Anti-CD19 Chimeric Antigen Receptor-Modified T Cells for Multiple Myeloma

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Multiple myeloma is a disease formed by malignant plasma cells that accumulate in the bone marrow. The lifetime risk of multiple myeloma in the U.S. is 1/140, making it the second most common hematologic malignancy and it was expected that 22,350 new cases to be diagnosed in the US in 2013 [1]. In the past decade, we have witnessed dramatic changes in the treatment of multiple myeloma. Proteasome inhibitors such as bortezomib and carfilzomib target the ubiquitin pathway, resulting in cytotoxic injury due to disruption of protein degradation in myeloma cells. When compared with melphalan–prednisone–lenalidomide (MPR), combine therapy with high-dose melphalan and stem-cell transplantation significantly prolonged progression-free survival among patients with multiple myeloma who were in the age group of 65 years or younger [2]. Discovery of anti-tumor efficacy of the graft vs. myeloma response, such as CAR T cell therapy seems likely to herald the beginning of a revolution in the treatment of multiple myeloma. Several observations have fostered optimism that more specific immunotherapeutic approach such as chimeric antigen receptors (CARs) modified autologous T cells might exhibit more potent anti-myeloma activity with less toxicity. Currently all ongoing CAR studies employ first-generation anti-CD19 CAR and a second-generation version, usually with CD28. In pre-clinical studies, anti-myeloma second-generation CARs are developed to target the Lewis Y antigen (Ley), B Cell Maturation Antigen (BCMA), cell surface glycoprotein CS1 and CD38. Ley is overexpressed in many epithelial malignancies. In a recent study, multiple myeloma cell lines were injected into a immunocompromised mice followed by the injection of anti-Ley CAR T cells that significantly exhibited prolonged survival and delayed development of symptomatic plasmacytomas [3]. The National Cancer Institute (NCI) has recently identified BCMA which is expressed on most multiple myeloma cells. Anti-BCMA CAR is a second-generation CD28-based CAR that showed quite favourable efficacy and toxicity profiles against multiple myeloma [4]. CS1 is over-expressed in multiple myeloma cells. The CD28-based anti-CS1 CAR-modified natural killer (NK) cells revealed cytotoxicity against multiple myeloma cell lines and prolonged survival in patients with multiple myeloma [5]. CD38 is a transmembrane glycoprotein and a second-generation 4-1BB-based anti-CD38 CAR was proved to be effective against multiple myeloma cell lines [6]. In a phase I/II study, anti-CD38 antibody daratumumab showed a remarkable efficacy for the treatment of patients with multiple myeloma [7]. The most clinical experience so far has been with anti-CD19 CARs that have been utilized in several phase I trials targeting B cell malignancies. Genetically engineered CARs that couple with an anti-CD19 single chain Fv domain to intracellular T-cell signalling domains of the T-cell receptor transmits cytotoxic T lymphocytes to antigen expressing cells. CAR-mediated T-cell responses can further be enhanced with the addition of a co-stimulatory domain. CD3 zeta domain has been used in CAR-modified T cells that lead to the activation of T-cell signal and it has been referred as a first generation CAR. In recent competitive re-population studies, CAR designs have been executed based on the addition of a single (second generation) or multiple co-stimulatory domains (third generation) [8]. In preclinical models, it has been found that antitumor activity and in vivo persistence of chimeric antigen receptors significantly increase with the inclusion of CD137 (4-1BB) signalling domain as compared with the inclusion of CD3-zeta chain alone [9]. CTL019 is a chimeric antigen receptor that includes a CD137 (4-1BB) signalling domain and is expressed with the use of lentiviral-vector technology for gene transfer and permanent T cell modification.

In a perspective piece of publication, Garfall et al. (Sept. 10 issue; N Eng J Med 2016; 374: 193-194) described an interesting case of a patient with multiple myeloma who was treated with autologous stem cell transplantation followed by the infusion of anti-CD19 chimeric antigen receptor-transduced CTL019 cells led to a complete response with no evidence of progression and no measurable serum or urine monoclonal protein was detected after 12 months of treatment [10]. The majority (99.95%) of the patient's myeloma cells did not express CD19 and this indicates that the CTL019 is not responsible for the direct cytoxicity against the predominant malignant clone itself. The possible mechanism of action underlying the efficacy of CTL019 in the case of multiple myeloma is that CTL019 mediated elimination of non-neoplastic B cells might be at least partially responsible for its therapeutic activity as B cells and CD19-positive plasma cells showing the tumor-promoting capabilities and can be the tractable targets for anticancer therapy in selected tumors [11,12]. Through this mechanism, CTL019 may have clinical usefulness in multiple myeloma that does not express CD19, particularly in combination with other immunotherapies. Patients with multiple myeloma have altered B-cell homeostasis with a characteristic development of a novel type of memory B cells [13]. Therefore, CTL019-mediated depletion of a promyeloma B-cell population could contribute to the clinical benefit of CTL019. The most clinical experience so far has been with anti-CD19 CARs that have been utilized in several phase I trials targeting B cell malignancies. Clinical efficacy has been promising and is an association with persistence of the CAR-modified cells and in vivo expansion results in contemporaneous development of inflammatory syndromes such as cytokine release syndrome and macrophage activation syndrome, which have been the predominant toxicity [14]. The cytokine-release syndrome is a major toxic effect associated with CTL019. Elevated levels of cytokines generate a systemic inflammatory response and these elevations are associated with T-cell activation and proliferation (Figure 1).
Figure 1: CAR T cell activation, killing of tumor targets and clinical responses in the patients.

Panel A shows tumor cell recognition occurs when a CAR on a T cell ligates its antigen on the tumor. Signaling and activation is mediated by the intra-cytoplasmic signaling domains within the CAR. Activation can lead to direct cytotoxicity of tumor target by CAR T cell mediated release of granzyme and perforin. Tumor killing can also be mediated by activation of other components of the immune system through release of cytokines by CD4+ T cells. Long-term eradication and prevention against tumor relapse may be provided by long-term memory CAR T cells that form after the initial activation.

Panel B shows bone marrow-biopsy specimens obtained 3 days after chemotherapy (day -1, before CART19-cell infusion) and 6 months after CART19-cell infusion (hematoxylin and eosin). The baseline specimen shows hypercellular bone marrow (60%) with trilineage hematopoiesis, infiltrated by predominantly interstitial aggregates of small, mature lymphocytes that account for 40% of total cellularity. The specimen obtained 6 months after infusion shows trilineage hematopoiesis, without lymphoid aggregates and continued absence of CLL [10].

Panel C shows bone marrow core-biopsy samples of a multiple myeloma patient whose cancer had stopped responding after receiving an investigational personalized cellular therapy known as CTL019. The investigational treatment was combined with chemotherapy and an autologous stem cell transplant-a new strategy designed to target and kill the cells that give rise to multiple myeloma. The bone marrow sample obtained before the second Autologous Stem-Cell Transplantations (ASCT) shows more than 95% involvement by multiple myeloma on hematoxylin and eosin staining. The sample obtained 100 days after the ASCT shows 1 to 2% overall cellularity and no plasma cells on hematoxylin and eosin staining [4].

Several studies with different anti-CD19 CARs provide exciting evidence that response rates have been higher in acute lymphoblastic leukemia (ALL) than chronic lymphocytic leukemia (CLL). Therefore much to be learned about disease- and patient-specific factors that influence responses to CAR therapy. CAR T cells may persist indefinitely, the potential for long-lived toxicity, such as the B cell aplasia and hypogammaglobulinemia observed in some patients who have received anti-CD19 CARs. CAR targets should be functionally essential for the oncologic phenotype of the target cell to minimize the chance of resistance through target down-regulation which was observed in a pediatric B ALL patient treated with an anti-CD19 CAR who relapsed as CD19-negative ALL [14]. Patients with acute complications require prompt therapy, though currently available CAR T cell manufacturing processes require at least two weeks. Therefore, they are unsuited to such urgent therapy. An alternative is to use CAR T cells either coupling or replacing with autologous hematopoietic stem cell transplantation (auto-HSCT) as a consolidation strategy to deepen and prolong responses after initial therapy for multiple myeloma. The period immediately after auto-HSCT seems to be uniquely suited to the in vivo expansion of adoptively transferred T cells. After extensive expensive investigations, coupling auto-HSCT to other immunotherapies becomes the subject of attention [15]. The dramatic evidence based observations of CAR T cell therapy in patients with relapsed, refractory B-ALL reinforces researchers to work with it in different areas. The factors require for the adoption of CAR T cell therapy to individuals with different haematological malignancies includes CAR design, disease burden, chemotherapy conditioning regimens and tumor target antigens. Multiple myeloma offers several appealing targets for the development of CAR-based immunotherapies along with several potential points of integration with current treatment paradigms and would be an impactful advance in the treatment of this incurable and morbid disease.

References


