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CARs and other T cell therapies for MM: The clinical experience

Sophia Danhof, MD[a], Michael Hudecek, MD[a], Eric L. Smith, MD PhD[b,*]

[a] Department of Hematology and Medical Oncology, University Hospital Wuerzburg, Versbacherstrasse 5, 97078 Wuerzburg, Germany
[b] Myeloma Service, Cellular Therapeutics Center, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, NY 10065, New York, USA

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ABSTRACT

Harnessing the endogenous immune system to eliminate malignant cells has long been an intriguing approach. After considerable success in the treatment of B-cell acute lymphoblastic leukemia, chimeric antigen receptor (CAR)-modified T cells have entered early clinical evaluation in the field of multiple myeloma (MM). The choice of suitable non-CD19 target antigens is challenging and a variety of myeloma-associated surface molecules have been under preclinical investigation. Most recent clinical protocols have focused on targeting B-cell maturation antigen (BCMA), and early results are promising. The trials differ in receptor constructs, patient selection, dosing strategies and conditioning chemotherapy and will thus pave the way to eventually define the optimal parameters. Other sources for autologous T-cell therapy of MM include affinity-enhanced T-cell receptor-modified cells and marrow infiltrating lymphocytes. In summary, adoptive T-cell transfer for the treatment of MM is still in its infancy, but if early response rates indicate durability, will be a paradigm changing therapeutic modality for the treatment of MM.

1. Introduction

Multiple myeloma (MM) is the second most commonly diagnosed hematologic malignancy. Despite considerable improvement in therapeutic approaches, it still remains an incurable disease in most cases [1,2]. Recent treatment strategies are increasingly focusing on a redirection of the immune system to harness the intrinsic immune defense against the disease [3]. The prime example of immunotherapy is allogeneic hematopoietic stem cell transplantation (alloHSCT) with its desired graft-versus-myeloma effect. While alloHSCT and donor lymphocyte infusions have demonstrated the curative potential that can be mediated by T-cell anti-myeloma immunity [4], transplant related mortality and graft-versus-host disease limit their clinical application for MM [5,6]. Therefore, other concepts to exploit the anti-myeloma capacities of autologous lymphocytes are desirable. Here, we discuss the three major concepts for adoptive transfer of T cells with reactivity against MM: chimeric antigen receptors, affinity-enhanced T-cell receptors, and marrow infiltrating lymphocytes.

2. Chimeric antigen receptors

In order to recognize a specific tumor-associated surface antigen, T cells can be redirected by genetic modification to express a chimeric antigen receptor (CAR). In 2017, the FDA granted approval of CD19-directed CAR-T cells for young patients with relapsed/refractory B-cell acute lymphoblastic leukemia and for adults with certain types of relapsed/refractory aggressive non-Hodgkin lymphomas. The success stories from CAR T cell therapy for CD19-positive B-cell malignancies [7–10] have attracted enormous attention to the field and currently, a large variety of alternative target antigens for various types of cancer are under investigation.

* Corresponding author.
E-mail addresses: danhof_s@ukw.de (S. Danhof), hudecek_m@ukw.de (M. Hudecek), smithe3@mskcc.org (E.L. Smith).

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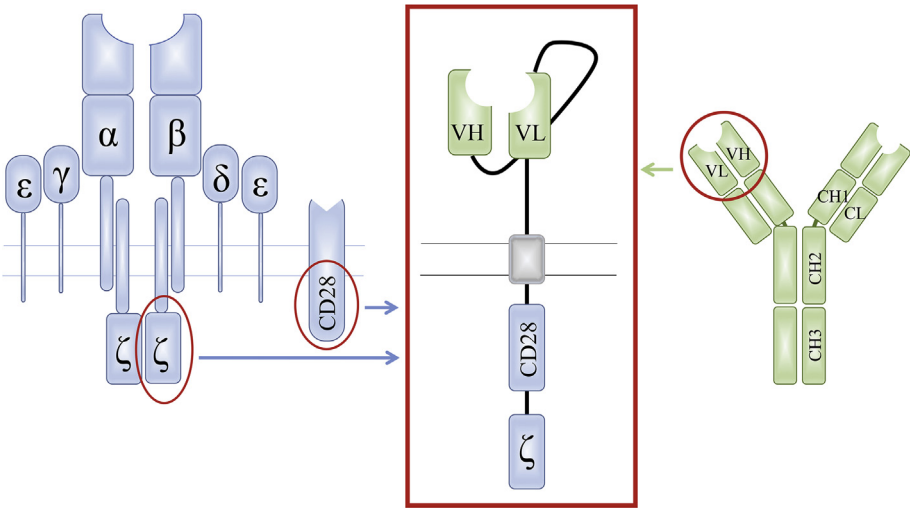

Fig. 1. Schematic composition of a second generation chimeric antigen receptor. The extracellular domain of the chimeric antigen receptor (CAR, red box) contains a single-chain variable fragment (scFv), most commonly derived from the heavy (VH) and light (VL) chain variable fragments of a monoclonal antibody (green). The components of the CAR are connected by an extracellular spacer and a transmembrane domain. The intracellular moiety comprises the CD3ζ signaling domain of the T-cell receptor (blue) and, in a second generation CAR, a co-stimulatory domain derived from a co-receptor like CD28 (blue).

The basic property of the CAR construct is to establish cell surface antigen-specific binding to a target cell and thereon initiate supra-physiologic T-cell activation in an HLA-independent manner. For this purpose, the CAR consists of an extracellular targeting moiety and intracellular signaling domains [11,12]. For antigen binding, most commonly, single-chain variable fragments (scFv) derived from murine immunoglobulins or human antibody libraries are used (Fig. 1). The scFv is connected to the intracellular moiety by an extracellular spacer and a transmembrane domain, often derived from IgG4 and CD8, respectively. Historically, the intracellular component of the CAR consisted solely of the CD3ζ signaling domain of the T-cell receptor [11]. The failure of the CAR-T cells to proliferate led to the development of dual-signaling receptors to provide the cells with a co-stimulatory signal [13]. These second generation CARs most commonly contain co-stimulatory domains derived from either CD28 or 4-1BB in addition to CD3ζ (Fig. 1). Whether combination of multiple co-stimulatory domains in so-called third generation CARs can convey improved antitumor efficacy in a clinical context is yet to be determined.

3. CAR-T cell associated toxicities

Apart from the toxicities of pre-conditioning regimens for lymphodepletion prior to adoptive transfer, a new complex of side effects has been observed in CAR-T cell trials. This includes cytokine release syndrome (CRS), resulting from the excessive release of cytokines after T-cell activation, neurologic toxicities, and “on-target, off-tumor” targeted destruction of healthy tissue [12].

CRS can range from flu-like symptoms to hypotension, capillary leak, coagulopathy and organ dysfunction [14]. Besides supportive measures like fluid replacement and vasopressor support, the specific IL-6 receptor blockade by tocilizumab has proven an extremely effective treatment strategy at rapidly reversing toxicity; potentially without compromising CAR-T cell efficiency. Approaches to prevent the development of CRS in the first place by modification of T-cell composition and dose reduction have also been successful in some trials [10].

Most neurologic adverse events are observed during or after severe CRS. Clinical presentations range from mild confusion to seizures or coma requiring ventilatory support [15]. Pathophysiological correlates of severe neurotoxicity appear to be high cytokine levels in the cerebrospinal fluid and increased permeability of the blood-brain barrier [16]. Unlike for CRS, the effect of tocilizumab on neurologic sequelae is so far unclear and alternative treatment strategies are under development.

“On-target, off-tumor” toxicity is highly dependent on the chosen antigen. One of the best examples is the B-cell aplasia associated with CD19 CAR-T cell treatment [14], but while this side effect can be addressed by immunoglobulin replacement, damage to more essential tissue types can be fatal. Reportedly, targeting her2 in a patient with advanced colonic cancer resulted in severe pulmonary edema and cardiac arrest due to low-level antigen expression in the heart and lung vasculature [17]. The fact that CAR-T cells require extremely low antigen densities for activation limits the transferability of safety observations from monoclonal antibody therapies.

4. CAR targets

For safe and efficient integration of CAR-T cell therapy into clinical practice, the choice of a suitable target antigen is crucial [18]. As the antigen recognition of the CAR is independent from HLA-molecules, the antigen must be expressed on the surface of the malignant cells. Homogeneous expression in the tumor cell population is required to prevent the outgrowth of antigen deficient