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Targeted immunotherapy for acute myeloid leukemia

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Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) demonstrated convincingly the potential of allogeneic T cells in causing sustained remissions in high-risk hematologic malignancies. However toxicity of allogeneic HSCT limits its application to a broader group of patients. An improved understanding of NK biology along with mechanisms of natural killer (NK) cell and T-cell-mediated alloreactivity against leukemia has led to several clinical immunotherapeutic strategies that preserve graft versus leukemia (GVL) while minimizing the toxicity of HSCT. Here we review strategies being explored both in HSCT and non-HSCT settings that include an emphasis on two key aspects: (a) Maximizing cytotoxicity of alloreactive cells, ie, NK cells and T cells, and (b) Targeted manipulation of critical pathways in T and NK cells contributing to sustained anti-leukemia effects.

Keywords

acute myeloid leukemia; AML; allogeneic; graft versus leukemia; GVL; hematopoietic stem cell transplantation; HSCT; interleukin-2; IL-2; killer immunoglobulin-like receptors; KIR; natural killer; NK; T cell

Introduction

The graft versus leukemia (GVL) effect, whether mediated by T cells or by natural killer (NK) cells, is truly a wonder of modern medicine. It is the culmination of first,

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Conflict of interest

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understanding how these immune effector cells recognize self from non-self, and then testing hypotheses as to where such basic immunology might be applicable in clinical medicine [1]. Acute myeloid leukemia (AML) is one such disease where the application of these immunotherapies has resulted in the cure of an otherwise often fatal disease [2], and where additional basic immunology and clinical immunotherapy studies will very likely further increase the fraction of AML patients successfully treated with cellular therapy [3].

In the early days of cellular therapy for AML, the notion emanating from the laboratory was that enhanced T- and NK cell activation would improve tumor cell kill. The agent of choice was interleukin (IL)-2, a T-cell-derived cytokine that induced both T cells and NK cells to proliferate and kill tumor cell targets with significantly enhanced efficiency in vitro. All clinical studies with high-, medium- or low-dose IL-2 for patients with AML were performed in the autologous setting, as there was virtual certainty that IL-2 therapy would gravely exacerbate T-cell-mediated graft versus host disease (GVHD) in the allogeneic setting [4,5]. As a single agent, IL-2 has thus far not proven to be highly efficacious in improving the fraction of patients cured of AML when compared to AML patients not receiving IL-2 [5]. The reasons for this are not yet completely known, but recent advances in our understanding of the negative regulatory networks of the immune response do provide some explanations as well as directions for moving forward.

The human immune system: a question of balance

As it turns out, a normal immune response results from the balance between the forces of activation with those of tolerance or suppression [6]. Excessive immune activation and/or the absence of natural tolerance can result in autoimmune diseases, such as systemic lupus erythematosus or rheumatoid arthritis, whereas excessive immune suppression or the induction of tolerance can result in infection and/or cancer, especially those cancers associated with viruses, such as Epstein–Barr virus (EBV)-associated lymphoma or human herpes virus 8-associated Kaposi's sarcoma. In the case of EBV lymphoma, immune tolerance can be induced iatrogenically with the administration of powerful immunosuppressive, anti-graft rejection drugs such as cyclosporine and azathioprine. When such drugs are reduced or withdrawn, the suppressed immune system can sometimes reverse and eliminate cancer with startling efficiency in the absence of any chemo- or radiotherapy [7]. Thus, the ability of the immune system to patrol for and effectively prevent or eliminate certain cancers can result from the discontinuation of immune suppression, even in the absence of additional immune activation.

Indeed, many “successful” cancers have genetic alterations that disarm the activating arm of the immune system, allowing for tumor escape. For example, MICA/B are the cognate cell surface ligands for NKG2D, a lectin-like receptor expressed on NK cells and some T cells [8]. In murine models, when ligands of NKG2D are expressed on tumor cells, they can be recognized by T cells or NK cells and lead to tumor clearance [9]. However, certain epithelial cancers secrete or shed an abundance of MICA in a soluble form, thereby occupying NKG2D on T cells and NK cells such that they cannot recognize and eliminate the tumor itself (Fig. 1) [10].

If tumors can disarm the activating arm of the immune system and escape cell death, one might speculate that tumor cell death could be enhanced by disarming immune tolerance. Indeed there have been an abundance of instances where, in murine tumor models, the blockade of molecules that induce immune tolerance leads to tumor clearance [11]. One such molecule expressed on T cells, CTLA-4, has been exploited clinically in the treatment of malignant melanoma. In a randomized controlled trial, it was demonstrated that the administration of a monoclonal antibody that blocked CTLA-4 significantly improved survival of patients with metastatic melanoma when compared to the administration of a vaccine alone (Fig. 2) [12]. The presumption is that reversal of immune tolerance via the blockade of CTLA-4 led to T-cell recognition of tumor-associated antigens expressed on the surface of malignant melanoma cells. Thus, T-cell elimination of malignant melanoma cells was thought to result in the extended survival of patients treated with the CTLA-4 monoclonal antibody. Below, we discuss various immunotherapeutic approaches, including the reversal of immune tolerance, for the treatment of AML.

Limiting immune tolerance for curative therapy in AML

Killer immunoglobulin-like receptors (KIR) expressed on the surface of NK cells normally recognize self HLA Class I ligands expressed on all cells. When this occurs, an inhibitory response dominates, preventing the NK cell from implementing cytotoxicity against self. Hence, one could hypothesize that when the NK cell cannot recognize inhibitory KIR ligands, it has enhanced license to kill, in the same way T cells do by blocking CTLA-4. This could be explored clinically in the setting of hematopoietic stem cell transplant (HSCT), where donor NK-cell KIR do not recognize recipient HLA Class I molecules (so called haplo-mismatched HSCT). The role of NK cells in mediating GVL while mitigating GVHD was first demonstrated by Ruggeri et al in the setting of T-depleted HLA mismatched transplantation [13]. In a study of 92 high-risk acute leukemia recipients who received grafts from an HLA haplotype mismatched family donor, recipients lacking HLA ligands for donor KIR were found to have a lower rate of rejection, relapse, and GVHD.

Ruggeri et al. [13] evaluated the mechanism for these effects in a mouse model of mismatched allogeneic transplantation. When alloreactive donor NK clones were infused pre-transplant, a reduction of recipient antigen presenting cells (APC) was noted in the bone marrow, spleen, and gut. These data suggest that alloreactive NK cells prevent GVHD by elimination of recipient APCs that are known to be critical for initiating the GVHD cascade. Importantly, these data further established that alloreactive donor NK cells can be used safely and do not cause GVHD.

Other mechanisms have also been postulated to explain NK cell reduction of GVHD, including evidence that donor NK cells are capable of killing donor T cells that mediate GVHD. In an MHC mismatched setting, mouse recipients of an allogeneic transplant that received donor NK cells and T cells on day 0 along with T-depleted bone marrow had longer survival and a lower incidence of GVHD compared with controls that received donor T cells alone [14]. Furthermore, donor T cells exhibited less proliferation and decreased interferon-gamma (IFN- γ) production in the presence of NK cells. These N-cell effects appeared to be mediated through both perforin and FasL, resulting in a reduction of donor T-

cell proliferation and apoptosis of alloreactive donor T cells. Remarkably, despite reducing GVHD, the graft-versus-tumor effects mediated by donor T cells were retained in this model.

Another study by Rivas et al. [15] showed the regulatory effect of NK cells on minor antigen specific T cells that mediate GVHD. When male minor antigen-reactive CD4 T cells were injected into murine recipients without NK cells, they noted extensive expansion of CD4⁺ T cells with infiltration into organs causing chronic GVHD. In contrast, when NK cells were present, minor antigen-reactive T-cell proliferation and GVHD did not occur. The authors postulated a mechanism whereby chronically activated T cells up-regulate NKG2D ligands, which render them susceptible to NK-cell killing via NKG2D activation. Furthermore, they showed evidence that chronically stimulated T cells mediating GVHD up-regulated Fas, rendering them susceptible to apoptosis via NK cell Fas-ligand.

As our understanding of the mechanisms of NK cell alloreactivity have grown, more data have accumulated on the importance of donor selection. The different KIR that are expressed on NK cells recognize disparate HLA molecules and are divided into two different haplotype groups: (a) Group A haplotypes that have a fixed number of genes that encode inhibitory receptors with the exception of KIR2DS4, and (b) Group B haplotypes that have variable gene contents including additional activating receptor genes [16,17]. All individuals can be categorized as having the following KIR genotypes: A/A, which is homozygous for group A KIR haplotypes, or B/x, which contains either 1 (A/B heterozygotes) or 2 (B/B homozygotes) group B haplotypes. Recent studies [18,19] have suggested that the donor's NK cells expressing group B haplotypes, compared with group A, yield significantly superior protection against leukemic relapses and improved disease-free survival (DFS) in patients undergoing T-cell depleted HSCT for AML.

Sivori et al. [20] show that expression of KIR2DS1 confers a remarkable advantage in the ability of NK cells to kill allogeneic dendritic cells (DCs) and T-cell blasts. We now have compelling evidence [19,21,22] from both the haploidentical and matched unrelated transplants that donor KIR2DS1 and 2DS2 genotypes are associated with a significantly lower relapse rate. These data point to the importance of donor selection in order to choose the donor with maximal alloreactivity as a promising strategy for maximizing GVL while minimizing GVHD and infection-related mortality.

Natural-Killer cell based Immunotherapy in the non-HSCT setting

Up to 50% of patients will not have an HLA-identical donor, which has led to an increase in the use of alternative donor grafts. However, the mortality associated with HSCT is high, in the range of 10%–20%. In an effort to maximize GVL effects and to minimize transplant-related mortality, donor NK cell infusions in the non-HSCT setting have been explored. Miller et al first reported the transfer of haploidentical NK cells in the non-HSCT setting [23]. Rubnitz et al. [24] studied haploidentical KIR-mismatched NK infusions as post remission therapy in childhood AML after low intensity immuno-suppression. Ten patients (0.7–21 years old) who were in first complete remission of AML received conditioning with cyclophosphamide and fludarabine, followed by infusion of KIR-HLA mismatched NK cells (median, $29 \times 10^6/\text{kg}$ NK cells) and six doses of interleukin-2 (1 million U/m²). With a

median follow-up time of 964 days (range, 569 to 1162 days), all patients remain in remission. A phase II trial is being conducted evaluating efficacy of KIR-mismatched NK cells as consolidation therapy for AML in pediatric AML.

Curti et al. [25] studied feasibility of KIR-mismatched alloreactive NK cell infusion with low-dose IL-2 in elderly AML patients as post remission therapy, followed by immunosuppression with fludarabine and cyclophosphamide. Three of 6 patients in complete remission remain leukemia free at 34, 32, and 18 months of follow-up. These data suggest that NK cell therapy has potential clinical benefit in this patient population traditionally considered to have a poor prognosis.

The GVL effect mediated by NK cell KIR mismatch has been shown in T-cell depleted haploidentical allogeneic HSCT for AML. One could speculate that, like CTLA-4, blocking the inhibitory KIR could potentiate tumor cell kill by NK cells in the autologous setting for AML. Romagne et al. [26] generated a fully human monoclonal antibody, 1-7F9, which cross-reacts with KIR2DL1, -2, and -3 receptors, thereby preventing their inhibitory signaling (Fig. 3). The 1-7F9 monoclonal antibody augmented NK-cell-mediated lysis of HLA-C-expressing tumor cells, including autologous AML blasts, but did not induce killing of normal peripheral blood mononuclear cells. This antibody was well tolerated in a phase I trial in elderly patients with AML in complete remission [27]. At a median follow-up of 47 weeks, 6/21 patients continue to be in remission. This trial showed the feasibility and safety of initial and repeated treatment with anti-KIR monoclonal antibody therapy and correlative studies confirmed the specificity of the immunological effects.

PD-1 blockade and AML

Programmed-death receptor-1 (PD-1) is a type 1 membrane protein and a member of the extended CD28/CTLA-4 family [28]. It is expressed on activated T and B cells and macrophages and compared to CTLA-4, PD-1 more broadly regulates immune tolerance.

Zhou et al showed that PD-1 knockout mice were more resistant to AML despite the presence of similar percentage of Tregs compared with wild type mice [29]. In vitro, the Tregs' ability to blunt the CD8⁽⁺⁾ cytotoxic T-cell response to AML cells was dependent on a PD-1/PD-1-ligand interaction with antigen presenting cells. In vivo, an antibody blocking this interaction enhanced T-cell immunity against AML and improved survival. Studies examining PD-1 blockade are ongoing in humans, but this experimental data would support exploration of this approach in AML.

Cytokines

As mentioned earlier, studies with IL-2 as a single immunomodulatory agent in the treatment of AML have not shown reproducible efficacy of IL-2 [5]. IL-2 preferentially expands Tregs that inhibit antitumor immunity. IL-15, like IL-2, binds to the IL-2 α and γ receptor (R) chains, but has distinct effects on T cells. It expands NK cells and CD8⁺ memory T cells with minimal increases in Tregs [30]. Low-dose IL-15 administration can enhance the efficacy of adoptively transferred tumor-specific T cell therapy, which is distinct from IL-2 administration [31]. Also, recent data [32] show that cytokine production and cytotoxic function, by reconstituting donor-derived NK cells after HSCT, do not coexist

in a consistent manner, but exogenously administered IL-15 in this setting increased cytokine production by NK cells. As IL-15 becomes clinically available, it will be interesting to evaluate its optimal administration in regards to timing in the HSCT and non-HSCT setting for AML.

Direct targeting of AML with monoclonal antibodies

Monoclonal antibodies can kill leukemic cells via a variety of mechanisms and have emerged as promising therapeutic tools, due to their specificity and potential for reduced toxicity compared to conventional chemotherapy. AML cells express several surface molecules that have been explored as targets for monoclonal antibody therapy. These include CD33, CD123 (IL-3 receptor alpha chain) [33], CD47 (integrin-associated protein) [34], C-type lectin [35], and CD64 (high-affinity Fc gamma receptor) [36]. With the exception of CD33, these agents have documented efficacy in vitro and are being actively developed for clinical trials. Gemtuzumab, a monoclonal antibody against CD33, was used together with other agents to treat relapsed or refractory leukemia [37]. This agent was FDA approved but has recently been withdrawn from the market for lack of a survival benefit. It continues to be evaluated in the setting of clinical trials.

Conclusion

The goal of immunotherapy in the treatment of leukemia is to sustain remission after remission induction is achieved with cytoreductive chemotherapy. We are beginning to discern the beneficial immune effects of chemotherapy, such as lymphopenia, which sets the stage for administration of further immune therapies. We are also beginning to realize that chemotherapy may have detrimental effects, such as upregulation of cytokines like FLT3 ligand, potentially fueling resurgence of FLT3-addicted leukemic blasts in FLT3-ITD mutated AML [38,39]. Monitoring for minimal residual disease after HSCT allows us to explore preemptive cellular therapy or vaccine-based approaches for relapse in high-risk situations. It is foreseeable that soon we will be pursuing a multi-pronged strategy with selection of induction regimens that will promote synergy of immunotherapy in the treatment of AML. The future of immune therapy will likely continue to be explored with the reduction or a limitation of immune tolerance by careful donor selection in transplantation, anti-PD1, CTLA-4, and/or anti-KIR therapies. Collectively, these therapies can be incorporated into harnessing and maintaining the potent GVL effects with HSCT.

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Fig. 1.

Tumor cells expressing MICA or MICB can be recognized and eliminated by NK cells or T cells expressing NKG2D. Certain epithelial tumors can shed MICA, which in turn binds to NK and T cells, down regulating NKG2D from their cell surface and thus preventing the NK or T cell from recognizing the tumor [10].

Fig. 2.

Improved overall survival of patients with metastatic melanoma treated with anti-CTLA-4 monoclonal antibody ipilimumab (with or without vaccine gp 100) compared to vaccine gp 100 alone. From Hodi et al. [12].

Fig. 3. Killer immunoglobulin-like receptors (KIR) expressed on NK cells recognize self HLA molecules expressed on all cells which in turns sends a negative or inhibitory signal to the NK cell. Blockade of this KIR-HLA interaction with an anti-KIR monoclonal antibody results in lysis of autologous AML blasts [26].