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REVIEW

Integrating CAR-T cell therapy into the management of DLBCL: what we are learning

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ABSTRACT

Introduction: Chimeric Antigen Receptor ;(CAR) T cells therapies have become part of the standard of care for patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). The weakness of CAR-T therapies is that there are no comparative clinical trials, although many publications based on real-life data have confirmed the results obtained in pivotal studies. After several years of the commercialization of CAR-T, some points still need to be fully clarified. Healthcare professionals have questions about identifying patients who may benefit from therapy. There are aspects inherent in the accessibility of care related to improved relationships between CAR-T-delivering and referral centers.

Areas covered: Open questions are inherent in the salvage and bridge therapy, predictive criteria for response and persistence of CAR-T after infusion. Managing toxicities remain a top priority and one of the points on which further knowledge is needed.

Expert opinion: This review aims to describe the current landscape of CAR-T cells in DLBCL, outline their outcomes and toxicities, and explain the outstanding questions that remain to be addressed.

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CAR-T; diffuse large B-cell lymphoma; cells therapies; ICANS; CRS; bridging therapy

1. Introduction

Although approximately 60% to 70% of patients with diffuse large B-cell lymphoma (DLBCL) are cured with first-line chemoimmunotherapy, the prognosis is poor for patients who have primary refractory (R) disease, who have R disease after two lines or more of therapy, and who have relapsed (R) within 12 months after autologous stem cell transplant (ASCT) [1]. Chimeric antigen receptor (CAR) T-cell therapy can be essential in managing R/R DLBCL. We have three approved autologous CD19-directed CAR-T products; the commercial indications are summarized in Table 1. Barriers to effective CAR-T cell therapy include severe life-threatening toxicities, and healthcare professionals have questions about identifying patients who may benefit from CAR-T-cell therapy [2]. This review aims to describe the current landscape of CAR T cells in DLBCL, outline their outcomes and toxicities, and explain the outstanding questions that remain to be addressed.

1.1. CAR T-cell therapy as third-line treatment

Three single-arm phase 2 trials analyzed this population, the ZUMA-1 study (axi-cel) [3,4], the JULIET study (tisa-cel) [5,6], and the TRANSCEND study (liso-cel) [7] (Table 2). These studies differed in construct, manufacturing, and time from collection to infusion. The overall response rates (ORR) range from 60% to 80%, and complete response (CR) rates from 50% to 60%. The recently updated follow-up of ZUMA-1 after five years suggested that ~ 40% of patients might be cured with CAR-T in this setting [8]. The studies are summarized in Table 2. Based on data from these trials, regulatory agencies have approved CAR-T therapy for patients with R/R DLBCL after two prior lines of therapy.

Despite the not stringent patient selection compared with clinical trials, many publications based on real-life experiences have confirmed the high response rates, prolonged response duration, and survival achieved with CAR-T [9–13].

1.2. CAR T-cell therapy as second-line treatment

Several phase III trials have evaluated CD19-targeted CAR-T cell therapy as second-line therapy for R/R DLBCL (Table 3). The ZUMA-7 trial compared axi-cel to standard of care (SoC) [14]. Patients randomized to axi-cel did not receive bridging therapy, whereas the patients in the SoC arm were treated with second-line chemotherapy and, if they had a response and were candidates for transplant, proceeded to receive an ASCT. The primary endpoint of event-free survival (EFS) favored axi-cel, and the two-year EFS was 40.5% compared to 16.3% in the SoC arm. The estimated two-year OS was slightly higher in the axi-cel group than in the SoC group.

The TRANSFORM trial was similar and compared liso-cel to SoC. In this trial, patients could receive bridging chemotherapy in the experimental arm. The median follow-up was 6.2

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Article highlights

- Anti-CD19 CAR-T cell therapy shows high rates a long term high rates of durable remissions in patients with DLBCL.
- Current guidelines indicate that CAR-T therapy is the standard of care in patients with refractory disease, early relapse after first-line chemotherapy, and in third-line.
- Frontline CAR-T cell therapy should be explored in patients with aggressive double/triple hit lymphoma.
- Open questions are inherent in the salvage and bridge therapy, predictive criteria for response and persistence of CAR-T after infusion.
- Managing short and long terms toxicities remain top of mind and one of the points on which further knowledge is needed.

months, and EFS in the liso-cel arm showed a benefit of 10.1 months compared to 2.3 months on SoC, as well as a trend toward a difference in survival rates [15].

By contrast, in the BELINDA study, tisa-cell was not superior to standard salvage therapy [16]. EFS in both groups was 3.0 months, and response occurred in 46.3% of the patients in the tisa-cell and 42.5% in the standard care group.

Results from ZUMA-7 and TRANSFORM trials suggest that CAR T cells in the second-line setting may offer superior EFS and response rates, compared with current standard approaches that include ASCT, thus relegating ASCT to later-stage therapy.

The choice of CAR-T therapy as second-line treatment depends not only on the disease (refractory or early relapse) but also on patient characteristics. There is much debate as to whether the eligibility criteria for CAR-T are the same as for autologous transplantation (auto-SCT). In the PILOT study, Liso-cel was administered to patients ineligible for auto-SCT. Many criteria defined ineligibility for transplant. However, at least one of the following had to be present: age >70 years, ECOG performance status of 2, DLCO of < 60%, LVEF between 40 and 50%, or a creatinine clearance between 30 to 60 ml/min [17]. The overall response rates (ORR) were in the 70–80% range, and complete remission (CR) rates were between 50 to 60%.

The ALYCANTE study evaluates CAR-T therapy with axi-cel as second-line therapy for patients with R/R DLCBL who are ineligible for auto-SCT. The complete metabolic response (PET negative during or after treatment) was 71% at three months versus 12% compared with standard of care from historical controls, remaining just under 60% at six months [13–18]. At three months, approximately 75% of patients had a partial or complete response, while overall survival at 12 months was approximately 78%, and median overall survival (OS) was not reached.

1.3. CAR T-cell therapy as a first-line option in DLBCL

An ongoing study explores axi-cel as frontline therapy in patients with high-risk large B-cell lymphoma (LBCL) (NCT03761056) [19]. The primary endpoint in efficacy-evaluable patients ($n = 37$) was met, with 78% CRR and 89% ORR. After a median follow-up of 15.9 months, 73% of patients remained in objective response; median DOR, EFS, and PFS were not reached. Frontline therapy clinical studies in high-risk LBCL are uncommon and difficult to execute due to the danger of disease progression during screening.

2. Predictors of response

Several parameters can impact the efficacy of CAR-T therapy. Predictors of improved response can be related to tumor features, such as MYC overexpression, absence of CD58 mutations, high tumor-infiltrating lymphocyte, and low tumor myeloid-derived suppressor cells [20,21]; patient's characteristics, such as absence of medical comorbidities, LDH, low tumor burden, and pre-treatment inflammatory markers [22,23]; and T-cells in terms of faster doubling time in vitro, and higher CAR T-cell peak to tumor burden ratio [24]. Other parameters are using a bridging therapy to control disease progression during product manufacturing [25], the tumor bulk, or the delay between leukapheresis and infusion.

3. Accessibility of care

Patient access is often still limited or delayed. In a recent paper, researchers discuss access challenges and possible solutions in the four largest European countries [26]. The researchers calculated that in 2020, between 58% and 83% of patients

Table 1. Current commercial Indications for DLBCL.

Product	Lymphoma Indications
Tisagenlecleucel (Tisa-Cel)	• Adults with R/R LBCL after ≥ 2 lines of systemic therapy, including DLBCL NOS, high-grade B-cell lymphoma, and DLBCL arising from FL • Adults with R/R FL after ≥ 2 lines of systemic therapy
Axicabtageneciloleucel (Axi-Cel)	• Adults with LBCL either refractory to first-line chemoimmunotherapy or relapsed within 12 mo of first-line chemoimmunotherapy • Adults with R/R LBCL after ≥ 2 lines of systemic therapy, including DLBCL NOS, DLBCL arising from FL, primary mediastinal LBCL, high-grade B-cell lymphoma • Adults with R/R FL after ≥ 2 lines of systemic therapy
Lisocabtagenemaraleucel (Lisa-Cel)	• Adults with LBCL, including DLBCL NOS, DLBCL arising from indolent lymphoma, high-grade B-cell lymphoma, primary mediastinal LBCL, and FL grade 3B, who have disease that is: • Either refractory to first-line chemoimmunotherapy or relapsed within 12 mo of first-line chemoimmunotherapy, *or* • Refractory to first-line chemoimmunotherapy or relapsed after first-line chemoimmunotherapy and ineligible for auto-SCT due to comorbidities or age, *or* • R/R after ≥ 2 lines of systemic therapy

Legend: *CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; auto-SCT, autologous stem cell transplantation; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; NOS, not otherwise specified; R/R, relapsed/refractory.*.

Table 2. DLBCL: CAR T-Cell in third lines of therapy.

Characteristic	ZUMA-1[1–3] Axi-cel ($n = 101$)	JULIET[3,4] Tisa-cel ($n = 111$)	TRANSCEND NHL 001[3,5] Liso-cel ($n = 269$)
Median age, yr (range)	58 (23–76)	58 (22–76)	63 (18–86
• ≥65 yr, %	24	23	42
HGBCL/DHL/THL, %	6	17	13
Refractory to last tx, %	98	45	67
Received bridging tx, %	0	92	59
Median DoR, mo (95% CI)	NR (10.9-NE)	NR (10.0-NE)	NR (8.6-NR)
• 12-mo DoR, % (95% CI)	–	65 (49–78)	54.7 (46.7–62.0)
• 24-mo DoR, % (95% CI)	–	–	52.1 (43.6–49.8)
Median OS, mo (95% CI)	NR (12.8-NE)	11.1 (6.6–23.9)	21.1 (13.3-NR)
• 12-mo OS, % (95% CI)	59 (49–68)	48.2 (38.6–57.1)	57.9 (51.3–62.8)
• 24-mo OS, % (95% CI)	50.5 (40.2–59.7)	40.0 (30.7–49.1)	44.9 (36.5–52.9)
Median PFS, mo (95% CI)	5.9 (3.3–15.0)	NR	6.8 (3.3–14.1)
• 12-mo PFS, % (95% CI)	44 (34–53)	–	44.1 (37.3–50.7)
• 24-mo PFS, % (95% CI)	–	–	42.1 (35.0–48.9)
Median follow-up, mo	27.1	32.6	12.0–17.5

Table 3. DLBCL: CAR T-Cell in second line of therapy.

Characteristic	ZUMA-7		BELINDA		TRANSFORM	
Inclusion criteria	Primary refractory or relapsed ≤12 months, EF ≥50%, CrCL ≥60mL/min		Primary refractory or relapsed ≤12 months, EF ≥45%, serum Cr ≤1.5, or eGFR ≥60mL/min		Primary refractory or relapsed ≤12 months, EF ≥40%, CrCL ≥45mL/min	
Histology	DLBCL-NOS, transformed FL, HGBCL with MYC rearrangement with BCL2/6, HGBCL without MYC rearrangement, EBV positive DLBCL, and leg type cutaneous DLBCL		DLBCL-NOS, transformed indolent lymphoma, HGBCL with MYC rearrangement with BCL2/6, HGBCL without MYC rearrangement, FL grade 3B, PMBCL, T/H-RLBCL, and intravascular LBCL		DLBCL-NOS, transformed indolent NHL lymphoma, HGBCL with MYC and BCL2/6, T/H-RLBCL, FL grade 3B, and PMBCL	
	Dexamethasone or equivalent		R-ICE, R-GDP, R-GemOX, R-DHAP		R-ICE, R-GDP, R-DHAP	
Bridging therapy allowed	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
Patients	180	179	162	160	92	92
Median age, yr (range)	58 (21–80)	60 (26–81)				
≥65 yr, %	28	32	33	28.8	39	27
Primary refractory (%)	133 (74)	131 (73)	107 (66)	107 (67)	67 (73)	68 (74)
Media time from leukapheresis to CAR-T infusion (days)	29		52		36	
Median follow-up, months	24.9		10		6.2	
Median EFS, months	8.3	2	3	3	10.1	2.3
EFS, %	41% at 24 months	16% at 16 months	NR	NR	63% at 6 months	33% at 6 months
ORR, %	83	50	46.3	42.5	86	48
CR%	65	32	28	28	66	39
Median PFS, months	15	4	NR	NR	15	6
PFS rate	46% at 24 months	27% at 24 months	-	-	45% at 12 months	24% at 12 months
Median OS, months	Not reached	25.7	16.9	15.3	Not reached	16.4

Legend: BCL2/6, B-cell lymphoma protein 2 and/or 6; CAR-T, chimeric antigen receptor T-cell; CR, complete response; DLBCL-NOS, diffuse large B cell lymphoma, not otherwise specified; EFS, event-free survival; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; NHL, non-Hodgkin lymphoma; NR, not reported; ORR, overall response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; R-DHAP, rituximab, dexamethasone, cisplatin and cytarabine; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; R-GemOX, rituximab, gemcitabine, oxaliplatin; R-ICE, rituximab, ifosfamide, etoposide and carboplatin; T/H-RLBCL, T-cell/histiocyte-rich large B-cell lymphoma.

Table 4. Toxicity management.

Protocols different by institution and product
Rates vary among products, patient characteristics, and disease states Appropriate screening following institutional standards Baseline • *Complete blood count* • *Comprehensive metabolic panel* • *C-reactive protein;* • *Ferritin* • *Coagulopathy*
Cytokine-release syndrome (CRS) • Tocilizumab is the first-line treatment for severe CRS (grade ≥2) • Corticosteroids typically reserved for tocilizumab-refractory CRS • IL-6 antagonist may increase IL-6 levels and worsen neurotoxicity • Siltuximab binds directly to IL-6 with no risk of increase in IL-6 levels
Antiepileptic drugs for patients with high risk of immune effector cell – associated neurotoxicity syndrome Bacterial/fungal/viral prophylaxis/vaccination following institutional standards
Immune effector cell – associated neurotoxicity syndrome (ICANS) • Corticosteroids are consensus first-line treatment • Tocilizumab does not penetrate *cerebrospinal fluid and can* increase IL-6 levels • Anakinra is a promising agent because neutralizes the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β)

with DLBCL R/R (EMA-approved label population) or between 29% and 71% of medically-estimated eligible DLBCL R/R patients were not treated with a CAR-T therapy. Common challenges have been identified along the patient pathway that may result in limited access or delays to CAR-T cell therapy. These include timely identification and referral of eligible patients, approval of pre-treatment funding by authorities and payers, and resource requirements at CAR-T centers. Retrospective data showed better outcomes if patients received CAR-T cells earlier (i.e. after two lines of chemotherapy or after auto-SCT) rather than later (i.e. after at least three lines of chemotherapy or after receipt of additional treatment after auto-SCT).A retrospective analysis of CAR-T cells or allogeneic SCT for R/R DLBCL showed, at 12 months, a significantly lower NRM, whereas differences in RR, PFS, and OS were not statistically significant [27,28].

4. Salvage and bridging therapy

Salvage therapy (ST) requires a washout period before apheresis, and the goal is to stabilize the disease. ST is recommended during the time between referral, consult, and apheresis [29].

Bridging therapy (BT) aims to maintain functional reserve during manufacturing and stabilize disease and quality of life. Moreover, BT reduces tumor burden and symptoms and is recommended during the waiting time between apheresis and lymphodepletion for patients with rapidly proliferating disease. BT has a potential impact on limiting cytokine release syndrome (CRS)/immune effector cell–associated neurotoxicity syndrome (ICANS) severity and on CAR T-cell efficacy [30].

5. Adverse events with CAR T-cell therapy

Since their development and early applications in clinical trials, CAR-T therapy has been characterized by a higher incidence of CRS [31] and ICANS [32]. CRS is rarely fatal and is not associated with worsening outcomes after CAR-T infusion. However, it is associated with prolonged hospital stays and frequently is associated with the development of other complications [33]. In order to limit the duration and worsening of CRS, clinical practice employs agents that limit the cytokine cascade underlying CRS. Tocilizumab is a monoclonal antibody directed against the interleukin-6 (IL-6) receptor already used to treat conjunctivitis and CRS after haploidentical transplantation [34]. In real-world analysis with commercial CAR-Ts, at least one dose of tocilizumab is used in 20% to 80% of patients with CRS grade 1 [35]. Although toxicity appears significantly lower in real life due to the earlier mitigating strategy with anti-IL-6 and steroid use [36,37], multiple doses are often necessary because of the exponential production of IL-6 [38,39]. Recent clinical trials have investigated the role of other interleukin inhibitors, such as anakinra [40,41] and siltuximab [42], in preventing and treating both CRS and ICANS showing results in mitigating CRS grade 3 and 4 when used after treatment with tocilizumab, decreasing the need for subsequent doses of this drug or the need to use corticosteroids. Anakinra is an IL-1 inhibitor used especially in arthritic diseases. Anakinra shows an ability to act not only on CRS but also on ICANS induced by CAR-T therapy. Its effects are due to its ability to reduce IL-1 levels and penetrate the blood-brain barrier to act on neurotoxicity [43], reducing the mortality associated with CRS and ICANS [44,45]. The use of siltuximab after a patient shows resistance to tocilizumab is considered an excellent therapeutic alternative to steroids due to siltuximab's strong ability to reduce the levels of IL-6 and sIL-6 R [46]. Table 4 summarizes the ongoing approach of CRS and ICANS.

Other AEs, such as cytopenias [47], infections [48], tumor lysis syndrome [49], and acute anaphylaxis, are also challenging [31]. Cellular therapy is reaching earlier lines of the treatment paradigm, and these challenges have become even more relevant.

6. Strategies to enhance T-cell expansion and persistence and efficacy post-CAR T-cell therapy

A few studies examine options for improving T-cell expansion and CAR-T cell therapy persistence. One study (NCT04484012) [50] explores BTK inhibitor use during the collection process and post-CAR T-cell therapy after engraftment. There is upregulation of PD-1 on CAR T-cells and in the tumor microenvironment, so we were all hopeful that incorporating this strategy post-CAR T-cell therapy or even around the time of infusion would prove beneficial [51]. T cell subsets have diverse features in terms of proliferation ability and antitumor effect that substantially contribute to the clinical efficacy of CAR-T cells [52]. CD19 CAR-T cells derived from T stem cell memory and T central memory [53,54] have better persistence and antitumor activity in vivo than T effectory memory and T terminal effector T cells [55,56].

7. Expert opinion

Anti-CD19 CAR T-cell therapy leads to high rates of durable remissions in patients with DLBCL. Current guidelines indicate that CAR-T is the standard of care in patients with refractory disease, early relapse after first-line chemotherapy, and third-line. At the same time, auto-SCT remains an option for late-relapse DLBCL [57]. The peremptoriness of the guidelines can be questioned, mainly because of the absence of comparative clinical trials [58]. Moreover, some authors argue that ASCT may be preferable to CAR- T cells for a subset of patients with relapsed diffuse DLBCL who continue to demonstrate chemosensitivity after salvage chemotherapy [59]. Furthermore, once CAR T cells are approved as second-line treatment in DLBCL, a randomized trial including only chemosensitive patients with DLBCL is unlikely to be conducted, leaving a void to guide practice in this subset of patients [60]. The role of allogeneic transplantation (ALLO-SCT) in this setting also needs to be clarified. ALLO-SCT can cure hematological malignancies, but toxicity represents a weakness. CAR-T therapy appears to have more manageable long-term toxicity, although follow-up is not yet adequate. Regarding relapse rates, CAR-T is less effective toward lymphoma, with a progression rate of around 60%. On the other side, TRM with allo-SCT is approximately 30%, and with CAR-T is less than 5% [61].

Frontline CAR-T cell therapy should be explored in patients with aggressive double-hit lymphoma characterized by MYC and BCL2 or BCL6 gene alteration [62]. Risk stratification remains crucial to identifying patients with DLBCL at the highest risk of relapse who would benefit from CAR T-cell therapy earlier in their disease. With the growing availability of choices, a shared decision-making approach between patients and CAR T-cell providers is essential to integrating CAR T-cell in the therapeutic armamentarium.

Real-life data have confirmed the results of pivotal trials regarding clinical outcomes. A topic of discussion is whether we can assert if one construct is more effective than another. Data on the use of liso-cel in clinical practice still needs to be made available. Many studies have indirectly compared axi-cel and tisa-cel. The results show that axi-cel is superior to tisa-cel for disease control but is associated with significantly more toxicity.

Another question is whether accessibility to treatment is adequate. Nevertheless, the number of centers licensed to deliver CAR-T therapy in Europe is adequate, the CAR-T use in relapsed/refractory DLBCL patients seems limited, with 29% and 71% of eligible patients not receiving treatment in 2020 in the four largest European countries. Currently, the general recommendation of the EBMT and JACIE is that CAR-T be provided as best as possible within an accredited transplantation program, both allo-SCT and auto-SCT, with shared care policies and service level agreements service incorporated into the program's quality systems. JACIE also provides a robust method for ensuring that the programs meet quality and other requirements for mandatory submission of long-term safety and efficacy data to the EBMT registry. The problem of accessibility to CAR-T treatment could be related to a nonfunctioning link between the CAR-T-delivering and referral centers. There are several reasons to refer early. First of all, it gets patients in the system even if not yet eligible, particularly if they have high-risk/aggressive disease; second streamlines getting regulatory authority approval and making an apheresis appointment; third, it helps reserve a manufacturing slot for a patient's CAR-Tcells; finally, can reduce the need for bridging therapy to control the disease. We recommend directly calling intake personnel or physician colleague at the treating center. The treating center will decide whether a patient should receive CAR-T cell therapy. Frequent communication with the patient, primary oncologist, and manufacturer is mandatory. The route must ensure a workup is completed, monitor the patient's status, choose the least toxic therapy, if possible, and allow hematologic recovery before lymphodepletion, considering that real-life time from apheresis to infusion is >30 days. Early referrals will ensure that both efficacy and safety are optimized, as outcomes are associated with patient fitness, T-cell fitness, and disease burden.

The risk of potentially life-threatening complications is another critical point. Earlier and more aggressive CRS and ICANS mitigation strategies have decreased in real-life high-grade toxicities, allowing treatment of a broader patient population. In some patients, standard treatment with tocilizumab and corticosteroids fails to reverse CRS or ICANS symptoms. As such, there is an urgent need better to characterize the second-line management of CRS and ICANS. Other inhibitors, such as anakinra and siltuximab, could be helpful alone or in combination with tocilizumab for treating severe CRS and ICANS. In addition, the new specific inhibitors could effectively mitigate CRS without affecting CAR-T therapy's cytotoxic efficacy.

In some countries, regulatory authorities have ensured patient safety by mandating high experience levels in the center delivering CAR-T [63]. In addition, it is crucial to remember how such a complex therapy in terms of patient selection, management of the preparatory phase to reinfusion, management of complications, and long-term follow-

up, as well as the organizational component, requires the work of a multidisciplinary team. We suggest the creation of a working group consisting not only of physicians such as the hematologist specializing in the treatment of lympho-proliferative syndrome and the expert of transplantation but also transfusion physicians who coordinate the apheresis phase, neurologists, resuscitators, and infectivologists who manage the treatment of severe complications and infectious risk. It must be emphasized that the medical figure must be supported by the nursing one [64], both in coordinating the different phases of the CAR-T and in the management and care of the patient before, during, and after cell infusion. Medical work must also be integrated with that of biologists, pharmacists, and data coordinators who manage the more practical and regulatory aspects of such treatment. Real-life experience showed the risk of developing new complications beyond the immediate weeks following cell infusion, such as hematological disorders, neurologic, autoimmune manifestations, or second malignancies [65]. Relationships between referring and referral centers and oncologists are vital in the short and long term.

Deficiency of specific tumor antigens is one of the challenges to avoid damaging healthy tissues [66]. In the absence of specific antigens, 'associated tumor antigens' can be used. Selectivity can be improved by using different antigens as targets, for example through the creation of bispecific CAR-Ts directed against a dual target on the tumor cell surface. This mechanism makes it possible to reduce the risk of developing resistance to therapy [67]. In addition to the search for new specific antigens, research is directed toward implementing strategies to evade the processes of tumor immunosuppression, upon which some mechanisms of resistance to CAR-T therapies are based.

The CAR-T success was explosive but not without dark sides, linked above all to the safety and extreme personalization of the therapy. On average, all these steps take up a fortnight and have some weaknesses: the distance between the hospitals where patients are admitted and the engineering sites, the criticality of the production process, and the conditions of patients who, in some cases, cannot tolerate the impact of these therapies. Finally, since it is a therapy for the individual patient, the 'cost' factor takes over that makes CAR-T, and more generally advanced therapies, difficult to frame in the logic of national health systems. The need to take the patient's cells, send them to the production workshops where they can be engineered, and, in the end, send them back for infusion requires weeks and a widespread organizational strategy. Manufacturing modes are crucial in implementing their use and overcoming cost and availability issues. The competitors to CAR-Ts are bi-specific antibodies. These are therapies to be administered until progression, so in a hypothetical cost analysis, it is a parameter to be considered, as well as, the quality of life of the patient, who might prefer one-shot therapy, as opposed to continuous therapy.

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