

Anti-natural Killer Inhibitory Receptors in Elderly Patients with Acute Myeloid Leukaemia

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Abstract

Treatment with anti-killer-cell immunoglobulin-like receptor (KIR) monoclonal antibody (mAb) is a new approach aimed at harnessing the antileukaemic potential of natural killer (NK) cells for the treatment of acute myeloid leukaemia (AML). NK cell antitumour activity is regulated by a balance between activating and inhibitory receptors (KIR). 1-7F9/IPH2101 is a fully human immunoglobulin G4 (IgG4) mAb that binds to inhibitory KIR and blocks binding with its ligand (human leukocyte antigen C [HLA-C] molecule) on leukaemic cells. *In vitro*, and in a surrogate *in vivo* model in mice, treatment with 1-7F9/IPH2101 was able to induce NK cell activation and cytotoxicity against leukaemic cells. Patients with AML often display abnormal NK cell function, while evidence of an impact of NK cell status on AML outcome has been reported in allogeneic transplantation. 1-7F9/IPH2101 is currently under clinical investigation in patients with AML. This article reviews the mechanisms of NK cell antileukaemic activity and its role and defects in AML. Currently available data on the pre-clinical and clinical development of 1-7F9/IPH2101 are presented, and the rationale for its future use as a single agent or in combination is discussed.

Keywords

Immunotherapy, acute leukaemia, elderly, natural killer cells, NK, killer-cell immunoglobulin-like receptor (KIR), monoclonal antibodies, phase I clinical trial

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Since the discovery last century of the role of the immune system in cancer surveillance, many attempts to manipulate immune effectors have been made. The allogeneic haematopoietic stem cell transplant (HSCT) model remains the most successful example of such a strategy and has confirmed its clinical relevance. However, in spite of recent progress, access to HSCT is still limited to a minority of patients and alternative strategies based on the same principle are warranted. Recent knowledge about natural killer (NK) cells, the cell surface receptors involved in their regulation and, specifically, the identification of various families acting as negative regulators of their responses – particularly the killer-cell immunoglobulin-like receptor (KIR) family¹ – has led to the development of therapeutic blocking antibodies that are currently under clinical investigation. In this review, we will focus on the rationale for and use of the anti-KIR antibody 1-7F9/IPH2101 for the treatment of acute myeloid leukaemia (AML) and present the pre-clinical and clinical data that are currently available.

Acute Myeloid Leukaemia in the Elderly

The problem of the treatment of AML in the elderly is of growing importance. The median age of patients with AML is 65 years and the incidence of the disease increases steeply after 60 years of age.² In western countries where the population is ageing, there is therefore an absolute increase in the incidence of AML.³ In spite of the significant progress made in the treatment of AML in young patients over the last 30 years, no improvement in the prognosis of elderly patients has been achieved.⁴ Induction chemotherapy produces remissions in approximately 50% of patients, but more than 80% of

them relapse shortly after the end of treatment. This results in median remission duration of nine months, with fewer than 20% of patients surviving at three years.^{5,6} The reasons for such a poor outcome reside in both the patient and the disease; in the patient because ageing is associated with a reduction of functional reserves and an accumulation of co-morbidities, which increases the risk of chemotherapy-related mortality and morbidity and precludes the use of intensive regimens shown to be effective in younger patients.^{7,8} AML in the elderly is more frequently associated with poor-prognosis features such as unfavourable cytogenetics,⁹ antecedent of myelodysplastic syndrome, immature forms expressing CD34¹⁰ or multidrug-resistant gene expression.¹¹

The development of alternatives to cytotoxic therapies such as immunotherapy might contribute to improving the outcome of this population. Indeed, immunotherapy is by nature a targeted strategy from which limited toxicity is expected and that therefore can be tolerated by fragile patients. In addition, there is no cross-resistance between immunotherapy and chemotherapy, supporting its use in the chemo-resistant leukaemia seen in the elderly.

NK Cells and Acute Myeloid Leukaemia

From the Interactions Between NK and Autologous Blasts to the Receptors Involved in Their Recognition

One of the tenets of tumour immunology is the ability of the immune system to discriminate between normal and cancer cells. Tumours express either surface receptors that are targets of innate immunity

or antigens recognised by the adaptive immunity. Most innate immunity effectors including T *gamma delta*, NK and monocytes play an anticancer role. NK cells have been extensively analysed in AML and chronic myeloid leukaemia (CML).

Different NK cell subsets can efficiently lyse target cells or produce cytokines and chemokines in the absence of prior stimulation. A hypothesis called 'the missing self-hypothesis' predicts that NK cells will be no more inhibited and lyse target cells when expression of major histocompatibility complex (MHC) class I is lost or deficient on the target cells. Human NK cells have inhibitory receptors that recognise MHC class I molecules as their cognate ligands on virtually every cell in the body. These receptors include the inhibitory KIRs that bind to classical MHC class Ia ligands (human leukocyte antigen [HLA]-A, B and C) (see *Table 1*) and the inhibitory CD94-NKG2A heterodimeric receptors that bind the non-classic MHC class Ib (HLA-E). Another inhibitory NK receptor is the C-type lectin-like receptor NKR-P1A (CD161) that interacts with lectin-like transcript-1, a host-encoded non-MHC ligand. NK cells also express activating receptors such as the natural cytotoxicity receptors (NCRs) NKp30, NKp44 and NKp46. NK cell function is thus governed by both inhibitory and activating surface receptors.

It has been shown that NK cells can lyse the different subtypes of leukaemia or leukaemic cell lines, but the mechanisms underlying the interaction and destruction of these cells are not clearly defined (see *Figure 1*).

In AML patients, NK cell activity correlates positively with relapse-free survival, which suggests that NK cells may play an important role in the control and clearance of leukaemia.¹² On the other hand, the activity of autologous NK cells against leukaemic cells is frequently reduced¹³ and abnormalities of NK cell phenotype or activity during leukaemia have recently been identified.¹⁴ A variety of escape mechanisms to the immune system and especially NK cells have been found in AML patients and are described below.

Inhibitory Receptors and Acute Myeloid Leukaemia

There is a dominance of inhibitory over-activating signals in leukaemic patients.¹⁵ Deficient HLA class I expression (reduced expression or loss of HLA class I alleles) has been described in malignant cells. HLA class I molecules belonging to the Bw6 group were more frequently downregulated than those belonging to the HLA-Bw4 group.¹⁶ However, until now the expression of the ligands for KIR2DL4 and NKG2A, namely HLA-G or HLA-E, has not been demonstrated on leukaemic cells.¹⁶

Activatory Receptors and Acute Myeloid Leukaemia

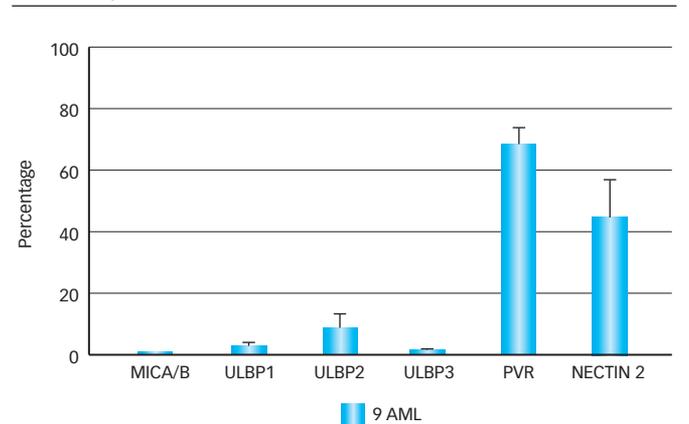
Defective cytotoxicity of AML cells can be explained by abnormalities of activating NK receptor expression.¹⁴ *In vitro* data show that NCRs mediate NK-dependent leukaemia cell lysis.^{17,18} We have demonstrated that the majority of NK cells in AML patients display an abnormal phenotype characterised by a downregulation of NKp30 and NKp46 NCR that correlates with a defective cytolytic function against autologous AML cells (NCR-dull).¹⁸ Interestingly, the NCR surface density is restored completely (NKp46) or partially (NKp30) when a complete remission is obtained with chemotherapy.¹⁹ In addition, there is defective killing of dendritic cells by autologous NK cells from AML patients, which may contribute to leukaemia escape.²⁰ Finally, a correlation between the downregulation of NCR and shorter survival was seen in AML patients.¹⁹

Table 1: Killer Inhibitory Receptors

KIR	CD	Inhibition	Charged TMAa	Ligand
2DL1	CD158A	Strong	None	HLA-Clys80 C2 (HLA-Cw2/4/5/6/15/17)
2DL2	CD158B1	Strong	None	HLA-CAsn80 C1 (HLA-Cw1/3/7/8/12,13,14)
2DL3	CD158B2	Weak	None	HLA-CAsn80 C1(HLA-Cw1/3/7/8/12/13/14)
2DL4	CD158D		Arginine	HLA-G, A3, B46
2DL5	CD158F		None	?
2DS1	CD158H		Lysine	HLA-Clys80 C2
2DS2	CD158J		Lysine	HLA-CAsn80 C1?
2DS3	No CD		Lysine	?
2DS4	CD158I		Lysine	?
2DS5	CD158G		Lysine	?
3DL1	CD158E1		None	HLA-Bw4(B51/52/53/57/58/13/27/37/44 A24)
3DL2	CD158K		None	HLA-A3,A11
3DL3			None	?
3DS1	CD158E2		Lysine	HLA-Bw4?

HLA = human leukocyte antigen; KIR = killer inhibitory receptors.

Figure 1: Interaction Between NK Cells and Primary Acute Myeloid Leukaemia Blasts



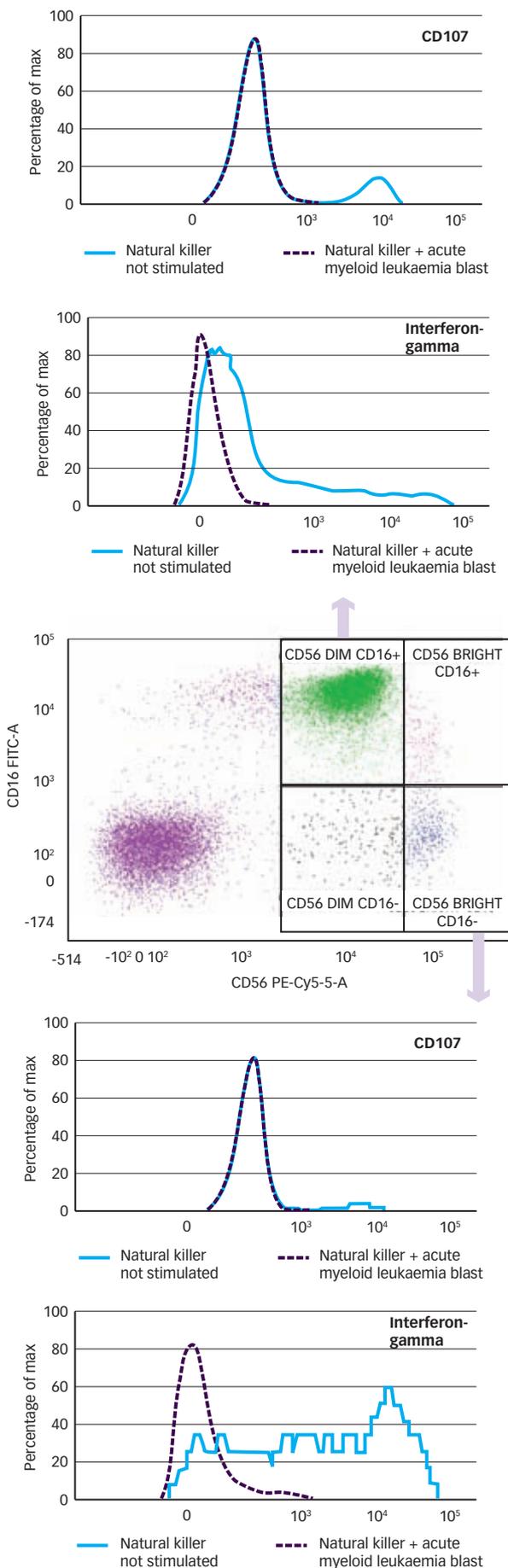
The putative NCR ligands that are expressed during the maturation of normal myelo-monocytic cells have weak expression on AML blasts.²¹ The expression of NKG2D ligands by leukaemic cells has been observed by Salih et al.,²² but not by Pende et al.²³ A recent study has showed the expression of NKG2D ligands on AML blasts at diagnosis but only on AML of M4 and M5 subtypes²⁴ (see *Figure 2*). Finally, recent studies have demonstrated significant expression for PVR and Nectin-2, the ligands of the DNAX accessory molecule-1 (DNAM-1 or CD226) on leukaemic cells.¹⁷ This central role for DNAM-1 is confirmed by monoclonal antibody (mAb)-mediated blocking experiments.¹⁷

In vivo, the activity of NK cells against AML blasts has been shown in a mice xenograft model.²⁵ Altogether, these data demonstrate that NK cells can recognise, be activated by and eventually kill AML blasts *in vitro* and *in vivo* and that AML blasts alter NK functions *in vivo*.

What Has Haematopoietic Stem Cell Transplantation Taught Us Regarding Interactions Between Allogeneic NK and Acute Myeloid Leukaemia?

Both murine and human studies show that NK cells mediate a number of potentially beneficial functions following allo-HSCT, including eliminating residual malignant cells (the graft-versus-leukaemia [GVL]

Figure 2: Expression of the Receptors for NK-activatory Receptors



effect), removing host antigen-presenting cells (thereby reducing graft-versus-host disease [GVHD]) and mediating immunity to viral pathogens directly through the cytolysis of virally infected tissues or indirectly by elaborating inflammatory cytokines, such as interferons (IFNs).²⁶ Evidence of the role of NK cells and KIRs in the allogeneic setting in humans came from the haplo-identical transplant model developed by the Perugia group.²⁷ Following conditioning chemotherapy, patients received T-cell-depleted and CD34⁺-selected haplo-identical grafts. In some recipient-donor pairs, the donor possessed MHC alleles (i.e. KIR ligands) that were not expressed by the recipient. In this 'KIR ligand-mismatched' situation, NK cell clones that are not restrained by host MHC class I can exist and have GvL potential. In a series of 112 AML patients who received haplo-identical transplants from NK-alloreactive (n=51) or non-NK-alloreactive donors (n=61)²⁸ for AML, the former group showed a significantly lower relapse rate (3 versus 47%; p<0.003) and better event-free survival (EFS: 67 versus 18%; p=0.02) in patients transplanted in complete remission. In those patients transplanted for relapsed AML, there was also an improved EFS (34 versus 6%; p=0.04) in the NK-alloreactive group compared with the non-NK-alloreactive group.

After matched donor peripheral blood stem cell transplantation following a reduced-intensity conditioning (RIC-PBSCT) regimen, a rapid CD56⁺ NK cell reconstitution was noticed as early as 1.5 months.^{29,30} Interestingly, Clausen et al. showed that patients receiving RIC and transplanted with high numbers of donor NK cells had a reduced relapse rate.³¹ In another study, high NK counts at day 30 were associated with improved outcomes in patients with acute leukaemia who received T-cell-depleted allografts.³² Altogether, these data demonstrate that NK cells are readily present early following HSCT and are likely candidates to exert their functions against AML blasts. Unfortunately, due either to its toxicity or to the lack of a suitable donor, allo-HSCT can only be offered to a minority of patients, and this is particularly true for elderly patients.

Targeting KIRs Using Monoclonal Antibodies
Description of Anti-KIR Ab

Are there ways to therapeutically design agents that would mimic haplo-identical therapy? One approach is based on therapeutic use of mAb targeting the inhibitory receptors.³³⁻³⁵ The ideal mAb candidate characteristics are:

- recognition of most if not all inhibitory receptors present on patients' NK cells;
- discrimination between inhibitory KIR (with a long intra-cytoplasmic tail (KIR* L*) and activating KIR (with a short intra-cytoplasmic tail (KIR*DS*));
- absence of KIR expression down-modulation to allow for a long-term effect; and
- absence of complement or antibody-dependent cellular cytotoxicity (ADCC) activation in order to avoid NK depletion.

A first generation of these mAbs has been devised.³⁶ 1-7F9/IPH2101 is a fully human immunoglobulin G4 (IgG4) anti-KIR mAb that blocks the interactions of the three main inhibitory KIR2DL with their HLA-C ligands, thereby enhancing NK activity, as shown in Figure 3. It was generated by immunisation of KM mice and was selected as lead candidate for clinical development on the basis of its binding to KIR2DL-1, -2 and -3 at the surface of NK cells. 1-7F9 blocks binding of these KIR to their HLA-C ligands. It enhances the function of NK clones

and polyclonal NK-cell populations. Importantly, as an IgG4, an isotype that does not activate complement and is not bound by CD16, 1-7F9/IPH2101 should not deplete the NK cell population. In addition, it exhibits only residual binding to CD64 on monocytes.

Rationale for Clinical Use in Acute Myeloid Leukaemia

AML patients are likely candidates to be enrolled in clinical trials using these new regimens. As reviewed above: NK-cells derived from AML patients are functionally impaired; these alterations are associated with relapse; NK cells activated through KIR–ligand mismatch play an important role in the leukaemia-free survival of patients treated with haplo-identical HSCT; a status of minimal residual disease prior to anti-KIR treatment can be achieved in the majority of AML patients using induction chemotherapy; and functional NK are restored upon remission achievement.

Pre-clinical and Clinical Experience with 1-7f9 Anti-KIR Monoclonal Antibodies Animal Models

KIRs are not expressed in mice. These animals use a family of inhibitory Ly49 receptors for recognition of MHC class I allotypes on target cells. Therefore, the *in vivo* effects of 1-1-7F9/IPH2101 mAb were evaluated using two different approaches in humanised mice.³⁶ First, a strain of mice expressing a KIR2DL3 transgene on a Rag^{-/-} background that lack B and T- cells was developed. In this model, 1-7F9 induced rejection of HLA-Cw3^{+/+}, K^bDb^{-/-} splenocytes without the addition of exogenous cytokines. The degree of rejection correlated with both 1-7F9/IPH2101 dose and KIR occupancy by the antibody and no depletion of NK cells was detected, even following long exposure to 1-7F9. Second, the *in vivo* efficacy of 1-7F9/IPH2101 was evaluated in a non-obese diabetic (NOD)–severe combined immunodeficiency disease (SCID) mouse model of NK-mediated rejection of transformed B cells. Inoculation of transformed human B cells together with autologous NK cells resulted in a high rate of mortality. A single injection of 1-7F9/IPH2101 was sufficient to rescue the mice, resulting in long-term survival. Similarly, pre-incubation *ex vivo* of the NK-cells with 1-7F9/IPH2101 prior to inoculation was sufficient to induce elimination of the autologous tumour cells *in vivo*. When using primary human AML blasts injected together with HLA-C-matched NK cells, strong *in vitro* NK-mediated killing of AML blasts was observed in the animals treated *in vivo* with 1-7F9/IPH2101 but not in the control animals. It is worth noting that in these experiments, NK cells were incubated with interleukin-2 (IL-2) prior to inoculation.

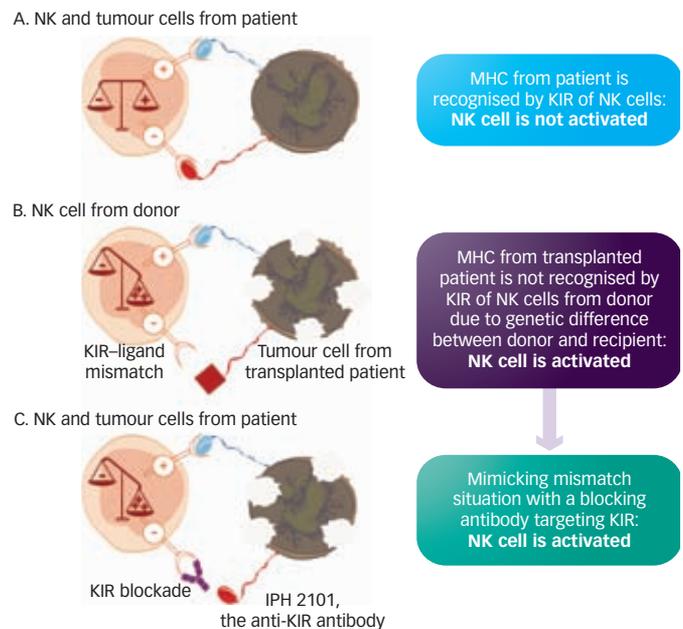
Taken together, these results indicate that 1-7F9/IPH2101 is capable of increasing natural cytotoxicity towards AML blasts *in vivo*.

Phase I Trial of Anti-Kir 1-7f9/Iph2101 in Elderly Patients with Acute Myeloid Leukaemia

Since the most convincing evidence of the antitumour effects associated with antibody-mediated blockade of inhibitory KIRs was achieved in AML, this model was chosen for the clinical development of 1-7F9/IPH2101.

A phase I first-in-human trial was conducted in elderly patients with AML. Preliminary results have been presented.³⁷ To be eligible for the study, patients had to be 60–80 years of age, be in first complete remission (CR) of AML achieved with one or two courses of conventional induction chemotherapy and followed by one to six

Figure 3: Role of KIRs in the Activation of NK Cells Following Interaction with Leukaemic Blast



A. The physiological situation; B: After human leukocyte antigen (HLA) haplo-mismatched haematopoietic stem cell transplant; C. After treatment with anti-killer inhibitory receptor (KIR)-blocking antibodies.
MHC = major histocompatibility complex; NK = natural killer.

courses of consolidation chemotherapy, have a life expectancy of at least four months and have received the last chemotherapy courses at least 30 days and no more than 120 days before inclusion. Patients with auto-immune disease were excluded. Use of growth colony-stimulating factor (G-CSF) and systemic steroids was not permitted.

The study was an open-label, dose-escalation, single-dose safety and tolerability study using a standard modified Fibonacci design with three patients included at each dose level (and three additional patients in the case of dose-limiting toxicity [DLT]). Patients received a single intravenous injection of 1-7F9/IPH2101. Seven dose levels have been explored: 0003, 0.003, 0.015, 0.075, 0.3, 1 and 3mg/kg. Twenty-three patients 71 years of age (range 61–79) in first CR of AML were included in the study. Twenty-one patients were evaluable. Only one grade III adverse event was recorded and no DLT was observed, allowing for completion of the planned dose escalation. Side effects were mild and transient. Full KIR saturation (i.e. >90%) was achieved for at least four weeks for doses of 0.3mg/kg and above. The preliminary results of the phase I trial in AML thus showed that the administration of 1-7F9/IPH2101 is safe with only limited side effects. Full saturation for more than four weeks could be achieved for doses below the maximal tolerated dose (MTD). Detailed analyses of the immunological effects are currently under way and a longer follow-up is required for the evaluation of the antileukaemic effects of 1-7F9/IPH2101.

Future Developments

The initial results obtained with 1-7F9/IPH2101 in AML show the feasibility of the approach in an elderly population. The limited clinical and immunological side effects observed confirm the specificity of this approach. These results encourage us to continue the clinical development and to envisage phase II and III studies in order to establish the clinical activity of the mAb. The role played by NK cells

Table 2: Potential Use of Anti-KIR 1-7F9/IPH2101 in the Treatment of Acute Myeloid Leukaemia

Single agent	Maintenance therapy for AML in first CR after chemotherapy and/or autologous SCT
Combination with adoptive immunotherapy	Post-allogeneic HSCT treatment
Combination therapy	Demethylating agents: HDACis (vorinostat, entinostat, panobinostat); IMiDs (lenalidomide, pomalidomide)
ADCC enhancement	Combination with anti-CD33 mAbs for AML
Combination with cytokines	IL-2, histamine hydrochloride + IL-2

AML = acute myeloid leukaemia; CR = complete remission; HDACi = histone deacetylase inhibitor; HSCT = haematopoietic stem cell transplant; IL = interleukin; IMiDs = immunomodulatory drugs; mAb = monoclonal antibody; SCT = stem cell transplant.

and their receptors is not restricted to AML. For instance, multiple myeloma cells are sensitive to NK-cell attack.³⁸ *In vitro*, 1-7F9/IPH2101 was able to induce interferon (INF) and granzyme B release from NK cells against autologous myeloma cells.³⁹ In an ongoing phase I study, 14 patients with advanced refractory or relapsed myeloma have been treated with escalating doses of 1-7F9/IPH2101. In this population, as in elderly patients, the antibody was safe and well tolerated. Pharmacokinetic as well as KIR occupancy data were comparable to those in the AML trial.³⁹

However, it is likely that 1-7F9/IPH2101 as a single agent will not be enough to achieve disease control. In this regard, its combination with adoptive immunotherapy is interesting since it might reproduce the effects observed in the haplo-mismatched HSC transplant setting. Anti-KIR 1-7F9/IPH2101 could thus be administered following matched donor allogeneic HSCT or NK cell infusion in order to reinforce the GvL effects without increasing GvHD. Concomitant treatment with 1-7F9/IPH2101 and pharmacological agents represents another promising approach. Indeed, new therapies such as the immunomodulatory drugs (IMiDs) or demethylating agents have shown activity against a variety of haematological malignancies including AML, myelodysplastic syndromes⁴⁰ and myeloma.⁴¹ In addition to their antitumour effects, these agents have shown immune modulatory effects including NK cell activation,⁴² which could be reinforced by the combination with 1-7F9/IPH2101. In addition, these strategies make it possible to treat patients with active disease, since they allow control of the disease burden while not impairing immune function, as is the case for conventional cytotoxic agents.⁴³ Future directions for the use of 1-7F9/IPH2101 are presented in *Table 2*.

Conclusions and Questions

1-7F9/IPH2101, the first compound in the class of anti-KIR mAbs, might still be improved. Indeed, in addition to the inhibitory KIR2DL-1, -2 and -3, it also binds to the KIR2DS-1 and -2 molecules. This mAb might inhibit the activation of NK cells via the KIR2DS receptors. Such cross-reactivity is not surprising because the extracellular portions of KIR2DS1 and KIR2DS2 only slightly differ from those of KIR2DL1 and KIR2DL2/3. However, the relevance of blocking KIR2DS receptors remains to be demonstrated. Various reports analysing the expression of the KIR receptors have suggested that the expression of the KIR2S receptors was associated with less relapse and cytomegalovirus (CMV) reactivation. In these studies the function of the receptors against AML was not demonstrated but only suggested. Hence, mAbs targeting only KIR2L but not KIR2DS receptors have to be tested. In addition, some NK cells may still receive inhibitory signals via other KIRs, specific for HLA-A or -B allotypes, and via CD94/NKG2A, which recognises HLA-E, or other inhibitory receptors that recognise non-MHC ligands and still prevent NK function. Hence, other mAbs targeting other inhibitory receptors might be of interest.

The inhibition of KIR will not guarantee the full activation of NK cells and its functional consequences, such as AML control. In fact, target cell recognition by NK cells is complex and involves an alteration in the balance between activating and inhibiting signals that are provided at the same time by the leukaemic cell to NK cells following the engagement of ligands of NK receptors. However, expression on AML cells of the ligands of the activating receptors is weak. Are there ways to upregulate these ligands? Histone deacetylase inhibitors (HDACis) or IMiDs might play this role.⁴⁴ Therapeutic mAbs are readily used in NHL and breast cancer in order to target tumours and destroy them, in part via the activation of CD16⁺ cells. The major population of CD16⁺ cells corresponds to NK cells in the blood. Will we be able to use mAbs to target AML blasts, such as CD33, together with agents that enhance NK functions such as 1-7F9 or related products? This strategy would combine the direct anti-AML function of NK cells and their ADCC.

Finally, is there a need for further activation of the NK cells to reinforce the activation of NK-cells together with the KIR inhibitory mAbs? In fact, we do not know whether patients' levels of bone marrow cytokines provided by the micro-environment such as type 1 IFN, IL-2, IL-15 or IL-21 will be sufficient to further allow their expansion and enhance their survival and function. If not, cytokines or agents that will induce their endogenous increase might be useful to further enhance their function, some of which, such as IL-2, have already proved to play a role in AML treatment.⁴⁵⁻⁴⁷ ■

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