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Chimeric Antigen Receptor–Engineered T Cell Therapy in Lymphoma

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Abstract

Purpose of Review Chimeric antigen receptor (CAR) T cells are a form of adoptive therapy employing autologous T cells engineered with an artificial receptor, able to recognize tumor antigens through an HLA-independent mechanism. We will review data on safety and efficacy outcomes with CAR T cell therapy in lymphomas.

Recent Findings Multicenter trials evaluating three CAR T cell products targeting CD19 have shown that they are highly effective and induce durable remissions in a substantial proportion of patients with relapsed or refractory aggressive B cell non-Hodgkin lymphoma (NHL). The most common toxicities were cytokine release syndrome and neurotoxicity.

Summary Two anti-CD19 CAR T cell products were approved by the FDA for the treatment of patients with relapsed or refractory aggressive B cell NHL. Ongoing research is aimed at investigating their use in earlier lines of therapy and in other B cell lymphomas, improving CAR T cell efficacy and safety, and evaluating novel targets.

Keywords CAR T cell therapy · Lymphoma · CD19 · Axicabtagene ciloleucel · Tisagenlecleucel

Introduction

Approximately 60% of patients affected by aggressive B cell lymphoma are cured with the use of frontline chemoimmunotherapy [1–3]. For the remaining 40% of patients, salvage high-dose chemotherapy followed by autologous stem cell transplant gives the best chance of cure [4]. However, only 50% of patients who relapse after frontline chemoimmunotherapy are transplant-eligible, because of age, performance status, or comorbidities. Of these, only half will respond to salvage chemotherapy, and of those who will respond and will be able to proceed to transplant, less than half will be cured. [5, 6] As a consequence, novel effective and safe therapies are desperately needed for patients with relapsed or refractory aggressive B cell lymphoma.

Chimeric antigen receptor (CAR)–modified T cells are a form of adoptive cellular therapy, employing genetically engineered T lymphocytes, created in the laboratory in 1989, but refined and brought to the clinic only in the last few years [7]. Autologous T cells are collected from the patient usually through leukapheresis, engineered with CAR and expanded ex vivo, and subsequently reinfused (ideally after conditioning). Unlike donor T lymphocytes employed in allogeneic stem cell transplant or endogenous T cells that recognize unique antigens expressed on tumor cells through a HLA-restricted manner via their naturally expressed T cell receptor, CAR T cells recognize antigens on tumor cells in an HLA-independent mechanism via their artificially expressed receptor. This allows broad therapeutic use of CAR T cells generated from either autologous or allogeneic source and also likely overcomes tumor escape mediated by low HLA expression [8].

CAR Structure

CARs are formed of three parts: an extracellular, a transmembrane, and an intracellular domain. The extracellular domain is usually a single-chain variable fragment (scFv) derived from the variable heavy and light chains of an antibody targeting a specific tumor antigen (e.g., CD19 in B cell lymphomas). Upon engagement with its cognate antigen, the extracellular domain initiates the activation signal to the CAR T cell via the intracellular domain [9].

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The first generation of CAR T cells was composed of an extracellular domain recognizing a target tumor antigen, and an intracellular signaling domain, CD3ζ, which mediates signal 1 to the T lymphocyte. Four patients with either relapsed or refractory diffuse large B cell lymphoma (DLBCL) or transformed follicular lymphoma (t-FL) were treated on two phase I trials at the City of Hope with first-generation CAR T cells (2 with a product targeting CD20, and 2 with a product targeting CD19, respectively). Of interest, no conditioning therapy was given before the infusion. While no toxicity was reported, CAR T cells were observed in the peripheral blood of recipients for no more than 7 days (with consequent poor clinical efficacy), and rejection due to development of cellular immune responses against the transgene was reported in 2 patients [10]. This early experience highlighted the importance to refine CARs in order to achieve longer persistence and led to the subsequent design of second generation CARs.

In the second-generation CARs, the intracellular domain is typically composed of two signaling domains: CD3ζ to provide signal 1 and a co-stimulatory domain, which mediates signal 2 and promotes the proliferation, cytotoxic activity, and persistence of CAR T cells. The two most commonly used co-stimulatory domains are CD28 and CD137 (4-1BB) [11]. Investigators at the Baylor College of Medicine treated 6 patients affected by relapsed refractory B cell lymphoma (including DLBCL, t-FL and chronic lymphocytic leukemia (CLL)) with an anti-CD19 CAR T cell product, engineered to express CD28 as co-stimulatory domain. No conditioning regimen was used. As opposed to first-generation CAR T cells, persistence of the product was observed up to 6 months, with stable disease obtained in 2 patients [12]. A similar construct was used at the same time by investigators at the National Cancer Institute (NCI), first in a patient with relapsed FL, and subsequently in 15 patients with either relapsed or refractory DLBCL, CLL, or indolent lymphomas. Conditioning with 7 days of fludarabine and cyclophosphamide was used, to decrease the risk of rejection of the CAR T cells. This approach resulted in prolonged product persistence and significant clinical activity with eight complete responses (CR) and four partial responses (PR) in the 13 evaluable patients. However, grade 3 or greater toxicity was observed in all patients, including cytokine release syndrome (CRS) and neurotoxicity, but all resolving within 3 weeks [13, 14]. Of interest, in a subsequent trial conducted by the same group, the use of a less intense conditioning therapy resulted in a significantly lower rate of severe toxicity (55%), despite comparable product persistence and clinical activity [15]. Of interest, this less intense conditioning regimen, similar to that used in non-myeloablative stem cell transplant, has been incorporated in the majority of subsequent trials investigating the activity of CAR T cell therapy in patients with relapsed refractory B cell lymphoma.

Second-generation CAR products using 4-1BB as costimulatory domain have been investigated by two separate groups, at the Fred Hutchinson Cancer Research Center and at the University of Pennsylvania. The former group treated 32 patients with relapsed or refractory B cell lymphoma (including both aggressive and indolent histologies), using either cyclophosphamide alone or in combination with fludarabine as conditioning regimen. A CD4:CD8 CAR T ratio of 1:1 was a unique feature of this product. Higher response rates were observed among patients who received the cyclophosphamide plus fludarabine combination compared with non-fludarabine-containing conditioning (overall response rate (ORR) 72% vs 50%, CR rate 50% vs 8%). Grade 3 or greater toxicity was reported in 28% of patients [16]. The second group treated 28 patients with relapsed or refractory aggressive or indolent B cell lymphomas, using a CAR product containing 4-1BB as costimulatory domain. Conditioning regimens were very heterogeneous. ORR was 64%, CR rate was 57%, and grade 3 or greater CRS and neurotoxicity were reported in 18% and 11% of patients, respectively [17].

The encouraging results observed with some of the above second-generation CARs led to their evaluation further in multicenter single-arm phase II clinical trials in relapsed or refractory aggressive B cell lymphomas: axicabtagene ciloleucel or axi-cel (developed at the NCI) through the ZUMA-1 study, tisagenlecleucel (developed at the University of Pennsylvania) through the JULIET trial, and lisocabtagene maraleucel or liso-cel (developed at the Seattle Children's Hospital and Fred Hutchinson Cancer Research Center) through the TRANSCEND trial (Table 1). The structure of these three CAR T products are shown in Fig. 1.

Multicenter Anti-CD19 CAR T Trials and FDA Approvals

Seven patients with relapsed or refractory DLBCL were enrolled in the phase I component of the ZUMA-1 trial, and conditioning consisted of both cyclophosphamide and fludarabine [18]. In the subsequent phase II component of the study, 101 patients with relapsed or refractory DLBCL, t-FL, and primary mediastinal B cell lymphoma (PMBCL) were treated using the same conditioning regimen. In the combined phase I plus phase II study of 108 patients, ORR was 83%, CR rate was 58%, and grade 3 or higher CRS and neurotoxicity were reported in 13% and 31% of patients, respectively [19•, 20]. These results led to FDA approval of this product, marketed as Yescarta®, in October 2017, for patients with relapsed or refractory DLBCL, PMBCL, t-FL, and high-grade B cell lymphoma after at least two lines of systemic therapy. Recently, the long-term activity of axi-cel has been reported: at a median follow-up of 27.1 months, the median progression-free survival was 5.9 months, median overall

Table 1 Summary of the three pivotal multicenter clinical trials investigating CAR T cell therapy in relapsed or refractory aggressive B cell lymphoma

	ZUMA-1 ($N = 108$)	JULIET ($N = 93$)	TRANSCEND ($N = 73$)
Histology	DLBCL, t-FL, PMBCL	DLBCL, t-FL	DLBCL, t-FL
Product	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Developed at	NCI	UPenn	SCH/FHCRC
Sponsor	Kite	Novartis	Juno
Costimulatory domain	CD28	4-1BB	4-1BB
CD4:CD8	Variable	Variable	1:1
Conditioning	Flu-Cy	Flu-Cy or benda	Flu-Cy
Median age (years)	58 (31–69)	56 (22–76)	59 (37–79)
Median number of previous therapies	3 (2–4)	3 (1–6)	3 (2–9)
ORR	83%	52%	80%
CR rate	58%	40%	59%
Grade $\geq$ 3 CRS	13%	22%	1%
Grade $\geq$ 3 neurotoxicity	31%	12%	13%
FDA approval	2017 (Yescarta®)	2018 (Kymriah®)	Pending

DLBCL, diffuse large B cell lymphoma; *t-FL*, transformed follicular lymphoma; *PMBCL*, primary mediastinal B cell lymphoma; *NCI*, National Cancer Institute; *UPenn*, University of Pennsylvania; *SCH*, Seattle Children's Hospital; *FHCRC*, Fred Hutchinson Cancer Research Center; *Flu-Cy*, fludarabine-cyclophosphamide; *benda*, bendamustine; *ORR*, overall response rate; *CR*, complete remission; *CRS*, cytokine release syndrome; *FDA*, Food and Drug Administration

survival has not been reached, and 39% of the patients were in ongoing remission [20].

Ninety-three patients with relapsed or refractory DLBCL or t-FL were treated in the JULIET phase 2 study. Conditioning consisted of cyclophosphamide and fludarabine or bendamustine as a single agent. The best ORR was 52% and CR rate was 40%; grade 3 or greater CRS and neurotoxicity were reported in 22% and 12%, respectively [21•]. At a median follow-up of 14 months, the median progression-free survival was 2.9 months, median overall survival was 12 months, and 34% of the patients were in ongoing remission [22, 23••]. These results led to the FDA approval of this product, marketed as Kymriah®, in May 2018, for the treatment of patients with relapsed or refractory DLBCL, t-FL, and high-grade B cell lymphoma (but not PMBCL) after at least two lines of systemic therapy.

On the TRANSCEND trial, 73 patients with relapsed or refractory DLBCL or t-FL have been treated to date after

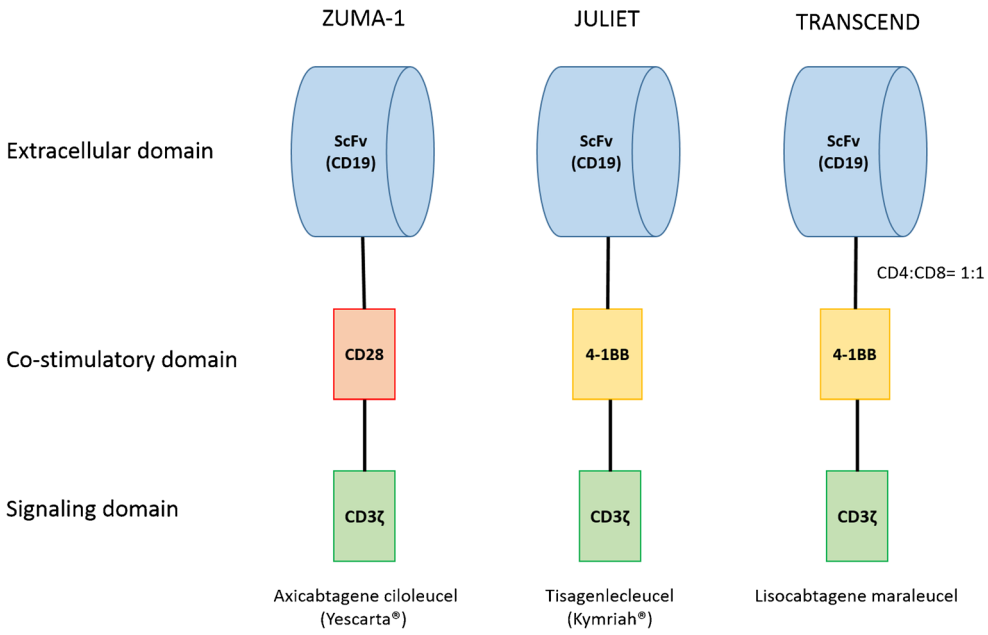

Fig. 1 Anti-CD19 CAR T cell products evaluated in pivotal trials in B cell lymphomas

lymphodepletion with cyclophosphamide and fludarabine. While the publication of final results is still pending, at most recent follow-up, ORR in this cohort was 80%, and CR rate was 59%; grade 3 or greater CRS and neurotoxicity rates were 1% and 15%, respectively [24].

While all these strategies are very promising and are rapidly changing, the therapeutic scenario for patients with relapsed or refractory aggressive B cell malignancies, multiple attempts are being made to better understand their toxicities and resistance mechanisms to improve their safety and efficacy.

Toxicity: Cytokine Release Syndrome

CRS results from rapid activation and proliferation of CAR T cells, with subsequent supraphysiologic release of pro-inflammatory cytokines from the CAR T cells themselves as well as bystander immune cells [25•]. It can manifest with fever, hypotension, hypoxia, and signs/symptoms of organ dysfunction. CRS typically peaks at time of maximal in vivo CAR T cell expansion and resolves within 3 weeks from the infusion [26, 27]. Most patients experience grade 1–2 CRS; however, severe toxicity may occur in patients with bulky disease. Severe CRS has been associated with serum IL-6 levels, and tocilizumab, an anti-IL-6 receptor antibody, has been used successfully for CRS management. Severe CRS, refractory to tocilizumab, may require use of corticosteroids, which can suppress multiple immune cells and downregulate production of multiple cytokines [28•]. Rarely, patients may develop fulminant macrophage activating syndrome or hemophagocytic lymphohistiocytosis following CAR T therapy [19•, 28•]. Such patients are also initially managed with anti-IL6 and corticosteroid therapy, before considering other therapies such as etoposide [29].

Toxicity: Neurotoxicity

The pathophysiology of neurotoxicity, also referred to as CAR-related encephalopathy syndrome (CRES) or immune effector cell–associated neurotoxicity syndrome (ICANS), remains largely unknown [25•, 28•]. Possible mechanisms include diffusion of cytokines and transmigration of CAR T cells into the central nervous system, activation of endothelial cells and disruption of the blood-brain barrier, and activations of myeloid cells by IL-1, GM-CSF, and possibly other cytokines [30–35]. It typically presents as toxic encephalopathy, with word-finding difficulty, aphasia, altered level of consciousness, and impairment of cognitive skills, and in more severe cases, motor weakness, seizures, and cerebral edema. Like CRS, most patients experience grade 1–2 neurotoxicity and it is usually self-limiting and completely reversible. Neurotoxicity occurring concurrently with CRS can be successfully treated with CRS-directed therapy. However, severe neurotoxicity occurring in the absence of CRS may require use of corticosteroids and intensive monitoring and supportive care through a multidisciplinary team [28•].

Toxicity: B Cell Aplasia

As CD19 is also expressed on non-malignant B lymphocytes, prolonged B cell aplasia is an expected on-target but off-tumor effect and has been invariably observed in all studies employing anti-CD19 CAR T cell therapies [36]. Similar to what is done in other conditions of iatrogenic hypogammaglobulinemia, immunoglobulin replacement therapy can be used, in case of associated severe or frequent infections [37]. On the ZUMA-1 study, 31% of the patients needed immunoglobulin replacement therapy but most patients with ongoing remission eventually recovered their normal B cells by 2 years, suggesting loss of functional persistence of CAR T cells over time [20].

Relapse After Anti-CD19 CAR T Cell Therapy

At least 60% of the patients with aggressive B cell lymphoma relapse after anti-CD19 CAR T cell therapy. In some of these patients, the relapse appears to be due to immune escape from antigen loss of CD19 [19•, 20, 21•], whereas in others, CD19 positive relapses have been observed. While retreatment is a potential option for patients with CD19-positive relapse, particularly in case of initial response to CAR T cell therapy, it is frequently either not effective or not feasible because of patient's clinical condition. Therefore, additional investigations are needed to better characterize mechanisms of relapse and identify targets for novel treatment strategies.

To this regard, overexpression of PD-L1 has been noted in DLBCL tumors in approximately two-thirds of the patients relapsing after axi-cel CAR T cell therapy, prompting the investigation of experimental strategies aimed at reverting tumor-induced immunosuppression and immune exhaustion using immune checkpoint inhibitors [38–41]. To overcome immune escape due to CD19 loss, CAR T cell products targeting other B cell antigens such as CD20, CD22, and CD79b [42–44], or alternative adoptive T cell therapy approaches such as Epstein-Barr virus–specific or cancer-testis antigen-specific cytotoxic T lymphocytes, are in development [22, 45]. In addition, the role of either autologous or allogeneic stem cell transplant remains unclear after CAR T failure, and their optimal sequencing still remains to be investigated.

Future Directions

Given the complex process required for the manufacturing of CAR T cells and for their post-infusional managements, multiple steps can be targeted to improve their efficacy and safety. The immunogenicity of murine scFv, currently used in the extracellular domain of FDA-approved products, could be significantly decreased by using fully human scFv or adnectin, a fibronectin-based protein [46], thereby decreasing host rejection and improving CAR T persistence. The potency of CAR T cells may also be improved by incorporating additional costimulatory domains such as OX40, CD27, and ICOS, into the intracellular domain to generate a stronger signal 2 (third-generation CARs) [47]. Another strategy to improve the efficacy is to develop multi-specific CAR T cells to target multiple tumor antigens simultaneously and minimize immune escape [48–50].

In patients with multiply treated B cell malignancies, autologous T cells are frequently functionally impaired, resulting in ineffective CAR T cells at time of apheresis and ex vivo engineering and expansion [40, 41]. Agents able to improve T cell function, such as ibrutinib, lenalidomide, immune checkpoint inhibitors, IL-2 or IL-12, may successfully be combined with CAR T cell therapy, to improve their efficacy [51, 52]. In addition, the production of off-the-shelf healthy donor-derived allogeneic CAR T cell products may bypass the need for autologous T cells, and decrease time to first infusion [53].

CAR T products against other lymphomas are also in development. Anti-CD30 CAR T cell therapy appears to be promising for Hodgkin lymphoma and certain CD30+ T cell lymphomas such as anaplastic large cell lymphoma [54, 55]. CD5 and CD7 are also being investigated as potential targets for CAR T cell therapy for T cell lymphomas [56–59]. Finally, incorporation of safety switches, including inducible suicide genes such as caspase 9, and elimination genes such as truncated epidermal growth factor receptor, are being investigated to improve safety and help management of life-threating toxicities [60, 61].

Conclusions

In conclusion, the introduction of CAR T cells has revolutionized in a short time the therapeutic scenario for the treatment of patients with relapsed or refractory aggressive B cell lymphomas. Ongoing studies are focused on improving their efficacy and safety, understanding and overcoming resistance, and clarifying their advantage over stem cell transplant. In the future, the use of CAR T cells may progressively be moved to the frontline setting and be extended to other lymphomas, potentially increasing the rate of cure for patients with any type of lymphoma.

Authors Contributions PS and SSN have coauthored the paper.

Compliance with Ethical Standards

Conflict of Interest Paolo Strati declares that he has no conflict of interest. Sattva S. Neelapu has received research support from Kite/Gilead, Celgene, Cellectis, Poseida, Merck, Acerta, Karus, and Bristol-Myers Squibb and has served as a consultant and advisory board member for Kite/Gilead, Celgene, Novartis, Unum Therapeutics, Pfizer, CellMedica, and Merck.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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