CAR T Cell Therapy in Hematological Malignancies

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Chimeric antigen receptor (CAR) T cell therapy has ushered in a new era in cancer treatment. Remarkable outcomes have been demonstrated in patients with previously untreatable relapsed/refractory hematological malignancies. However, optimizing efficacy and reducing the risk of toxicities have posed major challenges, limiting the success of this therapy. The tumor microenvironment (TME) plays an important role in CAR T cell therapy's effectiveness and the risk of toxicities. Increasing research studies have also identified various biomarkers that can predict its effectiveness and risk of toxicities.

1. Introduction

Traditionally, cancer treatment is known to be synonymous with chemotherapy, radiation therapy and surgical resections. However, with technological advances and exponential development in scientific research, a growing interest in new forms of cancer treatment such as immunotherapy and, specifically, chimeric antigen receptor (CAR) T cell therapy has emerged [1]. CAR T cell therapy, recognised by the US Food and Drug Administration as a "breakthrough therapy", has demonstrated remarkable outcomes in certain B cell malignancies [2][3][4][5], and its application is expanding to include myeloma, leukemia and solid organ cancers. Despite the successes that this new cancer therapy has seen, there is still much to understand with regards to its efficacy and safety, and when best to administer this form of therapy to patients.

CAR T cells (CARs) are genetically modified T cells engineered to express receptors that better assist effective targeting of the tumor antigen and subsequent elimination of tumor cells. CARs are typically designed with a single chain fragment consisting of several domains comprising both extracellular and intracellular domains that are important in CAR T cell function [1][2][5][6]. Extracellular domains of CARs are antibody-derived segments directed towards specific tumor antigens. These extracellular domains are able to recognise tumor antigens in a major histocompatibility complex (MHC)-independent manner [7]. This gives CAR T cells an advantage over naturally occurring T cells that recognise tumor cells in an MHC-dependent manner, a mechanism of recognition that is often evaded by tumor cells [7][8]. The intracellular domains on the other hand possess signaling functions that help sustain the immune responses by CAR T cells including activation and proliferation. In the past few years, there has been much focus on improving the design of these CAR T cells, resulting in various intracellular domains being explored to improve the efficacy and safety of these therapies. Currently, there are more than four generations of CARs available. While all generations of CARs make use of CD3ζ as the primary signaling intracellular domain, the first generation CARs only had this as their sole intracellular signaling domain. Even though this generation of CAR T cells were able to trigger immune responses against their intended target, the clinical benefits from these responses were often limited as they neither achieved enough of a level of toxicity to fight the tumors nor were they long lasting owing to their lack of proliferation [9][10]. To overcome these downsides, a co-stimulatory signaling domain (e.g., 41BB, CD28, CD134, etc.) was added into the second generation of CARs and beyond [9][10][11]. This resulted in enhanced cytokine release correlating with increased cytotoxicity, and proliferation was also increased correlating with sustained benefits [10][11]. Overall, the second generation CAR T cells displayed a better immune response. Subsequently in the third generation CARs, more co-stimulatory domains were added in order to improve the function of CAR T cells. While some combined both the 41BB and CD28 signaling domains, others combined 41BB with CD137 [1][2][5][9]. Even though the third generation CARs were developed as an improvement from their predecessor, the clinical advantages they have to offer over second generation CARs are still unclear.

2. Biomarkers and Tumor Microenvironment

Biomarkers represent an important aspect of precision medicine. They allow the objective characterization of biological processes. This method of study has proven to be more advantageous given that medical symptoms can vary significantly from patient to patient and are potentially absent in certain cases. Biomarkers are objective, accurate and reproducible within an entire population [12]. According to the National Institute of Health's Biomarkers Definitions Working Group, a

biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [13]. By this definition, a biomarker is not limited to the mere understanding of a disease, but can serve as a predictor, or as a prognostic and treatment marker. There are various different categories of biomarkers, each providing different information about a disease process. These include diagnostic, prognostic, predictive and response biomarkers and more. **Table 1** summarizes the different types of biomarkers as well as each ones scientific value [14]. In CAR T cell therapy, where disease and response are heterogenous, there is an increasing need and importance to find novel biomarkers within the product and host that can better assess immune characteristics pre and post treatment with the ultimate aim of optimizing efficacy and reducing the severity of toxicity.

Table 1. The different types of biomarkers as well as each ones scientific value [14].

Type of Biomarker	Scientific Value	In the Context of CAR T Cell Therapy
Diagnostic	To confirm the presence of a disease and the extent of a specific subset	Assess CAR T cell product characteristics (e.g., T cell quality, proportion of phenotypes) pre-infusion
Prognostic	To identify the likelihood of clinical outcomes such as disease progression or overall survival	Assess reasons for CAR T cell therapy resistance and disease relapse (e.g., loss of target antigen, expression of inhibitory ligands)
Predictive	To identify individuals who are more likely to benefit from a certain type of therapy	Assess patient and disease characteristics pre and post CAR T cell therapy to predict response and risk of toxicity
Response	To show that a biological response has occurred from exposure to treatment	Assess function of CAR T cell therapy through identification of biomarkers that can measure host immune response to cell therapy
Safety	To indicate the presence or extent of toxicity related to treatment	Aid in early identification and quantification of severity of CAR T cell-related toxicities (e.g., measuring cytokines)

3. Role of Tumor Microenvironment and Biomarkers in CAR T Cell Response and Resistance

The response to CAR T cell therapy varies between hematological malignancies. The best response has been seen in adult B cell acute lymphoblastic leukemia (B-ALL) patients with complete remission (CR) rates ranging from 83% to 93% [15][16][17][18]. Less optimal responses were seen in patients with diffuse large B cell lymphoma (DLBCL), with CR rates between 39% and 54% [19][20][21][22]. CR rates were even lower in chronic lymphocytic leukemia (CLL) patients, ranging between 20% and 30% [23][24][25]. Aside from initial response rates, the duration of response is equally important and has been shown to, likewise, vary between hematological malignancies treated. Interestingly, while B-ALL patients had higher initial response rates, their duration of response seemed lesser than patients with DLBCL and CLL [26][27]. Numerous emerging studies detailing outcomes of patients with hematological malignancies have observed that while initial response rates were good, the risk of relapse was high. An increasing amount of work has focused on dissecting the tumor microenvironment and discovering biomarkers that can predict the response, persistence and resistance to CAR T cell therapy.

3.1. Tumor Microenvironment

Postulated mechanisms for resistance were reviewed by Lemoine et al. with a focus on three aspects—CAR T cells (e.g., lack of expansion and defective effector function (exhaustion), the tumor microenvironment and the cancer cells (e.g., loss of target antigen and expression of inhibitory ligands (PD-L1 expression) [28]. While the relevance of TME may be more obvious in solid organ cancers due to hypoxia/metabolism-related factors and tumor trafficking, it is the heterogenous population of immunosuppressive cells and acellular elements such as immunosuppressive cytokines that affect the response of hematological malignancies to CAR T cell therapy. The diverse set of components in the TME interact with

each other and create a balance between pro-immune and immunosuppressive signaling. CAR T cells proliferate and expand in the recipient patient in response to in vivo signals. As such, the functions of CAR T cells are susceptible to the immunosuppressive nature of the TME. Consequently, many groups have explored the individual roles of the different cellular and acellular elements implicated in CAR T cell inhibition that affect its therapeutic efficacy.

3.2. Immunosuppressive Cells

Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells that arise from bone marrow myeloid progenitors [29]. These immature myeloid cells differentiate into mature cells in healthy adults, but in pathological conditions where levels of inflammation are high, the differentiation process is interrupted with the consequent expansion of a heterogenous clump of immature myeloid cells including immature macrophages, immature granulocytes and immature dendritic cells [30][31]. These cells are able to suppress both the innate and adaptive response: specifically, the suppression of T cell function [32]. MDSCs are also major sources of reactive oxygen and nitrogen species, which are harmful to T cells [33]. In cancer patients, tumor cells release signals that recruit these MDSCs and subsequently expand them, resulting in a tumor-promoting milieu. The inhibitory effect of MDSCs on CAR T cells has been mainly demonstrated in patients with solid organ tumors, including breast, liver and prostate cancer and sarcoma [34][35][36][37].

Moving forward, functional assessment of the interplay between the tumor, TME and CARs will also allow further understanding of the factors promoting or inhibiting T cell trafficking and infiltration into tumor sites. In cellular therapeutics, this interaction needs to be assessed at multiple levels—at the tissue architectural level as well as at the single-cell level. Spatial profiling of the immune cells with concurrent single-cell level proteomic and transcriptomic profiling has started to provide a peek into this dynamic interaction [38]. Imaging modalities can also assist in providing spatial assessment of tumor–CAR T interaction. Novel non-immunogenic reporters in PET imaging can now be deployed to trace CAR T cells to provide a real-time assessment of the in vivo distribution and fate of CAR T cells [39].

3.3. Biomarkers

Biomarkers can also aid in predicting the response to CAR T cell therapy. When thinking about biomarkers, patient characteristics and disease markers in the form of laboratory tests are first to come to mind as they are readily available and easy to perform. One such biomarker is lactate dehydrogenase (LDH). A marker correlated with high tumor burden, studies have consistently demonstrated an association between its higher levels and poorer outcomes in patients with B cell malignancies receiving CAR T cell therapy [40][41][42]. Garcia et al. also demonstrated the possibility of employing risk indexes to predict outcomes. In a study involving R/R DLBCL patients treated with CAR T cell therapy, a higher age-adjusted international prognostic score (aaIPI) was associated with poorer progression free survival (PFS) and overall survival (OS). High-risk IPI was associated with poorer PFS [43].

However, these biomarkers and risk scores may not be universally applicable to all hematological malignancies, and, thus, the exploration of other biomarkers that may influence the efficacy of CAR T cells is crucial. In this regard, the identification of molecules that play a role in proliferation, differentiation potential, effector function and exhaustion hold promise for optimizing the proliferative capacity and antitumor activity.

The percentage composition of T cell subsets can influence CAR T cell function. T cell subsets are grouped according to differentiation levels and can be distinguished based on the presence of different surface markers (e.g., CD45RA, CD45RO, CD27, CD28). These subsets include stem cell memory (T_{scm}), central memory (T_{cm}), effector memory (T_{em}), effector memory that re-express CD45RA (T_{emra}) and effector (T_{eff}) T cells. Better CAR T cell therapy outcomes have been observed in patients with a higher proportion of less differentiated T cell subsets in the CAR T cell product [44][45][46]. This is likely due to these less differentiated T cells having higher expansion capabilities and potential to differentiate into other T cell subsets such as T_{cm} and T_{eff} that have both persistence and cytotoxic capabilities.

Cytokines are another group of novel biomarkers that have gained attention and spurred modifications to CAR T cell products that have enhanced proliferation, and are able to revert T cell exhaustion and promote antitumor abilities. Multiple inflammatory cytokines such as IL-6, IL-7, IL-8, IL-12, IL-15, IL-18, IFN-y and TNF-a have been shown to be able to enhance the cytotoxic functions of T cells and NK cells [42][47][48][49][50]. Harnessing this knowledge, groups have modified CAR T cells to secrete cytokines such as IL-12 and IL-18 and observed that there was better tumor eradication and CAR T cell persistence [51][52]. On the other hand, IL-10, TGF-B and IL-4 are immunosuppressive cytokines that can contribute to CAR T cell dysfunction [53][54]. These cytokines can either directly inhibit the effector function of CAR T cells or can recruit and activate MDSCs and Tregs that can affect CAR T cell function as previously mentioned.

Combinations of patient and disease characteristics, laboratory tests and knowledge of more specific molecules can serve as important biomarkers in predicting therapy efficacy as well as for the future development of "armored" CAR T cells that have better efficacy.

4. Tumor Microenvironment and Biomarkers in CAR T Cell Toxicity

Despite the remarkable success of CAR T cell therapy, the incidence of CAR T-associated toxicities are high and represent a significant limitation to this form of therapy. These toxicities can be severe and fatal. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are two important toxicities in CAR T cell therapy. The pathophysiology of both conditions has been reviewed by Siegler and Kenderian [55].

Briefly speaking, CRS occurs due to activated CAR T cells triggering an inflammatory response of varying degrees. Symptoms include fever, headache, myalgia, malaise and, in severe cases, multiorgan dysfunction, hypotension requiring inotropic support and hypoxia requiring mechanical ventilation. Inflammatory cytokines such as tumor necrosis factor (TNF)α and interferon (IFN)γ are released and in turn activate monocytes and macrophages to release more cytokines including IL-1 and IL-6. Correspondingly, IL-6 levels are highly elevated in patients with CRS and treatment includes IL-6 inhibitors such as tocilizumab [56]. CRS severity is graded according to the ASTCT grading scale and its incidence has been reported as close to 100% of varying severity in CART 19 clinical trials [57][58][59][60]. ICANS also occurs as a result of activated CAR T cells triggering an inflammatory response. However, in addition, the systemic inflammation activates endothelial cells, which drive blood–brain barrier (BBB) dysfunction. BBB dysfunction results in increased permeability, allowing cytokines to accumulate in the cerebrospinal fluid causing neurotoxicity [61]. Symptoms reported include confusion, delirium, encephalopathy and cognitive dysfunction often associated with language dysfunction, which manifests as word finding difficulties, handwriting disturbances or, in severe cases, mutism. In severe cases, patients can lose consciousness requiring mechanical ventilation and the most feared neurological complication is cerebral edema, which is invariably fatal. Its incidence is lower than in CRS, varying anywhere between 5% and 70% [62].

Because of the high incidence and potential severe morbidity of both CRS and ICANS, predictive biomarkers for these toxicities are important. Identifying such biomarkers can allow early recognition, appropriate counselling to patients and early treatment. In addition, understanding the TME and its impact on these toxicities can pave the way for future strategies to optimize the TME and hopefully reduce the risk of CAR T toxicities.

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