Expert Review of Hematology

ISSN: 1747-4086 (Print) 1747-4094 (Online) Journal homepage: informahealthcare.com/journals/ierr20

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To cite this article: Tobias Riet & Hinrich Abken (2015) Chimeric antigen receptor T cells: power tools to wipe out leukemia and lymphoma, Expert Review of Hematology, 8:4, 383-385, DOI: 10.1586/17474086.2015.1043884

To link to this article: https://doi.org/10.1586/17474086.2015.1043884

Published online: 06 May 2015.

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Chimeric antigen receptor T cells: power tools to wipe out leukemia and lymphoma

Expert Rev. Hematol. 8(4), 383–385 (2015)

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Adoptive cell therapy for malignant diseases is showing promise in recent early-phase trials in the treatment of B cell leukemia/lymphoma. Genetically engineered with a tumor-specific chimeric antigen receptor, patient's T cells produce lasting and complete leukemia regression. However, treatment is associated with some toxicity which needs our attention and the field still faces some hurdles at the scientific, technologic and clinical levels. Surmounting these obstacles will establish chimeric antigen receptor T cell therapy as a powerful approach to cure hematologic malignancies, paving the way for the treatment of other common types of cancer in the future.

Adoptive cell therapy changed the scientific world when refractory advanced chronic lymphatic leukemia was turned into complete and lasting remission by treatment with genetically engineered T cells [1,2]. Patient's T cells were redirected toward leukemic cells by an engrafted chimeric antigen receptor (CAR) with specificity for CD19 (CTL019). With little alternatives left but still being sensitive to some chemotherapeutics, patients received CD19-specific CAR T cells in a split-dose manner within 3 days up to a total dose of 1.1×10^9 CAR T cells; the lowest dose was 1.4×10^7 CAR T cells [1]. T cell therapy produced remission in 12 out of 23 chronic lymphatic leukemia patients, with 6 complete responses remaining disease-free to date. The induction of lasting remissions makes the CD19 targeting CAR T cell trial [3] a milestone in the CAR field, although the trial at University of Pennsylvania is not the first or the only CAR T cell study to be launched in humans. Other centers including Sloan Kettering Memorial Institute successfully treated chronic lymphatic leukemia patients with anti-CD19 CAR T cells as well [4,5]. Of even stronger public perception was one of the follow-up trials targeting pediatric acute lymphoblastic leukemia (ALL) with CTL019 in 2012, when the first treated patient went into complete and lasting remission, and which was rewarded as 'Breakthrough Therapy' for relapsed and refractory ALL in adults and children by the US FDA in 2014. Taking pediatric and adult ALL together, 27/30 complete remissions have been achieved, 19 patients remain in remission to date and 6 patients experienced relapses [6,7,3,8]. These and other leukemia/lymphoma trials draw our attention on the outstanding potential of CAR T cells. Since the first clinical trial with anti-CD19 CAR T cells in B cell malignancies, more than 70 patients have been treated in different trials in the US, basically using two main clinical settings: one as additional therapy for human stem cell transplantation and the other one as stand-alone treatment [1,2]. These days, 28 CD19 CAR T cell trials are recruiting patients in the US, UK, Sweden, China and Japan, exploring CAR T cell treatment of B cell malignancies on a broad basis [9]. The spectacular therapeutic success of CAR-based cell therapy finally received attention of pharmaceutical and biotechnological companies, which had

EXPERT REVIEWS

KEYWORDS: adoptive cell therapy • chimeric antigen receptor • immunotherapy • leukemia • lymphoma • T cell

 10.1586/17474086.2015.1043884 © 2015 Informa UK Ltd ISSN 1747-4086

thus far feared the complexity of cellular therapy in both manufacturing and clinical application. Novartis announced to establish a Center for Advanced Cellular Therapy on the University of Pennsylvania Medical Campus; multiple other companies are joining the field investigating CAR T cell therapy applications in the treatment of cancer, infections and graft versus host disease [10].

While the efficacy of CAR T cells in eradicating large tumor burden in the treatment of leukemia/lymphoma cells cannot be any longer doubted, systematic comparison of the various trials is even difficult due to a number of differences in details, including the mode of pre-conditioning, the CAR construct itself, the genetic vector, the T cell amplification, the CAR T cell dose and others. However, some basic lines for the therapeutic efficacy become visible. First, there is no correlation between the number of infused CAR T cells or patients' tumor burden and the clinical outcome, pointing to the high proliferative potential and serial killing capacities of CAR T cells after administration [4,11]. Second, lymphodepletion prior to CAR T cell therapy seems to be mandatory to shape a favorite environment for the adoptively transferred T cells, to eradicate suppressor cells and to make a severely affected bone marrow more susceptible for T cell penetration [12]. Third, co-stimulation to push the transferred T cells to full activation is a prerequisite for their persistence and the establishment of a specific memory, both required for a lasting anti-tumor response. In this context, so-called second-generation CARs with co-stimulatory and primary CD3ζ signaling co-integrated into the same CAR molecule are an indubitable advantage over first-generation CARs with the CD3ζ signal only [13].

However, substantial risks and toxicities become obvious to be an imminent part of anti-CD19 CAR T cell therapy. Among them, B cell aplasia as a consequence of 'on-target, off-tumor' toxicity has been observed in all patients treated so far; however, it can be clinically managed by immunoglobulin replacement therapy. The severity of tumor lysis syndrome seems to be related with high tumor burden and its occurrence may be delayed by weeks; however, it occurred immediately at the second CAR T cell boost in the University of Pennsylvania trial [1]. Tumor lysis syndrome can be clinically identified in an early stage and treated without impact on the therapeutic efficacy [2]. In addition, macrophage activation syndrome may occur, which is indicated by elevated serum levels of ferritin (>500,000 ng/ml), C-reactive protein, D-dimer and the pro-inflammatory cytokines IFN-γ and IL-6; the effect of the latter can be blocked by the neutralizing anti-IL-6 receptor antibody, tocilizumab [6]. Tumor lysis syndrome is frequently coincident with the cytokine release syndrome which represents a life-threatening, although reversible, toxicity, requires intensive care and may be fatal if not immediately counteracted [6,14]. Corticosteroid therapy resolved the clinical symptoms, but also diminished the number of circulating CAR T cells, resulting in a less-effective clinical outcome. The pathophysiology of the cytokine release syndrome is not yet fully understood and requires the exploration of a more specific management without losing therapeutic efficacy. Lee *et al.* recently suggested a treatment algorithm where immune suppression should only be used in grade 3 or 4 toxicity; earlier intervention may be required if patients have extensive comorbidities or are of older age [15]. In order to reduce the risk of losing anti-tumor efficacy, patients with lower-grade toxicity are recommended to get vigilant supportive care including anti-cytokine therapy, vasopressors and an assessment for infection. Other concepts including specific depletion of CAR T cells by activating suicide genes, the integration of a targetable tag for depleting antibodies into the CAR molecule or the use of inducible promoters for CAR expression may provide a safer profile; however, they are unlikely to diminish toxicity when clinical symptoms already occurred [16,17]. These and other strategies to manage the side effects of CAR T cell therapy still need to be clinically validated in a larger cohort.

Another type of toxicity was observed in a trial targeting mesothelin by mRNA-modified CAR T cells to treat pancreatic adenocarcinoma [18]. The patient developed anaphylaxis with symptoms of systemic inflammation shortly after administration of the third T cell dose. Investigators hypothesized that the event was caused by an acquired immune response toward the CAR molecule itself or a carrier protein of the cell product. Repetitive administration of the cell product in high dose may potentiate the toxicity. The use of fully humanized CAR molecules may be a strategy to avoid anaphylactic reactions; however, some domains within the CAR molecule will still be recognized as immunologically foreign, in particular, the joining regions of the CAR modules. Anti-CAR immune reactions may more often occur once CAR T cell therapy becomes widely used and they need to be addressed in the near future.

The choice for a suitable target remains most challenging with respect to CAR T cell associated toxicity and selectivity in cancer cell targeting. While life-threatening 'on-target, off-organ' toxicity is more relevant in the treatment of solid tumors [19], targeting of healthy cells in the case of anti-CD19 CAR T cells is rather limited to B cell aplasia which requires life-long immunoglobulin substitution therapy. We expect that CARs with more selectivity for leukemia will emerge more and more but, nevertheless, the anti-CD19 CAR therapy will most likely be applied to larger patient cohorts as a clinical practice. The ideal CAR target should not be expressed by healthy cells or at least at such low densities that do not touch the CAR activation threshold. Low affinity, but highly specific CAR targeting may be an added choice. Instead of targeting one antigen, selectivity for malignant cells may be obtained by combinatorial recognition of two antigens on the same target cell; CAR T cells are only activated upon binding to both targets, while one target is not sufficient to induce T cell activation [20]. In the context of leukemic cell targeting, combinatorial recognition of CD5 and CD19 by two CARs may prevent B cell aplasia while targeting leukemic cells.

While CAR targeting is specific for the cognate antigen, mutant cancer cells with down-regulated or mutated antigens are invisible to CAR T cells. Loss of target occurs under selective

pressure and was observed in a recent trial for CAR T cell treatment of B-ALL [6]. To prevent the relapse of antigen-negative escape variants, the use of bispecific CAR T cells might be an option, either by engineering with two CARs, each of different specificity, or with one CAR with two specificities [21]. Alternatively, a mixture of two T cell populations, each expressing a CAR with a defined specificity, may be used [22].

Despite some unresolved hurdles at the moment, CAR T cell therapy in B cell malignancies is on the road to the finish line [10]. Nevertheless, CAR T cell therapy will remain an individualized therapy and a treatment regimen with a substantial risk of side effects, which requires our particular attention in both basic research and clinical care. Beyond that, the recent success in early-phase trials and the growing experience in managing adoptive cell therapy give hope that CAR T cell therapy will replace current standard treatment regimens to cure leukemia/lymphoma in the near future.

Financial & competing interest disclosure

Work in the author's laboratory is supported by the Deutsche Krebshilfe, the Deutsche Forschungsgemeinschaft, the José Carreras-Leukämie Stiftung, the Wilhelm Sander-Stiftung, the Else Kröner-Fresenius Stiftung, the European Union (European Regional Development Fund – Investing in Your Future), German federal state North Rhine-Westphalia (NRW) and the Medical Faculty of the University. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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