptors, including NKG2A, KIRs (such as KIR3DL2), PD-1, TIGIT, TIM-3, and LAG-3. Monoclonal antibodies that block inhibitory receptors have shown great efficacy in enhancing T cell/CAR-T cell anti-tumor activity, and a number of clinical trials are currently ongoing that are testing some of these checkpoint blockade molecules as a means to enhance endogenous T cell and NK cell activity (reviewed in [33]).

For NKG2A, Andre P. et al. [34] demonstrated that blocking of NKG2A with monalizumab (a humanized anti-NKG2A antibody) enhanced NK cell anti-tumor activity in various tumor cells. Moreover, monalizumab promoted NK cell ADCC, as when combined with cetuximab and obinutuzumab (anti-CD20) it led to the amplified activation of NK cells with enhanced ADCC. Thus, monalizumab can amplify the beneficial effects of other treatments which promote ADCC. Interim results of a phase II trial (NCT02643550) of monalizumab plus cetuximab in previously treated patients with squamous cell carcinoma of the head and neck showed a 31% objective response rate. However, in this study, patients did not receive NK cells [34]. In chronic lymphoid leukemia patients, tumor cells overexpress HLA-E, and NK cells overexpress NKG2A. Blocking NKG2A with monalizumab on CLL NK cells restored the cytotoxicity ability of NK cells against HLA-E-expressing targets, without impacting NK cell ADCC [35]. In addition, the blockading of NKG2A is an interesting approach that allows the enhancement of NK cell alloreactivity after haploidentical-SCT. In this setting, Roberto A. et al. characterized that after haploidentical-SCT there is a transient and predominant expansion of an unconventional NK cell population, characterized by NKp46^{-low}/CD56^{dim}/CD16^{-} with high levels of CD94/NKG2A. This expansion starts from the second week following

haploidentical-SCT. While present at low frequency in healthy donors, this unconventional NK cell population express high levels of NKG2D, NKp30, Granzyme-B, and Perforin, but displays defective cytotoxicity that could be reversed by blocking CD94/NKG2A [36].

Inhibitory KIRs are inhibited with lirilumab. Kohrt et al., using a KIR transgenic murine model, demonstrated that the blockade of inhibitory KIRs with lirilumab augments NK cell cytotoxicity. Moreover, in combination with rituximab (anti-CD20), anti-KIR treatment induced enhanced NK-cell-mediated, rituximab-dependent cytotoxicity in murine lymphoma models. These results support a therapeutic strategy combining rituximab and KIR blockade through lirilumab [37]. Lirilumab has demonstrated safety in cancer patients, being administered alone and in combinations with other drugs [38] [39]. However, clinical results in combination with NK cells are not available yet.

Regarding PD-1, it was observed that mature $CD56^{dim}$ NK cells display high levels of PD-1, being characterized by a $NKG2A^{-}$ KIR^{+} $CD57^{+}$ phenotype. This PD1+ NK cell population showed reduced functional activity, and is present in approximately one fourth of healthy subjects. Interestingly, these donors are always serologically positive for human cytomegalovirus. These NK cells might have a preferential expansion in tumor environments. Therefore, authors suggested that their blockade with anti-PD1 could promote NK cell-mediated cytotoxicity [40].

Based on these results, different studies are now considering the application of checkpoint inhibitors to improve NK cell function in adoptive therapy, particularly those that target PD-1 and its ligand, PD-L1. NK cells can promote the expression of PD-L1 in tumor cells through secretion of IFNγ, which generates an immunosuppressive tumor microenvironment that impedes NK cell activity [41]. Therefore, it is expected that the use of PD-L1 inhibitors could potentiate the activity of NK cells. On the other hand, PD-1 antibodies can bind to PD-1 molecules on NK cells' surface to prevent their depletion [42]. In the only clinical study combining NK cell therapy and a checkpoint inhibitor that currently has published results, Lin et al. performed a clinical trial in 109 patients with non-small cell lung cancer (NSCLC) that were randomly treated with pembrolizumab (anti-PD-1) plus NK cells or given pembrolizumab alone. Higher OS and PFS rates were achieved with the combination therapy compared to those obtained by the group in monotherapy (15.5 and 6.5 months vs. 13.3 and 4.3 months, respectively). Furthermore, better median OS was observed, comparing patients who received more than one infusion vs. a single infusion (18.5 months vs. 13.5 months) [43]. Many other clinical studies are currently ongoing. In one pilot study (NCT03958097), the combination of sintilimab (anti-PD-1), which is currently approved in China for R/R Hodgkin's lymphoma [44], is being tested as a dual therapy with autologous NK cells. No results have been posted yet.

Suppressor cells represent another major obstacle for optimal NK cell function in the tumor microenvironment. Tumor-associated neutrophils, which repress NK cell cytotoxicity through the PD-1/PD-L1 axis [45], and MDSCs are both potential target cells for checkpoint therapy. Indeed, CAR-NK cells that target PD-L1-expressing cells efficiently eliminate MDSCs in vitro [46]. Clinical trials that combine NK cells with monoclonal antibodies are summarized in Table 2.

Moreover, the efficacy of combining checkpoint blockade with other drugs to improve NK cell tumor clearance is beginning to be explored as an attractive approach that has enhanced NK cell efficacy. These combinations are discussed below in Section 6.

Table 2. Clinical results that have administered NK cells in combination with antibodies within the last 5 years.

Study Phase. NCT Number. Reference	Monoclonal Antibody	Source of NK and Method of Expansion	Condition (Disease) and Number of Patients	Clinical Outcome
Phase I/II NCT02030561 Lee et al. [31]	Trastuzumab (anti-HER2)	Autologous PBNK + K562-mb15-41BBL + IL-2 for 10 days	$HER2^{+}$ refractory cancer. Phase I (n = 9)/II (n = 20)	Phase I: well tolerated. 66.6% SD (>6 months). 11% PR.

Phase I/II NCT02845856 [32]	Cetuximab (anti-EGFR)	Allogeneic PB-NK + K562-mb15-41BBL	Non-small Cell Lung Cancer (*n* = 54)	OS 9.5 months and PFS 6 month vs. 7.5 and 4.5 given Cetuximab alone
Phase I/II NCT02843204 Lin, M. et al. [43]	Pembrolizumab (anti-PD1)	Allogenic PB-NK + 10 IU/mL IL-2	Advanced non-small cell lung cancer (*n* = 109)	OS 15.5 months and PFS 6.5 months vs. 13.3 and 4.3 given Pembrolizumab alone
Phase II NCT03958097 Hospital of Jilin University	Sintilimab (anti-PD1)	Autologous PB-NK	Non-small cell lung cancer	NRP
Phase I NCT03841110	Nivolumab (anti-PD1), Pembrolizumab (anti-PD1), Atezolizumab (anti-PDL1)	iPSC-derived NK cell (FT500)	Advanced solid tumors and lymphomas (*n* = 76 estimated)	NRP
Phase I NCT03815084	Pembrolizumab (anti-PD1)	DC and NK cells	Solid tumors	NRP
Phase I/IIa NCT03937895	Pembrolizumab (anti-PD1)	Allogeneic NK Cell (“SMT-NK”)	Advanced Biliary Tract Cancer	NRP
Phase II NCT03853317	Avelumab (anti-PDL1)	Off-the-shelf CD16-targeted NK cells with intracellular IL2 (haNK) and IL-15 Superagonist (N-803)	Merkel Cell Carcinoma	NRP

SD: stable disease; PR: partial response; OS: overall survival; PFS: progression free survival; ORR: overall response rate; NRP: no results posted; DC: dendritic cell; PB-NK: peripheral blood NK cells.

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