



Adverse Effects Associated with Clinical Applications of CAR Engineered T Cells

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Abstract

Cancer has been ranked as the second leading cause of death in the United States. To reduce cancer mortality, immunotherapy is gaining momentum among other therapeutic modalities, due to its impressive results in clinical trials. The genetically engineered T cells expressing chimeric antigen receptors (CARs) are emerging as a new approach in cancer immunotherapy, with the most successful outcomes in the refractory/relapse hematologic malignancies. However, the widespread clinical applications are limited by adverse effects some of which are life-threatening. Strategies to reduce the chance of side effects as well as close monitoring, rapid diagnosis and proper treatment of side effects are necessary to take the most advantages of this valuable therapy. Here we review the reported toxicities associated with CAR engineered T cells, the strategies to ameliorate the toxicity, and further techniques and designs leading to a safer CAR T-cell therapy.

Keywords Engineered T cells · Chimeric antigen receptors (CARs) · Immunotherapy · Adverse effects

Introduction

Since the first design and application in 1989 (Gross et al. 1989), chimeric antigen receptor engineered T cells (CARTs) have become the focus of intense research in the field of cancer cell therapy. To date, intensive research from preclinical to phase I and II clinical studies for hematologic and solid tumors introduces CARTs as potential candidates for clinical developments (Dai et al. 2016; Davila and Sadelain 2016). The most promising results belong to CD19 targeted CARTs (CD19 CARTs) for their dramatic effects on B-cell malignancies in human clinical trials (Tasian and Gardner 2015).

The structure of a chimeric antigen receptor (CAR) consists of an extracellular domain linking to an intracellular one via a transmembrane moiety. The extracellular part is a tumor antigen-binding moiety commonly derived from a monoclonal antibody (mAb) single chain variable fragment (scFv), while the intracellular part consists of single

or multiple T-cell co-stimulatory domains (Dai et al. 2016). With this structure, CARs can bind to tumor antigens in an MHC independent manner, which counts as an advantage over T-cell receptors (TCRs) (Dai et al. 2016; Namuduri and Brentjens 2016). The first generation of CARs had just CD3 ζ chain in their intracellular domain, which did not show high efficacy in preclinical studies. The second and third generations of CARs contain the intracellular domains of one or two co-stimulatory domains, respectively, and thus dramatically enhance CART cell survival *in vivo*. However, better *in vivo* persistence in the new generations of CARs correlates with higher toxicity (Ghosh et al. 2017; Magee and Snook 2014). In general, side effects correlate with tumor burden as well as dose and persistence of CARTs in a patient's body. Consequently, preconditioning chemotherapy to reduce tumor burden and splitting the required CARTs in multiple doses may alleviate the intensity and reduce the incidence of those side effects (Namuduri and Brentjens 2016).

This review summarizes the reported adverse effects associated with CART therapy, and strategies to manage them. The toxicities range from mild to life-threatening in various patients and include cytokine release syndrome (CRS), tumor lysis syndrome (TLS), neurotoxicity, on-target off-tumor toxicity, and anaphylaxis. New strategies such as designing CARTs with limited life-span or “on-switch CAR”

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are under investigation to ameliorate CARTs toxicities, as described at the end of this paper.

Cytokine Release Syndrome

CRS is the most prevalent toxicity associated with CART therapy (Xu and Tang 2014). CRS, which has been also reported with mAb therapies, is due to the activation of the considerable number of immune cells (B cells, T cells, NK cells, macrophages, dendritic cells and monocytes), and consequently massive release of cytokines, namely interferon (IFN)- γ , interleukin (IL)-6, soluble IL-2 receptor- α and IL-10 (Lee et al. 2014). As a result, patients with higher tumor burdens normally experience more severe CRS, owing to the potent and rapid stimulation and proliferation of large number of T cells in response to CAR engagement by the target antigen (Maus and Levine 2016).

The symptoms, which mimic an infectious disease, initiate within days to weeks after CARTs infusion (Lee et al. 2014). CRS symptoms vary from mild to life-threatening in different patients and include fever, fatigue, nausea, hypotension, hypoxia, anorexia, tachycardia, capillary leak syndrome, respiratory distress, and in some cases neurological disturbances (Fitzgerald et al. 2017; Namuduri and Brentjens 2016). CRS is self limiting and reversible in majority of patients (Namuduri and Brentjens 2016). However, severe cases can lead to organ failure and death, as it occurred in a patient with metastatic colorectal cancer treated with third-generation CARTs targeting epidermal growth factor receptor-2 (Morgan et al. 2010). In some patients, CRS may lead to macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH). The elevation of a large number of inflammatory cytokines in MAS/HLH is associated with liver dysfunction, hyperferritinemia, hepatosplenomegaly and coagulopathy (Maude et al. 2014; Maus

et al. 2014). Therefore, a reliable grading system and close monitoring of CRS/MAS symptoms are required if rapid intervention is necessary.

Due to lack of a unique grading system for CRS, clinicians in different institutions use different criteria to identify the CRS severity (Namuduri and Brentjens 2016). In this regard, Lee et al. (2014) introduced a CRS grading method which is independent from the causing agent and based on the blood pressure status and oxygen level (Table 1). Close monitoring and immunosuppressive treatments are advised in grade 3 and 4 in this method (Lee et al. 2014).

All patients diagnosed with severe CRS should be subjected to the intensive daily monitoring to prevent from progressive life-threatening complications. Although the concentration of serum cytokines is elevated in CRS, inflammatory cytokine levels themselves do not serve as suitable biomarkers for monitoring CRS. This is due to not-readily available laboratory tests for cytokine measurements, and various basal levels of cytokines in different individuals based on the underlying diseases (Lee et al. 2014). Currently, C-reactive protein (CRP), produced by liver in response to IL-6, is being used as a biomarker for daily monitoring (Davila and Sadelain 2016). The inexpensive and easily available laboratory tests for CRP make it a superior choice to the various circulating cytokines levels as biomarker of CRS (Lee et al. 2014).

Severe CRS is not responding to symptomatic and supportive treatments such as anti-pyretics and intravenous fluids. In these cases, treatment with immunosuppressive agents, namely corticosteroids and anti-cytokine agents are demanded (Bonifant et al. 2016). It is worth noting that clinical symptoms of CRS are indicating a patient's response to the immunotherapy, and to some extent contribute to anti-tumor efficacy of CARTs. Therefore, a prophylactic treatment of CRS is not applied to the current anti-tumor CART therapy (Ruella et al. 2017). In other words, the goal of CRS

Table 1 Management algorithm of CRS

Grade	Clinical symptoms	Treatment
1	Fever, constitutional symptoms	Vigilant supportive care (treat fever and neutropenia if present, monitor fluid balance, anti-pyretics, analgesics as needed) Assess for infection
2	Hypotension: responds to fluid or one low dose pressor Hypoxia: responds to $<40\%$ O_2 Organ toxicity: grade 2	Younger age or without extensive co-morbidities Older age or with extensive co-morbidities Vigilant supportive care (monitor cardiac and other organ function closely) Vigilant supportive care Tocilizumab with or without corticosteroids
3	Hypotension: responds multiple or high dose pressor Hypoxia: responds to $\geq 40\%$ O_2 Organ toxicity: grade 3, grade 4 transaminitis	Vigilant supportive care Tocilizumab with or without corticosteroids
4	Mechanical ventilation Organ toxicity: grade 4, excluding transaminitis	Vigilant supportive care Tocilizumab with or without corticosteroids

Redrawn with permission from Lee et al. (2014)

managing is to minimize the severe complications without compromising the anti-tumor activity of CARTs. In this regard, corticosteroids are not the optimal choice for CRS management as they have a broad suppressive effect on the immune system and hence can hinder the anti-tumor efficacy of CARTs (Davila et al. 2014). Therefore, anti-cytokine therapy appears to be considered as the first line to control CRS (Davila and Sadelain 2016). Supposedly, the strategy to modify the most prominent elevated cytokines in CRS, including IL-10, IL-6 and IFN- γ (Namuduri and Brentjens 2016), is expected to have the greatest effect to control CRS symptoms. IL-10 as a negative regulator for inflammatory response (Iyer and Cheng 2012), and IFN- γ (Saha and Jyothi 2010) as an effector cytokine released by cytotoxic T cells required for anti-tumor efficacy of CARTs are less likely to be the desirable targets for CRS management. On the contrary, IL-6 is an inflammatory cytokine produced by different immune and non-immune cells and plays important roles in inflammatory reactions (Hodge et al. 2005). Moreover, IL-6 shows a peak level in the maximum CARTs proliferation in patients with severe CRS. Therefore, Maude et al. (2014) hypothesized that targeting IL-6 could be an effective strategy to modulate CRS. They successfully proved their hypothesis using tocilizumab, an IL-6 receptor blocker, to control CRS following CD19 CART cancer therapy (Teachey et al. 2013). Tocilizumab, a humanized mAb against human IL-6 receptor, prevents IL-6 from binding to its receptor. Tocilizumab is the Food and Drug Administration (FDA) approved for rheumatoid arthritis (RA), juvenile idiopathic arthritis and polyarticular juvenile RA (Venkiteshwaran 2009). For amelioration of CRS symptoms, tocilizumab is being prescribed within the approved dosages for RA, and has shown a faster effect than corticosteroids (Lee et al. 2014). No serious side effect has been reported following the indication of tocilizumab in CRS management.

Recently, Ruella et al. (2017) showed that pre-emptive treatment of CRS with ibrutinib in CD19 CART therapy not only reduced the serum cytokine levels, but also led to CARTs expansion in a B-cell neoplasm mouse model with high tumor burden. Ibrutinib is a Bruton's tyrosine kinase inhibitor which is FDA approved for mantle cell lymphoma (Wang et al. 2013), and chronic lymphocytic leukemia (CLL) (Byrd et al. 2013).

Tumor Lysis Syndrome

Massive cell death following initiation of anti-cancer therapy in patients with significant tumor burden can lead to a sudden release of cell death byproducts and cause a kind of metabolic disorder known as TLS. In severe cases, TLS may result in serious complications such as renal failure (Tiu et al. 2007). TLS has been reported in a few CD19 CART-treated patients,

especially in CLL cases. Close monitoring, intravenous hydration and prophylactic administration of allopurinol are to minimize the risk of TLS (Namuduri and Brentjens 2016). TLS does not occur frequently in CART therapy, seemingly owing to the gradual expansion and proliferation of CARTs in vivo (Tasian and Gardner 2015).

Neurotoxicity

A number of patients treated with CARTs demonstrated neurologic toxicity with a wide range of symptoms comprising confusion, delirium, aphasia, and in severe cases seizure and coma (Bonifant et al. 2016). Whether the neurotoxicity is secondary to CRS or is the direct effect of CART entrance into central nervous system is not clear yet (Davila and Sadelain 2016). While neuronal disorders normally accompany CRS symptoms, some CARTs are detected in cerebrospinal fluid of patients treated with CARTs that may directly trigger neurotoxicity (Dai et al. 2016). Neurologic toxicity is reversible in majority of patients. In severe cases, nonetheless, corticosteroids such as dexamethasone help more than tocilizumab, as the former can pass through blood brain barrier (Davila and Sadelain 2016; Lee et al. 2014). In addition, in some cases of CD19 CART therapy, seizure prophylaxis was applied (Namuduri and Brentjens 2016).

One of the lethal neurologic side effects of CD19 CART trials was cerebral edema that occurred during the Juno Therapeutics' ROCKET phase II clinical trial. CARTs bearing the CD28 co-stimulatory domains were injected to patients who underwent cyclophosphamide and fludarabine preconditioning. Two patients died after treatment leading to a temporary hold on the trial by FDA. Juno argued that fludarabine preconditioning allowed rapid expansion of CD28 CARTs and therefore changed the conditioning regimen to cyclophosphamide alone. FDA reinstated the trial; however, two more deaths related to cerebral edema excluded fludarabine as the causative agent (DeFrancesco 2017). Cytokine diffusion and direct infiltration of CARTs across the blood brain barrier may be responsible for cerebral edema. The choice of co-stimulatory domains (CD28 vs 4-1BB), affinity and structure of scFv, the method of in vitro T-cell activation and expansion, the type of viral vector (retro- vs lentivirus) for gene transfer, preconditioning regimen, disease burden, type of cancer, age of patient and dose of T cells can determine the degree of neurotoxicity.

On Target Off-Tumor Toxicity

Antigens on cancer cells are commonly expressed on the normal cells as well. Therefore, on target off-tumor toxicity can occur upon stimulation of T cells following CARs binding to their antigens on the normal cells/tissues (Bonifant

et al. 2016). The most common example of this toxicity is B-cell aplasia following CD19 CARTs infusion. CD19 is expressing on malignant as well as normal B cells. The duration of B-cell aplasia appears to be correlated with persistence of CARTs in vivo, and normally is manageable with replacement therapy with immunoglobulins and in some cases antibiotic administration (Bonifant et al. 2016; Davila and Sadelain 2016; Tasian and Gardner 2015). In mouse models, CARTs bearing a truncated version of the epidermal growth factor receptor (tEGFR) were depleted via administration of the anti-EGFR mAb, cetuximab, leading to recovery of normal B cells without tumor relapse (Paszkiwicz et al. 2016). Life-threatening on target off-tumor toxicity may happen if the target antigen is expressed in the vital tissues such as respiratory system. This was reported in a patient with metastatic colorectal cancer following administration of ERBB2 CARTs where low expression of ERBB2 on respiratory epithelial cells led to acute pulmonary manifestations and patient death 5 days after CARTs injection (Morgan et al. 2010).

Anaphylactic Reaction

CARs contain the scFv mostly derived from a murine antibody, and thus can trigger both humoral and cellular immune responses (Curran et al. 2012). Hence, patients treated with CARTs are prone to anaphylaxis. Indeed, it has been reported in one out of four patients treated with mRNA-based mesothelin CARTs (Maus et al. 2013). Close monitoring, fast diagnosis and immediate treatment are required in anaphylactic reactions.

Further Investigations to Reduce CAR Toxicities

Most of the adverse effects, namely CRS, neurotoxicity and on-target off-tumor toxicity, are correlated with the persistence of the CARTs in vivo. Hence, a number of new strategies toward safer CARTs are aimed to limit the CARTs life-spans in patient's body (Bonifant et al. 2016). To this end, mRNA-based gene transfer instead of viral methods has been used to arm T cells with mesothelin CARs against solid tumors. Indeed, mRNA-based CARTs not only shorten the CARTs circulation in the body, but also can overcome the risk of insertional mutagenesis associated with virally transduced CARTs due to the integration of viral genome into the host genome. Although this has not been reported to date for CARTs, insertional mutagenesis remains a potential toxicity of virally engineered CARTs (Zhao et al. 2010). Another approach to limit the in vivo circulation of CARTs is encoding a suicide gene into the transduced T cells.

Two suicide genes have been evaluated in the human clinical trials, namely herpes simplex virus-derived thymidine kinase (HSV-tk) and inducible caspase-9 (iCasp9) (Jones et al. 2014). The iCasp9 activity is faster than that of HSV-tk (minutes vs days). Besides, the immunogenicity of the HSV-tk and the need for ganciclovir for its function limit its clinical applications. The iCasp9 does not have these shortcomings. As an alternative approach, some groups employed antibody targets to selectively eradicate CARTs. In this method, CARTs are engineered to express special cell surface antigens which will be targeted by antibodies to eradicate CARTs via antibody-dependent cell-mediated cytotoxicity. For example, depletion of engineered T cells expressing tEGFR or CD20 followed by application of cetuximab and rituximab, respectively, has been reported (Casucci and Bondanza 2011; Paszkiwicz et al. 2016; Wang et al. 2011). However, this method burdens the risk of on-target off-tumor binding of mAb to the normal tissues. Marin et al. (2012) showed that among different suicide systems, iCasp9 and CD20/rituximab, are superior.

Another novel approach to limit the risk of on-target off-tumor toxicity of CARTs is to produce bi-specific engineered T cells capable of co-expression of two different CARs, simultaneously. Bi-specific CARTs are targeting two different tumor antigens. This in turn can increase the tumor specific targeting of CARTs. In other words, for activation of bi-specific engineered T cells, binding of both CARs to their targets on malignant cells is necessary. Conversely, binding of bi-specific CARTs to the normal cells expressing just one of the antigens is not enough to completely activate the engineered T cells (Kloss et al. 2013). Alternatively, when co-expression of two antigens occurs only in normal cells, application of an additional inhibitory CAR on CARTs can suppress the activation of engineered T cells upon engagement of CARs to their targets on normal tissues. Malignant cells, which do not express both antigens, will not inhibit the T-cell activation followed by binding of the CAR to its target antigen (Fedorov et al. 2013).

To improve the safety and control the activation of CARTs in vivo, researchers have designed a new class of CAR engineered cells where the activation of CARTs depends on the presence of “on-switch” molecules. In “on-switch CARs”, the extracellular antigen recognition part is separated from the intracellular activator signaling, and the special small molecules are required to bridge these two together. As a result, for activation of an “on-switch CART”, not only engagement of CAR in its antigen, but also the presence of the small molecules are necessary (Wu et al. 2015). Recently, Rodgers et al. (2016) have reported an “on-switch CAR” capable of activation and retargeting of CARTs. This system contains two components: (1) a peptide switch which is composed of a peptide conjugated to a tumor antigen-specific antibody and (2) T cells armed with a CAR specific

for the peptide on the switch. The peptide switch mediates binding of CART to the tumor cell. The engineered T cells in this study were activated upon binding of their CARs to the peptide switch that in turn binds to the tumor cells. The author claimed that precise control of activation/retargeting of engineered T cells with the peptide switch could reduce the risk of CRS and off-tumor toxicity following by CARTs application (Rodgers et al. 2016).

Another strategy to control the off-target toxicity is using Fcγ chimeric receptor (FcγCRs)-engineered T cells. FcγCRs are different from CARs in their extracellular domains. For CARs, the antigen specificity is provided by a tumor-associated scFv molecule while for FcγCRs, the FcγRIIIA (CD16) that is engineered to be expressed on T cells will bind the Fc portion of an exogenously administered anti-tumor mAbs. As a result, the off-target toxicity can be controlled by withdrawing or tapering the dosage of mAbs. In case of high toxicity, high-doses of immunoglobulins can be prescribed to neutral the mAbs, and thus shut down the FcγCR T cells. In addition, FcγCR T cells are able to target multiple cancers, when the appropriate mAbs targeting cancer cells do exist. Despite these advantages over CARTs, further limitations are associated with FcγCR T cells. First, serum immunoglobulins can bind to extracellular Fcγ part and prevent FcγCR T cells from binding to mAbs and thus block the anti-tumor effect. Second, if a patient has an autoimmune disease or viral infection, the existing antibodies against patient's body or viruses can bind to and activate FcγCR T cells. In the former, FcγCR T cells get activated against patient's own cells, and in the latter, viruses can be redirected to CR T cells via binding to Fcγ and lead to viral infections of the cells (Caratelli et al. 2017).

Finally, designing CARs with lower affinity that can bind mostly to the malignant cell with high antigen expression (Caruso et al. 2015), or co-expression of chemokine receptors on CARTs that can contribute to a better homing of CARTs to malignant tissues (Di Stasi et al. 2009) were investigated to increase the specificity and decrease the toxicity following CARTs infusion.

Conclusion

Although the field is still young, CART therapy emerged as a promising approach for treatment of refractory cancers, especially B-cell malignancies. Hence, many phase I and II clinical trials are either undergoing or planned to manage the toxicity and enhance the efficiency of CART therapy in a wide range of hematological and solid tumors. Here we summarized the reported toxicities associated with CARTs infusion in clinical trials, and the successful strategies to manage the toxicities. In addition to the reported side effects here, the risk of potential side effects such as insertional mutagenesis,

off-target antigen recognition, and immunogenicity of genetically engineered T cells (Bonifant et al. 2016; Namuduri and Brentjens 2016), which may occur following CART therapy, should be considered. Furthermore, the majority of CART cell trials were conducted in an autologous setting and the use of allogeneic cells is in its infancy, mainly due to the risk of graft-versus-host disease (GVHD). Abrogation of endogenous TCR genes (MacLeod et al. 2017), inclusion of suicide genes (Gargett and Brown 2014), the use of CD28 vs 4-1BB domains in the CAR constructs to limit the survival of engineered cells in vivo (Ghosh et al. 2017) as well as the use of virus-specific T cells (Terakura et al. 2012) are some of the approaches that can limit the risk of GVHD. In total, overcoming the toxicities associate with CART therapy can facilitate its widespread applications and open new era for treatment of cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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