Natural Killer Cell–Based Immunotherapy in Acute Myeloid Leukemia: Lessons for the Future

Aura Muntasell and Miguel López-Botet

The article by Curti and colleagues highlights the potential of natural killer (NK) cell–based adoptive cellular immunotherapy in oncology, currently boosted by advances in the knowledge on NK cell biology and in their ex vivo GMP manipulation. However, several issues deserve attention to fully achieve the translation of these advances to the clinic. Along NK cell differentiation, KIR expression follows a clonal distribution pattern, leading to the development of NK cell subsets displaying different KIR combinations. NK cell maturation is favored by KIR interaction with HLA class I molecules, a process termed "licensing". Remarkably, human cytomegalovirus (HCMV) infection promotes a persistent expansion of mature NK cells hallmarking by the expression of the CD94/NKG2C–activating receptor and a predominant inhibitory KIR specific for HLA-C (KIR2DL3; ref.4). These "adaptive" NK cells display an enhanced cytokolytic potential, cytokine production, and prolonged survival. Hence, both genetic and environmental factors dictate the configuration of the individual NK cell receptor repertoire.

NK cell alloreactivity takes place upon encounter of cells lacking HLA class I molecules specifically recognized by their inhibitory KIR. In the context of allo-HSCT, KIR/HLA class I mismatches between donor (D) and recipient (R) promote NK alloreactivity. Remarkably, this effect is not encompassed by severe GVHD but favors the response against neoplastic cells. On that basis, several teams have developed allo-HSCT protocols assessing KIR and HLA class I genotypes, aimed to select for D/R mismatches promoting NK alloreactivity against MRD (5, 6).

The general principle of ACI is infusing into the patient immune cells that have been ex vivo selected, activated, expanded, and/or modified. Among a variety of approaches, pioneering studies with IL2-activated NK and T cells, termed lymphokine-activated cells (LAK), were developed in the 1980s for cancer immunotherapy by Rosenberg and colleagues. Currently, a substantial progress in the knowledge on NK cell biology and the development of methods allowing NK cell processing under GMP conditions have set the basis for a more accurate clinical use. In the context of allo-HSCT, Miller and colleagues (7) originally reported the feasibility and safety of infusing haploidentical NK cells following immunosuppressive chemotherapy in poor prognosis AML patients. Circulating donor NK cells were found up to 28 days postinfusion, and some patients achieved significant clinical responses without developing toxicity or GVHD, confirmed by others. Thus, harnessing NK cell activation is currently envisaged as a valuable strategy for cancer immunotherapy, and several considerations deserve attention in this regard.

1 As stressed by Curti and colleagues (1), increasing the numbers of alloreactive NK cells infused, rather than simply relying on immunogenetic analysis to predict KIR-HLA ligand
Assessing the antileukemic potential of distinct NK cell subsets is also warranted. In this regard, HCMV reactivation in HSCT recipients promotes the differentiation and expansion of adaptive NKG2C+ NK cells (10), and this effect has been associated with a reduced risk of early relapse post–allo-HSCT (11). On the other hand, allografts predominantly containing HLA-matched NK cells (8). Optimizing the conditions that promote engraftment, homeostatic proliferation, and survival of allogeneic NK cells is an important issue to enhance their antileukemic potential (9).

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The opportunity of combining NK cell–based ACI with mAbs or immunomodulatory drugs (e.g., tumor antigen–specific mAbs, immune checkpoint inhibitors, proteasome inhibitors) to enhance their response appears quite promising (13). In this regard, humanized mAbs aimed to promote NK cell activation blocking inhibitory receptors (i.e., KIR and NKG2A) have been developed to enslave the reactive NK cell pool overcoming the KIR-HLA mismatch requirement. Finally, the possibility of engineering chimeric antigen receptor (CAR) NK cells is currently envisaged.

In summary, a variety of approaches to infuse ex vivo–expanded NK cell populations activated under different conditions and characterized according to the current knowledge on NK cell biology are under development. The establishment of consensus-optimized protocols and product characterization criteria is essential to formally validate these procedures in clinical practice.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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