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REVIEW

Principles of adoptive T cell therapy in cancer

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Abstract
Adoptive cell therapy (ACT) utilizing either tumor-infiltrating lymphocyte (TIL)-derived T cells or T cells genetically engineered to express tumor recognizing receptors has emerged as a powerful and potentially curative therapy for several cancers. Many ACT-based therapies have recently entered late-phase clinical testing, with several T cell therapies already achieving regulatory approval for the treatment of patients with B cell malignancies. In this review, we briefly outline the principles of adoptively transferred T cells for the treatment of cancer.

Keywords Cancer immunotherapy · Adoptive cell therapy · Tumor-infiltrating lymphocytes · Chimeric antigen receptor · T cells

Introduction

Cancer immunotherapy is defined as the approach to combatting cancer by generating or augmenting an immune response against cancer cells. Over the past decade, two types of immunotherapy have emerged as particularly effective in cancer treatment: the use of immune checkpoint inhibitors to enhance natural antitumor activity and the administration of specific antitumor immune cells via adoptive cell therapy (ACT).

At present, the most widespread type of immunotherapy is the administration of monoclonal antibodies directed against regulatory immune checkpoint molecules that inhibit T cell activation, in particular, cytotoxic T lymphocyte-associated protein-4 (CTLA-4) [1], programmed cell death-1 (PD-1) [2], and programmed death-ligand 1 (PD-L1) [3]. As both a single-agent and in combination, these immune checkpoint inhibitors have demonstrated marked overall and disease-free survival benefits in multiple clinical trials, paving the way for regulatory approval of these drugs in a variety of solid tumors and hematological malignancies [4–10].

While this treatment modality has been successfully applied in many solid tumors, the main mechanism relies on boosting a pre-existing population of potentially tumor-reactive T cells in the patient. Thus, in poorly immunogenic cancer types, immune checkpoint therapy alone is likely to fail [11]. In this regard, the administration of tumor-recognizing T cells via ACT would enable immune-based therapies for these poorly immunogenic cancer types and potentially augment responses in tumors that are already responsive to immune checkpoint therapy.

In this review, we present a brief outline of the basic principles of ACT utilizing tumor-infiltrating lymphocytes (TILs) and genetically engineered T cells.

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ACT modalities

The ultimate goal of ACT is to generate a robust immune-mediated antitumor response via the infusion of ex vivo manipulated T cells. ACT-based strategies utilizing T cells to destroy tumors can be divided into (i) the isolation of naturally occurring tumor-specific T cells from existing tumor masses (TILs), and (ii) the genetic modification of blood-derived T cells to allow for specific recognition of tumor cells. In both settings, T cells are manipulated ex

vivo followed by an expansion and eventual reinfusion back into the lymphodepleted patient (Fig. 1).

Naturally occurring tumor-specific T cells

TILs are a heterogeneous population of lymphocytes, consisting primarily of T cells and natural killer (NK) cells, that naturally migrate into the tumor and are potentially present in any solid tumor. One of the earliest reports detailing the clinical benefit of lymphocyte infiltration was a case report from 1972 where it was reported that a gastric cancer patient demonstrated total regression of liver metastasis in the absence of prior therapy [12]. The dense infiltration of lymphocytes observed in the resected gastric biopsy suggested the importance of these TILs in curtailing cancer growth. Subsequently, the presence of TILs in tumors has been associated with a favorable prognosis in various cancer types [13–16].

TILs capable of recognizing tumor associated antigens (TAAs) through their endogenous T cell receptors (TCRs) can be isolated from resected tumors; however, the relatively small number of TILs recovered would be inadequate for ACT. The discovery of the T cell growth factor interleukin-2 (IL-2) [17] has allowed the development of a standard method for large-scale in vitro expansion of TILs isolated from patient tumors [18]. This method, involving the exposure of extracted TILs to high dose IL-2 followed by a rapid expansion process utilizing a mixed feeder cell population, was pioneered by Steven Rosenberg and his colleagues at the Surgery Branch of the National Cancer Institute (NCI) and resulted in the production of enough cells for ACT [20]. Initially tested in refractory metastatic melanoma patients, ACT of these cells was found to be an effective treatment option, particularly when preceded by nonmyeloablative lymphodepletion and followed by subsequent high-dose IL-2 treatment [21].

TIL-based ACT relies on (i) nonmyeloablative lymphodepletion, (ii) infusion of large numbers of expanded TILs isolated from a resected tumor, and (iii) IL-2 administration following TIL infusion.

The overall approach for growing and administrating TILs is depicted in Fig. 1**a**. The resected tumor specimen is divided into multiple fragments that are individually grown in IL-2 or enzymatically dispersed into a single-cell suspension. Lymphocytes will then overgrow and typically eradicate tumor cells within 2–3 weeks, resulting in pure TIL cultures. If autologous tumor cells are available, individual TIL cultures can be selected based on attributes such as tumor-reactive interferon-γ (IFN-γ) secretion and cytotoxicity [20]. Selected TIL cultures are then subjected to a rapid expansion protocol (REP) in the presence of excess irradiated feeder cells, an antibody targeting the CD3 complex of the TCR, and high dose IL-2. With this approach, up to $2 \times 10^{\wedge 11}$ lymphocytes can be obtained for infusion into patients [22]. However, difficulties in generating autologous tumor cultures and variations in target tumor quality have prompted many institutions to utilize minimally cultured TILs, where typically all isolated TILs are utilized for further massive expansion and

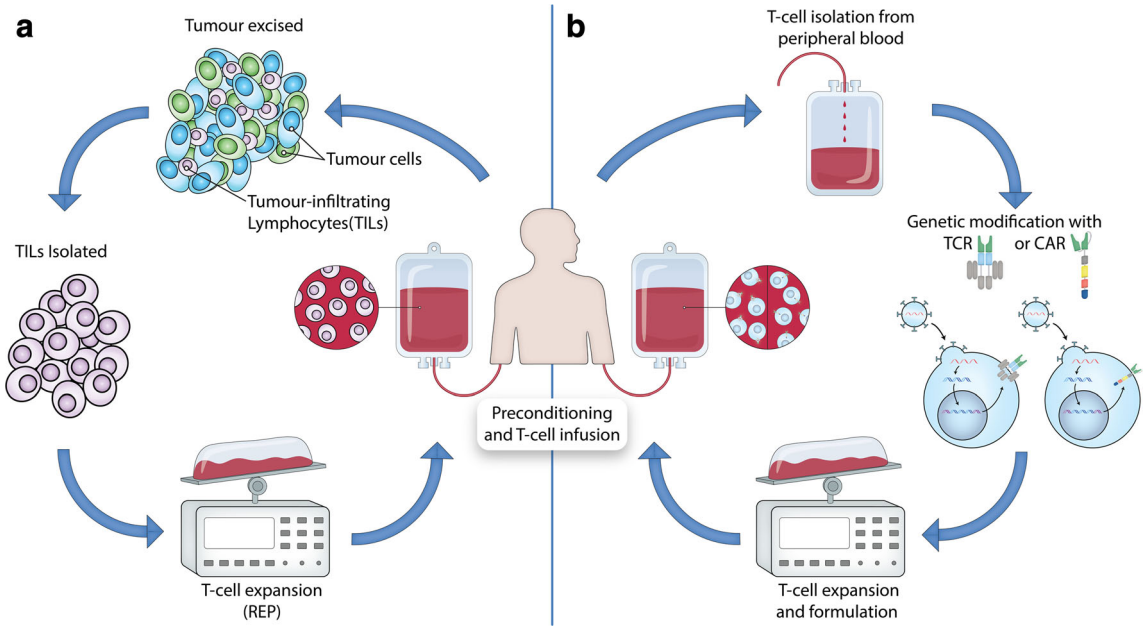

Fig. 1 Different adoptive T cell transfer (ACT) approaches to harness the immune system to treat cancer (**a**) Adoptive transfer of anti-tumor T cells isolated from within a patient's tumor. Tumor-infiltrating T cells (TILs) are extracted from surgically resected tumor samples, then expanded in vitro, followed by re-infusion into the lymphodepleted patient. (**b**) T cells from patient peripheral blood are isolated and expanded in culture and genetically modified to express either a T cell receptor (TCR) or a chimeric antigen receptor (CAR) that confers the ability to specifically recognize and destroy tumor cells when re-infused into the lymphodepleted patient. Reprinted with permission from: Svane el al [19]

infusion [23–25]. The main benefit of this approach is the considerably reduced culture period, which simplifies a significant portion of this complex expansion platform and is less labor-intensive and more cost-effective.

Prior to cell infusion, patients are subjected to a preconditioning regimen, commonly including the administration of cyclophosphamide and fludarabine, causing transient host lymphodepletion [26]. This has been shown to increase the persistence of infused TILs, as well as the incidence and duration of clinical responses after TIL therapy [27].

First observed at the NCI, the efficacy of this personalized immunotherapy has been confirmed by multiple independent studies reporting objective response rates of 40 to 50% in patients with metastatic melanoma, including complete tumor regression in 10 to 25% of treated patients (Table 1). The efficacy of adoptive TIL therapy can be put into perspective when considering that metastatic melanoma was a highly lethal neoplasm with only 10% 5-year survival prior to the initiation of TIL therapy [43]. In addition, TIL therapy has mainly been used in late-stage metastatic melanoma cases as a salvage treatment after the failure of standard therapies in patients with multiple metastatic sites. More importantly, the collective experience of various independent studies is that a substantial part of the observed responses are durable, especially in patients achieving complete tumor regression, and that the vast majority of these patients are disease-free many years after treatment [28–30, 44–46]. These findings clearly demonstrate the clinical efficacy of TIL-based ACT and highlight the curative potential of this treatment. For comparison, although objective response rates of around 57% were obtained with combined immune checkpoint blockade in patients with treatment-naive melanoma, the number of patients acquiring complete tumor regression was reported as 2.2%, 8.9%, and 11.5% when treated with antibodies targeting CTLA-4 or PD-1 as a monotherapy, or the combination of both, respectively [6].

Previous reports have shown that prior treatment with IL-2-based immunotherapy and/or anti-CTLA-4 antibodies does not appear to impact the response to adoptive TIL therapy [44, 47]. As PD-1 targeting immune checkpoint therapy has become the standard of care in recent years, we recently investigated whether patients progressing after anti-PD-1 immunotherapy could still respond to an infusion of TILs [22]. We demonstrated that these patients could indeed respond to TIL infusion, and in addition, we found that tumor-reactive T cells heavily infiltrated the tumor microenvironment of patients who had previously failed immune checkpoint treatment. These findings suggest that the mechanisms leading to resistance to current immune checkpoint therapy do not overlap with resistance to TIL-based ACT, and that despite the increasing number of treatment options in metastatic melanoma relegating TIL-based ACT to a third- or fourth-line therapy, the utilization of biomarker-driven strategies to study the tumor of individual melanoma patients failing immune checkpoint therapy can guide future treatment strategies [22].

Whereas treatment-associated mortality is considerably less than that seen with conventional treatments for relapsed or refractory cancers, significant toxicities have been observed in TIL-based ACT. In general, these have been categorized as Common Terminology Criteria for Adverse Events (CTCAE) grade 3 and 4 toxicities and are primarily related to the preconditioning regimen, particularly the administration of high-dose IL-2 after cell transfer [44–46]. In this regard, we have previously reported the use of an attenuated IL-2 decrescendo regimen and showed an objective response rate in 10 of 24 (42%) evaluable patients, including three durable complete responders (12%), which is comparable to what has previously been published with ACT plus high-dose bolus IL-2 [30]. Although IL-2-related toxicities were observed, this was generally manageable without requiring intensive care support. The use of attenuated doses of IL-2 may increase the applicability of TIL-based ACT to centers without readily available intensive care units. In addition, due to its high costs in terms of toxicity, it is important to discover predictive criteria for response in order to only expose those patients with a reasonable chance of obtaining a clinical benefit to TIL-based ACT. So far, contrasting results have been reported on the use of tumor mutational burden or tumor neoepitope burden as predictive criteria of response to TIL-based ACT [48].

The observation that melanoma TILs can mediate durable and complete cancer regression in patients with metastatic melanoma has raised considerable interest regarding the possible use of TILs for the treatment of other cancer types. Large-scale TIL growth has been described for a number of solid cancers other than melanoma, including ovarian, breast, colon, cervical, sarcoma, and renal [49–53]; however, only moderate clinical responses have been observed with TIL-based ACT.

Ongoing research is exploring how to improve the efficacy of TIL-based ACT in melanoma and to extend its efficacy to other common cancers using novel approaches to identify cancer mutations [54, 55], as well as to increase its availability to reference cancer centers.

Genetically modified T cells

In contrast to TIL-based ACT, the second approach for generating tumor-specific T cell therapies relies on the genetic modification of T cells to enhance antitumor immune function where natural tumor-specific immune responses have failed by manipulating antigen specificity. This is achieved via the transfer of genetic material encoding either a cloned TCR or a

Table 1 Clinical responses to different ACT modalities—Tumor-infiltrating lymphocytes (TIL) or genetically-modified T cells (TCR or CAR)

Study	Disease	Type of ACT	Antigen target	Conditioning	Number of patients	Clinical response
Rosenberg, 1988 (ref. [18])	Melanoma	TIL	Various	Cy	20	ORR 11 (55%) CR 1 (5%)
Dudley, 2005 (ref. [21])	Melanoma	TIL	Various	Cy + Flu	43	ORR 21 (49%) CR 5 (12%)
Itzhaki, 2011 (ref. [28])	Melanoma	TIL	Various	Cy + Flu	31	ORR 15 (48%) CR 4 (13%)
Radvanyi, 2012 (ref. [29])	Melanoma	TIL	Various	Cy + Flu	31	ORR 13 (42%) CR 2 (6%)
Andersen, 2016 (ref. [30])	Melanoma	TIL	Various	Cy + Flu	25	ORR 10 (42%) CR 3 (13%)
Morgan, 2006 (ref. [31])	Melanoma	TCR	MART-1 (aa27-35, HLA-A2)	Cy + Flu	15	ORR 2 (13%)
Johnson, 2009 (ref. [32])	Melanoma	TCR	gp100 (aa154-162, HLA-A2)	Cy + Flu	16	ORR 3 (19%) CR 1 (6%)
Robbins, 2011 (ref. [33])	Synovial sarcoma Melanoma	TCR	NY-ESO-1 (aa157165, HLA-A2)	Cy + Flu	17	ORR 9 (53%) CR 2 (12%)
Rapaport, 2015 (ref. [34])	Multiple Myeloma	TCR	NY-ESO-1 (aa157-165, HLA-A2)	Other	20	ORR 18 (90%) CR 16 (80%)
Davila, 2014 (ref. [35])	ALL (adult)	2nd CAR (CD28)	CD19	Cy	16	ORR 14 (88%) CR 14 (88%)
Maude, 2014 (ref. [36])	ALL (child/young adult)	2nd CAR (4-1BB)	CD19	Cy + Flu Other	30	ORR 27 (90%) CR 27 (90%)
Park, 2018 (ref. [37])	ALL (adult)	2nd CAR (CD28)	CD19	Cy Cy + Flu	53	CR 44 (83%) ORR 44 (83%)
Maude, 2018 (ref. [36])	ALL (child/young adult)	2nd CAR (4-1BB)	CD19	Cy + Flu	75	ORR 61 (81%) CR 61 (81%)
Kochenderfer, 2015 (ref. [38])	NHL/CLL	2nd CAR (CD28)	CD19	Cy + Flu	15	ORR 12 (80%) CR 8 (53%)
Neelapu, 2017 (ref. [39])	NHL	2nd CAR (CD28)	CD19	Cy + Flu	101	ORR (54%) CR (54%)
Porter, 2015 (ref. [40])	CLL	2nd CAR (4-1BB)	CD19	Cy + Flu Other	14	ORR 8 (58%) CR 4 (29%)
Turtle, 2017 (ref. [41])	CLL	3rd CAR (CD28/4-1BB)	CD19	Cy + Flu	24	ORR 16 (67%) CR 4 (17%)
Brudno, 2018 (ref. [42])	MM	2nd CAR (CD28)	BCMA	Cy + Flu	16	ORR 13 (81%) CR 10 (63%)

These trials make use of different preconditioning regimens (Cy, cyclophosphamide; Flu, fludarabine), and for CAR therapy trials, different signaling elements (CD28 or 4-1BB) are used. For TCR therapy trials target antigen, epitope and HLA-restriction is indicated

synthetic chimeric antigen receptor (CAR) targeting tumor specific antigens. Formed by combining the antigen-binding portions of an antibody molecule with the signaling components of various immunoreceptors and costimulatory molecules, CARs are designed to be highly specific and highly reactive. While many different approaches are utilized to generate genetically modified T cells, the general outline of this approach is depicted in Fig. 1b. Simply, T cells are obtained from peripheral blood, usually after leukapheresis, and activated before being genetically altered and expanded prior to their reinfusion back into the patient. The patient is often subjected to a preconditioning regimen similar to that of TIL-based ACT beforehand.

Gene transfer methods commonly used to genetically engineer T cells include the use of transient mRNA transfection [56], retroviral vectors [57], lentiviral vectors [58], transposons [59], or, most recently, homologous recombination after gene editing [60].

TCR-modified T cells

TCRs are naturally occurring surface receptors on T cells that can recognize peptide antigens presented on the surface of host cells via the major histocompatibility complex (MHC)/human leukocyte antigen (HLA) system.

Genetically modified TCR therapy alters T cell specificity through the expression of a new TCR alpha and beta chain pair that is tumor antigen-specific (Fig. 2a). For this purpose, the TCRs of T cells that can recognize naturally processed and expressed tumor antigens, and therefore specifically attack malignant tissue, have been identified. However, as TCRs bind to peptide/MHC complexes at the cell surface of tumor cells, the tumor-specific TCRs can only be used in a patient population that has this specific MHC or HLA allele.

After the isolation and sequencing of a tumor-specific TCR, it can be cloned into retro- or lentiviral vectors that are used to transduce peripheral blood T cells from patients ex vivo, followed by expansion and infusion into patients (Fig. 1b).

Typically, tumor antigen-specific T cells targeting self-antigens isolated from cancer patients are of low affinity, due to the impact of central tolerance on the T cell repertoire specific for these antigens. Attempts to overcome this issue have included the (i) engineering of high affinity TCRs by affinity maturation of the TCR [61], (ii) generation of murine TCRs by immunizing transgenic mice that express a HLA allele plus human tumor antigen [62], and (iii) isolation of TCRs in an allogeneic setting via in vitro induction of T cells specific for a foreign HLA-peptide complex [63], thereby bypassing the repertoire limitations imposed by thymic selection.

In the first proof-of-principle study using genetically modified TCRs, T cells from metastatic melanoma patients were transduced with a TCR directed against the HLA-A*0201/MART-1 peptide, which was cloned from a pure TIL culture isolated from a resected melanoma lesion of an HLA-*0201 patient that had responded to TIL treatment [31]. Sustained objective responses were observed in a minor proportion of the treated patients with no significant toxicity, and infused TCR-modified T cells were persistent for more than a year. Other trials have subsequently demonstrated significant and prolonged tumor regression in cancer patients using genetically modified TCRs against gp100 (melanoma) [32], NY-ESO-1 (melanoma, synovial sarcoma, multiple myeloma) [33], MAGE-A3 (myeloma, melanoma) [64], MAGE-A4 (esophageal cancer) [65], and CEA (colorectal carcinoma) [66] (Table 1).

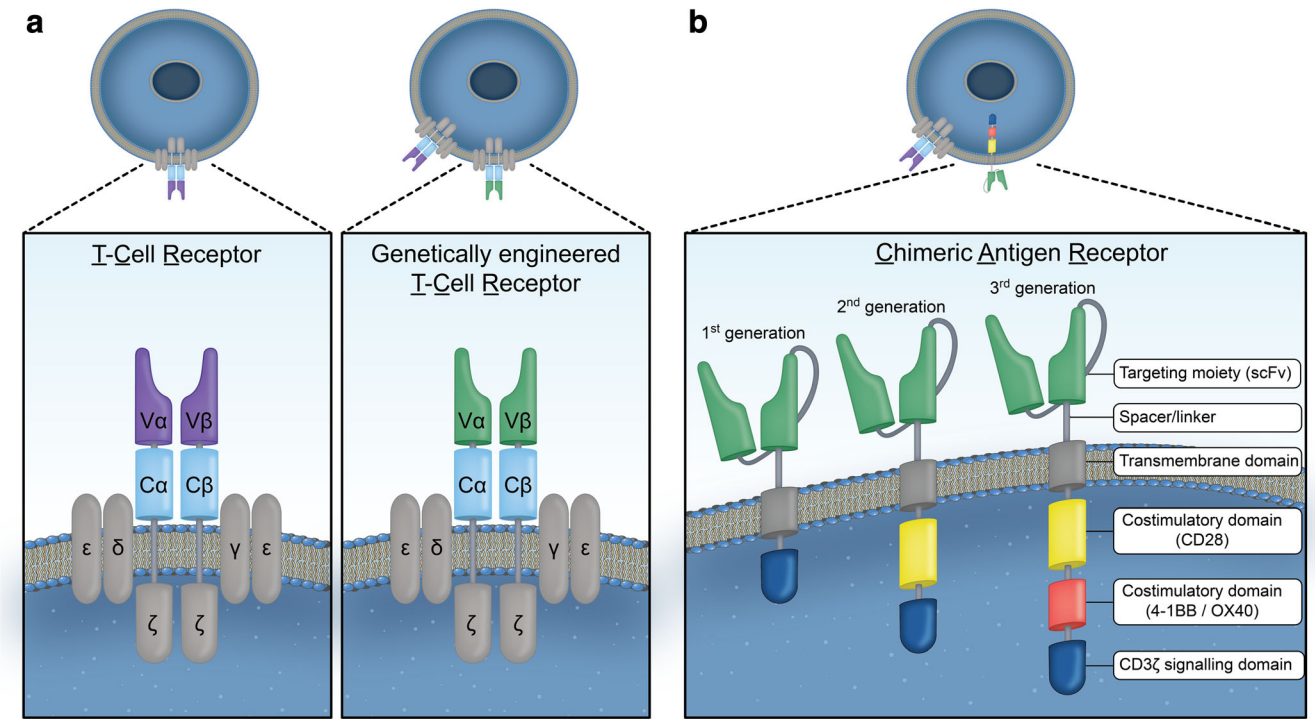

Fig. 2 Genetically modified T cells. (**a**) T cells recognize their target by the TCR complex, which is composed of the TCR α and β chain for recognition and the CD3 chains for signaling. T cells can be genetically engineered with defined specificity by expression of recombinant TCR αβ chains of known specificity. (**b**) CARs are composed of a single-chain fragment of variable region (scFv) derived from the antigen-binding domain of antibodies, fused to the CD3ζ transmembrane and intracellular signaling domains from the TCR complex. Additional intracellular signaling domains are added for costimulatory signals, such as the CD28 and 4-1BB signaling domains, to yield second- and third-generation CARs. Reprinted with permission from: Svane el al [19]

Although TILs have generally been safe, there are potential safety risks associated with the use of genetically modified T cell therapies, with the most critical being: (i) on-target off-tumor toxicity, when infused T cells recognize normal tissue due to expression of the same antigen, such as gp100 and MART-1 which are expressed by both melanoma cells and normal melanocytes, (ii) off-target reactivity, when infused T cells cross-react against peptides other than those targeted, and (iii) cytokine-release syndrome (CRS), where infused T cells induce a sudden and dramatic increase of inflammatory cytokines [34, 67].

CAR-modified T cells

The genetic modification of T cells with CARs combines the specificity of antibody-like recognition with the cytotoxic potency and activation potential of T cells (Fig. 2b). The construction of a CAR relies on the identification of a suitable antibody targeting a cell surface molecule of interest, and in contrast with the TCR modification approach, CAR recognition does not rely on peptide processing or presentation by MHC molecules. Thus, all surface-expressed target molecules represent a potential CAR-triggering epitope.

First-generation CARs are composed of an antigen-binding region (a single-chain antibody variable fragment (scFv)), based on the antibody of desired specificity, fused to the T cell signaling domains associated with native TCR signal transduction (Fig. 2b). These early CARs only provide activation signal 1 to T cells and have been shown to lead to CAR-T cell anergy upon repeated antigen stimulation [68]. Second generation CARs contain an additional co-stimulatory domain, such as CD28 or 4-1BB, which provides a second activation signal upon target antigen recognition (Fig. 2b). CAR-T cells carrying these CD28 or 4-1BB signaling moieties have demonstrated potent antitumor activity in clinical trials, resulting in meaningful clinical response rates that significantly outperform the previous generation (Table 1). Third generation CARs, which again incorporate another co-stimulatory domain (Fig. 2b), are now in development to further potentiate the persistence and activity of infused CAR-T cells.

Multiple clinical trials have demonstrated the robust efficacy and frequent durable responses induced by CAR-T cells targeting CD19, a B cell-lineage antigen expressed on the surface of both normal and malignant B cells. CD19-specific CAR-T cells have been successfully used to treat patients with chemotherapy-refractory B cell malignancies, including marginal zone lymphoma, aggressive B cell lymphomas, chronic lymphocytic leukemia (CLL), and adult and pediatric acute lymphoblastic leukemia (ALL). In particular, the treatment of CLL and non-Hodgkin lymphoma resulted in tumor regressions for a majority of patients [38, 40, 41, 69, 70]; however, the most impressive results were observed in ALL, where complete response rates (CRR) of 70–90% in heavily pre-treated patients were regularly reported by several institutions testing CAR-T cell therapy [35–37, 71] (Table 1).

Based on the collective experiences of these centers, which all utilized differing co-stimulatory domains and gene transfer methods, some key considerations can be identified: (i) patients should receive lymphodepleting chemotherapy, (ii) patients with acute lymphoid leukemia achieve very high response rates, (iii) off-tumor toxicity is primarily limited to B cell aplasia, a condition that can be clinically managed with prophylactic infusions of immunoglobulins, (iv) patients often develop severe CRS, and (v) there is no clear dose-response relationship between the number of CAR-T cells infused and the likelihood of response [35–39, 71–73].

Recent success among several groups exploiting CAR-T cell therapy targeting the B cell maturation antigen (BCMA) for the treatment of multiple myeloma, suggests that this modality may be extended to other hematological malignancies [42].

CAR-T cell therapy against solid tumors has yielded limited success thus far. Potential obstacles include (i) inefficient T cell localization to the tumor site, (ii) physical barriers preventing tumor infiltration by T cells, (iii) increased antigen selection difficulty due to the high antigen heterogeneity of solid tumors, (iv) high risk of on-target, off-tumor toxicity due to the increased potential of target antigen expression in healthy essential organs, and (v) potent immunosuppressive factors that render T cells dysfunctional in the tumor microenvironment [74]. Ongoing preclinical research and clinical trials are attempting to overcome these obstacles by using modified gene transfer methods and treatment protocols, assessing novel CAR designs utilizing additional receptors and ligands to “armor” the CAR, and developing new targets such as CEA for colorectal cancers, disialoganglioside GD2 for neuroblastoma and sarcoma, PSMA for prostate cancer and melanoma, and EGFRvIII and IL13Rα2 for glioblastoma [74].

Summary

The field of adoptive immunotherapy of cancer is a relatively new and rapidly expanding research area. Although immunotherapy techniques such as the adoptive transfer of tumor-infiltrating T cells and gene-modified T cells have been shown to mediate complete and durable responses in some patients with specific cancers, there are still many patients who derive no benefit from these therapies. However, there are many

promising ongoing research projects that may increase the number of patients that can benefit from this treatment modality and increase the feasibility of ACT as a standard of care treatment for all types of cancer.

Compliance with ethical standards

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

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