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Adoptive Immunotherapy for Acute Myeloid Leukemia: From Allogeneic Hematopoietic Cell Transplantation to CAR T Cells

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Abstract

Allogeneic Hematopoietic Cell Transplantation (allo-HCT) has improved outcome of patients with high risk Acute Myeloid Leukemia (AML), but it harbors a risk of morbidity and mortality due to damage to normal cells and tissues by the high intensity conditioning or due to Graft Versus Host Disease (GVHD). As a major component of the curative potential of allo-HCT is derived from the response of the donor immunity against the malignant cells through the so called Graft Versus Leukemia effect (GVL), novel adoptive immunotherapy strategies have been developed to generate immune response against the leukemic cells, while sparing GVHD.

Keywords: Graft Versus Host Disease (GVHD); Hematopoiesis; Leukemic cells

Allogeneic Hematopoietic Cell Transplantation

The principle of anti-leukemic adoptive immunotherapy, as coined by Georges Mathé in 1965, is an activity of allogeneic immunologically competent cells against the host's leukemic cells [1]. The best known model and the most commonly used method of anti-leukemic adoptive immunotherapy is allogeneic Hematopoietic Cell Transplantation (allo-HCT). The initial goal of allo-HCT was to eradicate leukemic cells by high doses of chemo or radiation therapy, which also destroys normal hematopoiesis, and then rescue the patient with a healthy hematopoietic progenitor cells from an allogeneic donor. However, it is now clear that the potential curative effect of allogeneic HCT is derived not only from the intense cytotoxic therapy, but also from the response of the donor's immune cells against the leukemic cells, through a so called graft versus leukemia (GVL) effect.

The evidence to support GVL effect of allo-HCT are: (i) lower relapse rate among recipients of HLA-identical sibling transplants than recipients of syngeneic transplants [2-5]; (ii) decrease relapse rate among patients who develop Graft Versus Host Disease (GVHD) after allo-HCT [2,6]; (iii) decreased GVHD, but increased relapse rate after T cell depleted allo-HCT [7,8]; (iv) anti-leukemic effect and curative potential of Donor Lymphocyte Infusion (DLI) in patients with relapse leukemia after transplant [9,10]; and (v) effectiveness of nonmyeloablative HCT [11].

GVL is mediated through the immunologic activity of donor T cells and Natural Killer (NK) cells recognizing Leukemia-Associated Antigens (LAA), minor histocompetability antigens (mHag), and in case of mismatch or haploidentical transplants also major histocompetability antigens that are expressed by the malignant cells [12,13].

Donor immunity may contribute to the cure of the leukemia by allo-HCT, but is also the cause of GVHD, mediated by donor T cell recognizing antigens expressing by normal cells. GVHD is a major cause of morbidity and mortality after transplant, and it was recently demonstrated that the beneficial effect of GVL may be outweighed by the morbidity and mortality caused by GVHD [11]. Thus, therapies that provide potent GVL while sparing GVHD are needed.

NK cell-mediated anti-leukemic adoptive immunotherapy

Clinical observations have shown that donor NK cells may contribute to GVL activity in HLA-mismatched allogeneic HCT. NK cells display a number of activating and inhibitory receptors that interact with a wide variety of ligands on target cells, and the function of the NK cell depends on the net effect of the activating and inhibitory receptors [14]. Among the NK cells inhibitory receptors are Killer Immunoglobulin Receptors (KIRs) that recognize certain groups of HLA class I molecules on the target cell. It has been demonstrated that donor NK cells expressing KIRs that are mismatched with the recipient HLA class I and therefore are not inhibited by the HLA molecules of the recipient, so called alloreactive NK cells, are associated with decreased relapse and decreased GVHD rates after T cell-depleted HLA-mismatched or HLA-matched HCT in patients with Acute Myeloid Leukemia (AML) [15-18]. A number of early stage clinical trials have demonstrated that NK cells can be safely infused in AML patients following immunosuppressive chemotherapy and, in some cases, clinical responses without GVHD have been observed [19-21]. The results of these clinical trials demonstrate that NK cell-based therapy, which may provide anti-leukemic effect without GVHD, is a potential strategy to consolidate leukemia remission in high-risk AML, without the need of allo-HCT.

T Cell Mediated Anti-Leukemic Adoptive Immunotherapy

A potential approach to generate GVL is by identifying and expending donor T cells that recognize LAA or mHags expressing on the malignant cells. Cytotoxic T lymphocyte (CTL) clones specific for hematopoietic restricted mHags have been shown to have anti-

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leukemic activity when used to treat patients with relapse leukemia after allo-HCT [22]. T cell clones specific for LAA as WT1, CD45, and PR1 have been generated to target leukemic cells [23-25], and recently Greenberg and colleagues reported results from a clinical trial using *ex vivo* expanded HLA-A*0201-restricted WT1-specific donor-derived CD8 CTL clones for treatment of relapsed or high-risk leukemia after allo-HCT [26]. This clinical trial demonstrated long term persistence and potential anti-leukemic activity of donor CTL clones specific for WT1. However, isolation and *ex vivo* expansion of high avidity mHag or LAA-specific T cell clones is challenging process, as it relies on the individual donor T cell repertoire and may result in products with variable quality and wide range of avidity, persistence, and function *in vivo*.

A potential way to circumvent the challenge of isolation and expansion of antigen-specific high avidity T cells is by using gene transfer technologies to genetically engineer T cell to express a unique high-affinity T cell receptor (TCR). The first successful TCR gene transfer to human peripheral blood lymphocytes conferring anti-tumor reactivity was reported by Clay and colleagues in 1999, using a TCR specific for an HLA-A2-restricted epitope of the MART-1 antigen, which is highly expressed by malignant melanomas [27]. Since then, several studies have demonstrated that transfer of a tumor antigen-specific TCR into T cells has successfully led to generation of an antigen-specific T cell population [28-41]. However there are a number of limitations to this approach:

1. The TCR recognizes a peptide fragment of its target antigen only when the peptide is presented by an HLA Class I molecule on the surface of the target cell. Therefore, antigen specific T cells are restricted to specific HLA allele, requires generation of patient-specific product. To date, most TCR gene transfer studies have focused on TCRs restricted to HLA-A2, as it is the most common HLA class I, present in ~50% of Caucasians [42,43].

2. Mispairing of the transduced and the endogenous TCR α and β chains that may lead to generation of non-specific TCR. A potential way to overcome this difficulty is insertion of point mutations into the constant regions of the transduced TCR α and β chains to create complementary cystein residues that form an inter-chain disulfide bond, which promotes preferential pairing between the transduced TCR chains and significantly reduces mispairing [44,45].

3. Downregulation of HLA class I expression by some leukemic cells have been reported [46], which may prevent recognition of the antigenic target by the TCR, and thus inhibits the antileukemic function of the T cell.

4. Chimeric Antigen Receptor (CAR) is another approach to T cell gene therapy. CAR is a genetically engineered molecule composed of an antigen-specific extracellular binding domain, fused to a transmembrane domain and intracellular T cell-specific signalling domain. The CARs are transduced into T cells, which become "CAR T cells" with specific target based on the CAR binding domain**.** Upon CAR binding to an antigen on the cell surface of a target cell, the CAR T cell induces apoptosis of the target cell using the same mechanisms of ordinary T cell. In contrast to a TCR, which recognizes a peptide fragment of an antigen only when the peptide is presented by an HLA Class I molecule on the surface of target cells, a CAR molecule recognizes an intact cell surface antigen, and it is HLA independent. Thus, the same CAR molecule may be used in a broad range of patients with different HLA types. CARs can target any cell surface antigen including carbohydrate and lipid moieties, which increases the repertoire of potential targets for CAR-base therapy. However CARs target only cell surface antigens, therefore, CAR T cells cannot target intracellular mutated or over expressed proteins.

Since the CAR concept was first introduced by Eshhar and colleagues in 1989 [47], CAR T cells have been generated to target several antigens on malignant cells [48-64], and a number of clinical trials are currently evaluating the use of CAR T cells, originated from allogeneic donors or patients, for treatment of different malignancies. In haematological malignancies there have been promising reports of using CAR-modified anti-CD19 T cells for treatment of B-cell malignancies [65-70]. CAR T cell targeting AML antigens as CD33 and CD123 have been reported [71,72], and recently early phase small clinical trial has demonstrated persistence and potential anti-leukemic effect of CAR T cell against the LeY antigen in AML [73].

Conclusions

Adoptive immunotherapy has the potential to provide long-term survival and even cure in patients with leukemia. The well-established allogeneic hematopoietic cell transplantation has improved outcome of patient with high risk AML, however it harbors the risk of morbidity and mortality due to damage to normal cells and tissues by the high intensity conditioning or due to graft versus host disease. Novel approaches using NK cells and T cells have been developed to provide more direct anti-leukemic therapy while sparing the risk of toxicity to normal tissues. However several obstacles need to be overcome in order to improve *in vivo* survival and antileukemic function of the transferred cells. Additionally, reliable large scale manufacturing of the therapeutic cells is essential to allow large clinical trials to evaluate the efficacy of various novel strategies before these therapies can be adopted for routine use to treat AML patients.

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