Chimeric antigen receptor T cell therapy for cancer: clinical applications and practical considerations

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Abstract

Chimeric antigen receptor T cells have revolutionized the treatment of hematological malignancies during the past five years, boasting impressive response rates and durable remissions for patients who previously had no viable options. In this review, we provide a brief historical overview of their development. We focus on the practical aspects of a patient’s journey through this treatment and the unique toxicities and current best practices to manage those. We then discuss the key registration trials that have led to approvals for the treatment of relapsed/refractory acute lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma, mantle cell lymphoma (MCL), and multiple myeloma. Finally, we consider the future development and research directions of this cutting edge therapy.

Introduction

The immune system has been recognized to play an important role in controlling carcinogenesis since the 1950s, when mouse models exemplified a genetic basis for self-recognition and rejection of non-self. Several years later, application of that concept in allogeneic stem transplantation demonstrated a more feasible approach to using the immune system to treat hematological malignancies. Patients who displayed signs and symptoms of graft-versus-host disease had lower risk of relapse of leukemia, providing tangible proof of the role of the immune system in anti-cancer therapy. This concept was further developed by the infusion of donor lymphocytes to recipients, successfully eradicating leukemia. Adoptive transfer of lymphocytes was also trialed in patients with metastatic melanoma, where tumor-infiltrating lymphocytes were extracted, cultured, and infused back into the patient, resulting in tumor regression.

The advent and refinement of gene modification and manipulation using retroviruses, among other techniques, allowed for precise modification of the T cell receptor (TCR) to identify and engage a cognate receptor. This helped further refine adoptive transfer of anti-tumor immunity to increase specificity and applicability to other tumor types. The co-stimulatory signal domain necessary for the improved function and persistence of T cells was eventually combined with the antigen binding, single-chain, variable, intracellular domain (CD3ζ) to produce one receptor capable of antigen recognition and T cell activation without being HLA-restricted (fig 1). The result was a chimeric antigen receptor (CAR).

A key component of the success of chimeric antigen receptor T cells (CAR-Ts) is the availability of a target which is uniformly expressed on tumor cells, but not on normal tissue. Finding such an antigen is challenging as most antigens expressed by tumors are either transient or are autoantigens. Leukemias and lymphomas of B cell origin uniformly express B cell antigens, namely CD19, CD20, and CD22. CD19 is expressed earlier on in the B cell maturation pathway and was therefore selected as a potential target. It is found on normal B cells and B cell aplasia was an expected off-target effect. However, this phenomenon is also frequently encountered with other therapies in B cell malignancies and immunoglobulin replacement can overcome any deleterious effects. One postulated benefit of B cell aplasia was that it would pre-emptively thwart the development of anti-chimeric CAR antibodies. After proof of concept was shown in a mouse model, individual patient cases were reported. Patients with chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and B cell non-Hodgkin’s lymphoma (NHL) were treated with encouraging results. Larger clinical trials subsequently ensued and will be the focus of this review. We will also cover the practical aspects of managing patients receiving CAR-T therapy.

Incidence and prevalence

CAR-T therapy is approved by the Food and Drug Administration (FDA) to treat five diseases and is being investigated in clinical trials for many others; indeed, there are currently >1000 CAR trials listed on clinicaltrials.gov. ALL is the most common childhood cancer and accounts for approximately one quarter of all childhood malignancies. Almost 3000 new cases of ALL are diagnosed in children every year in the US, with an incidence of approximately 3.4 cases per 100,000. ALL is rarer in adults, with an incidence of approximately 1–5/100,000 individuals; however, it remains the second most common acute leukemia in this age group. The Surveillance,
Epidemiology, and End Results (SEER) database recorded an incidence of 1.8/100 000 for the year 2018.21 NHL is more common, with an incidence of 88/100 000 for adults aged >65 and 20/100 000 when all ages are taken into account.21 Diffuse large B cell lymphoma (DLBCL), follicular lymphoma, and mantle cell lymphoma (MCL) are the three most common subtypes of B cell NHL. Multiple myeloma is considered rare as it constitutes only approximately 1-2% of malignancies diagnosed annually. The SEER database reported an incidence of 7.3/100 000 for all ages in 2018 although, given the extended survival of multiple myeloma, approximately 150 000 individuals are living with this cancer.21

Since the first approval in 2017, the number of patients treated with CAR-Ts has steadily increased and more than 4000 patients had been treated by 2020.22 The number of centers accredited by the Foundation for the Accreditation of Cellular Therapy (FACT) to administer CAR-Ts has also increased. FACT has established standards to ensure the safe administration of immune effector cells and reporting/monitoring of patient outcomes.23 As indications for this treatment are increasing and experience in administering and managing potential side effects is becoming more standardized, access to CAR-Ts is improving and referrals are increasing. The Center for International Blood and Marrow Research also hosts a central database to record and report outcomes and provides regular updates during their annual conferences.

Sources and selection criteria
We performed a search using PubMed and Medline databases, using the terms “CAR-T”, “CAR”, and “Chimeric Antigen Receptor” of all studies published from January 2000 through April 2022, and identified >3000 publications. We excluded studies that were not published in English and excluded reviews, editorials, and other articles of a non-interventional nature. We also excluded irrelevant studies that contained similar sounding MeSH terms. We then prioritized interventional studies that reported on CAR-T therapy in a clinical setting, focusing on phase 2 or later studies with sample sizes larger than 50 patients. Studies that focused on molecular structure and function in vitro were excluded, except when they were cited by a clinical study that incorporated the results of the experiments. For the toxicities section, we selected the largest case series regarding each of the known complications and examined the references from the long term, follow-up studies to capture all that is reported in the literature.

Practical considerations
The advent of CAR-T therapy has revolutionized the treatment of hematological malignancies and six FDA approved products are now available (table 1, fig 2). However, the treatment remains limited to larger centers that have the expertise and infrastructure required to successfully administer these products. The first step is referral to such a center where a physician specialized in CAR-T delivery obtains a history and physical examination, and reviews the records and pathology specimens. If the patient is deemed eligible and consents to the process, they undergo testing to objectively evaluate their organ function.

The next step is to obtain the autologous T cells, which are manufactured through apheresis. Patients typically must be chemotherapy and radiation free for approximately 14 days to ensure optimal health and an adequate number of lymphocytes. Several reports have been published regarding mechanisms of failure of these therapies and baseline characteristics of the apheresed product, number of previous therapies, and how the overall health of the lymphocytes measured by doubling time is correlated with outcomes.24-26 Early referral, and appropriate timing and sequencing of therapies are therefore critical to the success of this process.

After the lymphocytes are collected, they are sent to designated laboratories tasked with manufacturing, quality checking, and returning the product to the treating center. This requires a dedicated team of expert immunologists and geneticists who co-culture the product with pro-proliferative cytokines, select T cells for transfection with a lentivirus or a retrovirus, and finally check the product for sterility, number, and function of the CAR-Ts. This entire process takes three to four weeks, during which the patient might receive bridging therapy to keep the disease stable (fig 3).

Once confirmation of successful manufacturing is received, the patient undergoes another assessment to ensure no complications have arisen from either the disease or any bridging chemotherapy during that time. They are then scheduled to receive lymphodepleting chemotherapy, typically a combination of fludarabine and cyclophosphamide...
Table 1 | Summary of registration trials for FDA approved commercial CAR-T products

<table>
<thead>
<tr>
<th>Trial</th>
<th>ELIANA</th>
<th>ZUMA-3</th>
<th>ZUMA-1</th>
<th>JULIET</th>
<th>TRANSCEND</th>
<th>ZUMA-2</th>
<th>ZUMA-5</th>
<th>KarMMa</th>
<th>CARTITUDE-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Construct</td>
<td>19-41Bz</td>
<td>19-2Bz</td>
<td>19-2Bz</td>
<td>19-41Bz</td>
<td>19-41Bz</td>
<td>19-2Bz</td>
<td>19-2Bz</td>
<td>19-41Bz</td>
<td>19-41Bz</td>
</tr>
<tr>
<td>Approved indication</td>
<td>B-ALL (refractory or 2nd/3rd relapse) in pts &gt;5 years</td>
<td>R/R B-ALL in adults (18 years old)</td>
<td>R/R LBCL after &gt;2 lines of systemic tx in adults</td>
<td>R/R LBCL after &gt;2 lines of systemic tx in adults</td>
<td>R/R LBCL after &gt;2 lines of systemic tx in adults</td>
<td>R/R LBCL after &gt;2 lines of systemic tx in adults</td>
<td>R/R FL after &gt;2 lines of systemic tx in adults</td>
<td>R/R multiple myeloma after &gt;4 lines of tx in adults</td>
<td>R/R multiple myeloma after &gt;4 lines of tx in adults</td>
</tr>
<tr>
<td>Study type</td>
<td>Phase 2</td>
<td>Phase 2</td>
<td>Phase 1/2</td>
<td>Phase 1</td>
<td>Phase 1</td>
<td>Phase 2</td>
<td>Phase 2</td>
<td>Phase 2</td>
<td>Phase 1b/2</td>
</tr>
<tr>
<td>Number of patients (enrolled/infused)</td>
<td>92/75</td>
<td>71/55</td>
<td>111/101</td>
<td>165/111</td>
<td>342/268</td>
<td>74/68</td>
<td>146</td>
<td>140/128</td>
<td>97/113</td>
</tr>
<tr>
<td>Median age, y</td>
<td>11 (range 3–23)</td>
<td>40 (IQR 28–52)</td>
<td>58 (range 23–76)</td>
<td>56 (range 22–76)</td>
<td>63 (IQR 54–70)</td>
<td>65 (range 38–79)</td>
<td>61 (range 34–79)</td>
<td>61 (range 33–78)</td>
<td>61 (IQR 56–68)</td>
</tr>
<tr>
<td>Prior auto-HCT</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Prior allo-HCT</td>
<td>61%</td>
<td>42%</td>
<td>-</td>
<td>-</td>
<td>3%</td>
<td>-</td>
<td>3%</td>
<td>94%</td>
<td>90%</td>
</tr>
<tr>
<td>Lines of prior tx, median</td>
<td>3 (range 1–8)</td>
<td>2 (IQR 2–3)</td>
<td>3 (range 1–6)</td>
<td>3 (IQR 2–4)</td>
<td>3 (range 1–5)</td>
<td>3 (range 1–10)</td>
<td>6 (range 3–16)</td>
<td>6 (IQR 4–8)</td>
<td>6 (IQR 4–8)</td>
</tr>
<tr>
<td>Median time to infusion, d</td>
<td>45 (from enrolment)</td>
<td>13 (US), 14.5 (EU) (from apheresis)</td>
<td>17 (from apheresis)</td>
<td>54 (from apheresis)</td>
<td>37 (from apheresis)</td>
<td>16 (from apheresis)</td>
<td>NR</td>
<td>NR</td>
<td>29 (apheresis)</td>
</tr>
<tr>
<td>Bridging allowed?</td>
<td>Yes (87%)</td>
<td>Yes (93%)</td>
<td>No</td>
<td>Yes (92%)</td>
<td>Yes (59%)</td>
<td>Yes (37%)</td>
<td>NR</td>
<td>Yes (88%)</td>
<td>Yes (75%)</td>
</tr>
<tr>
<td>Lymphodepleting regimen</td>
<td>Flu-Cy or AraC-Etop</td>
<td>Flu-Cy</td>
<td>Flu-Cy</td>
<td>Flu-Cy or Benda</td>
<td>Flu-Cy</td>
<td>Flu-Cy</td>
<td>Flu-Cy</td>
<td>Flu-Cy</td>
<td>Flu-Cy</td>
</tr>
<tr>
<td>Response rate in infused (ORR/CR)</td>
<td>81%/60%</td>
<td>71%/56%</td>
<td>82%/54%</td>
<td>52%/40%</td>
<td>73%/53%</td>
<td>93%/67%</td>
<td>92%/76% (94%/80% for FL)</td>
<td>73%/33%</td>
<td>97%/67%</td>
</tr>
<tr>
<td>ORR by ITT</td>
<td>66%</td>
<td>55%</td>
<td>75%</td>
<td>34%</td>
<td>61%</td>
<td>85%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PFS (1 year/yr)</td>
<td>50% (EFS)/-</td>
<td>58% (RF5)/-</td>
<td>44%/38%</td>
<td>35%/33%</td>
<td>44%/34%</td>
<td>61%/34%</td>
<td>74%/59%</td>
<td>77%/-</td>
<td>77%/-</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>11.6 (2.7–15.5)</td>
<td>5.8 (3.3–NE)</td>
<td>NR</td>
<td>6.8 (3.1–14.1)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NE (16.8–NE)</td>
</tr>
<tr>
<td>OS (1 year/yr)</td>
<td>76%/66%</td>
<td>71%/18.2</td>
<td>59%/51%</td>
<td>49%/40%</td>
<td>58%/21.1</td>
<td>13.3–NR</td>
<td>83%/93%</td>
<td>78%/19.4</td>
<td>89%/18.2–NE</td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>76% (NE)</td>
<td>18.2 (15.9–NE)</td>
<td>NR</td>
<td>12 (7–NR)</td>
<td>21.1 (13.3–NR)</td>
<td>83% (NE)</td>
<td>93% (NE)</td>
<td>78% (NE)</td>
<td>93% (NE)</td>
</tr>
<tr>
<td>CRS (all grades/HG3) (grades system)</td>
<td>77%/46% (Penn)</td>
<td>89%/24% (Lee)</td>
<td>94%/13% (Lee)</td>
<td>58%/22% (Penn)</td>
<td>42%/22% (Lee)</td>
<td>91%/15% (Lee)</td>
<td>-7% (Lee)</td>
<td>84%/5% (Lee)</td>
<td>95%/4% (Lee)</td>
</tr>
<tr>
<td>ICANS/ neurotoxicity (all grades HG3)</td>
<td>40%/13%</td>
<td>60%/15%</td>
<td>64%/28%</td>
<td>21%/12%</td>
<td>30%/10%</td>
<td>63%/31%</td>
<td>-19%</td>
<td>18%/3%</td>
<td>21%/9%</td>
</tr>
</tbody>
</table>

AraC=cytarabine, Benda=bendamustine; B-ALL=B cell acute lymphoblastic leukemia; CI=confidence interval; CR=complete response; Cy=cyclophosphamide; FL=follicular lymphoma; Flu=fludarabine; Etop=etoposide; HCT=hematopoietic stem cell transplantation; ICANS=immune effector cell associated neurotoxicity syndrome; IQR=interquartile range; ITT=intention-to-treat; LBCL=large B cell lymphoma; MCL=mantle cell lymphoma; MM=multiple myeloma; MZL=marginal zone lymphoma; NE=not estimable; NR=not reported; ORR=overall response rate; OS=overall survival; pts=patients; R/R=relapsed/refractory; tx=treatment.

Over three days. This is a critical step to eliminate cytokine sinks and other homeostatic signals that allow adequate expansion of the cells. This is typically carried out in the outpatient setting. The cells are then infused after a two day rest period. Institutions have different criteria for whether the patient is hospitalized for this part of the treatment. It is also highly dependent on the actual pharmacokinetics of the cells given and reimbursement guidelines. Following infusion of the cells, the patient needs to be closely monitored for treatment related adverse events. During this time, their medical needs are typically addressed by the cellular therapy team. It is very important to minimize the use of corticosteroids unless necessary.

**Toxicities**

CAR-T treatment has toxicities like all novel immunonological treatments. The difference between CAR-Ts and other immunological treatments is that the main toxicities of CAR-Ts are intended on-target effects and are thus reversible when the CAR-Ts are removed, either pharmacologically or by the recipient’s immune system. They are also different to traditional chemotherapy toxicities in that there are no dose adjustments for certain high risk features such as frailty or poor organ function. For most patients, it is a single infusion followed by close monitoring and management. The bulk of the knowledge regarding how to evaluate, treat, and prevent these toxicities is based on CD19 CAR-Ts, which are widely used.

**Cytokine release syndrome (CRS)**

When CAR-Ts encounter their cognate antigen the signal is transmitted downstream leading to activation of a cascade, resulting in release of inflammatory cytokines, proliferation of the CAR-Ts, and recruitment of other cells including monocytes and macrophages. This systemic inflammatory response can cause endothelial damage and vascular leakage in multiple organs and tissues,
resulting in CRS. The clinical syndrome generally begins with high fevers and can progress to systemic inflammation with capillary leak, hypotension, hypoxia, and organ failure. It is characterized by high levels of interferon-γ, tumor necrosis factor-α, interleukin-1, and interleukin-6 (IL-6).27,28 The incidence, timing, and severity of CRS depends on the CAR-T product, as different CAR constructs have different expansion and proliferation kinetics; however, CRS of any grade uniformly occurs in more than 50% of patients with all products. Earlier pivotal trials used different severity grading systems and made treatment recommendations based on grade, which makes counseling, cross-product comparisons, and management more difficult. Moreover, staff at centers designated to administer CAR-Ts need to undergo risk evaluation and mitigation training. Standardization of all toxicity assessment scores and treatment guidelines would make these processes easier. More recently, in an effort to harmonize reporting and treatment guidelines, the American Society for Transplantation and Cellular Therapy (ASTCT) released a consensus grading system (tables 2, 3).29

The standard management consists of IL-6 antagonists with or without corticosteroids when the severity warrants interrupting the cascade, in addition to supportive care with fluids, antipyretics, or vasopressors if needed. Other more investigational agents that have shown promise for the treatment of CRS include the tyrosine kinase inhibitor dasatinib and IL-1 receptor antagonist anakinra.30-32 The care team needs to always keep a broad differential in mind as these patients are often severely immunocompromised, and it might be difficult to differentiate a fever of an infectious source from fevers related to CAR-T therapy. Procalcitonin can be a useful tool in these situations (especially for bacterial infections) as it appears to lag behind in the case of CRS, but more validation is needed.33 Rarely, an exaggerated form of CRS can lead to clinical manifestations of hemophagocytic lymphohistiocytosis syndrome.34,35 This requires prompt diagnosis and management, including treatment with immunosuppressants and anti-inflammatory medications similar to CRS.

Immune effector cell associated neurotoxicity syndrome (ICANS)
Neurotoxicity and encephalopathy can also occur with CAR-T therapy. While CRS has been extensively studied and a clear description of implicated cytokines and established treatments exist, the exact pathophysiology of ICANS is less clear. The current working hypothesis is that endothelial injury caused by the inflammatory milieu of the tumor,
lymphodepleting chemotherapy, and high-grade CRS leads to a breakdown in the blood-brain barrier, allowing influx of pro-inflammatory cytokines into the cerebrospinal fluid. This subsequently leads to activation of resident pericytes and microglial cells, leading to the observed clinical syndrome of encephalopathy. Similar to CRS, it can vary in severity from a simple headache, tremor, or word-finding difficulties, at its mildest, to confusion, aphasia, seizures, brain edema, and death in the most severe forms. ICANS is mostly reversible; however, recent clinical observations point to a small subset of patients who might experience subtle, prolonged, neurological manifestations including cognitive dysfunction. Treatment is predominantly with corticosteroids in addition to supportive care (antiepileptics and intensive care unit (ICU) level care/intubation if needed).

**Infectious complications**

Patients undergoing treatment with CAR-Ts have varying and complex risk factors that can weaken their humoral and cellular immune responses. In a real world study reporting on 60 consecutive patients...
receiving axicabtagene ciloleucel (axi-cel), an approved CD19 CAR-T therapy, 101 infectious events were reported in 63.3% of patients. The infections varied in severity and one was fatal. The most common type was bacterial, but fungal and viral infections were also prevalent. In multivariate analysis, poor performance status and prior infections within 30 days were risk factors for severe bacterial infections, whereas use of corticosteroids to mitigate CAR-T toxicities was associated with overall infection risk.40

In this cohort no standardized infection prophylaxis regimen was instated until approximately half of the patients had already been treated.

In another single center study looking at a similar population of 41 patients also receiving axi-cel, the estimated cumulative incidence of any infection by 12 months was 89.7% (confidence interval (CI) 83.9% to 93.4%). Again, in multivariate analysis, the use of corticosteroids was associated with severe infections. Patients in this cohort were also receiving institutional infectious prophylaxis, which was three months in duration, post treatment. Several patients developed Pneumocystis jirovecii pneumonia and varicella zoster infections once prophylaxis was terminated at the scheduled three month time point. Prolonged cytopenias and delayed immune reconstitution were also reported in patients with available data. Evidence of immune dysfunction as reported by neutropenia with an absolute neutrophil count <1000/µL, B cell aplasia, and low immunoglobulin levels <400 mg/dL, and CD4+ counts <200/µL persisted in a notable portion of patients up to 18 months post treatment. The authors provided guidelines for prolonged infectious prophylaxis for opportunistic infections up to 18 months based on immune reconstitution monitoring.41

Table 2 | American Society for Transplantation and Cellular Therapy consensus grading for cytokine release syndrome

<table>
<thead>
<tr>
<th>CRS parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever*</td>
<td>Temperature ≥38 °C</td>
<td>Temperature ≥38 °C</td>
<td>Temperature ≥38 °C</td>
<td>Temperature ≥38 °C</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>None</td>
<td>Requiring low-flow nasal cannula or blow-by</td>
<td>Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask</td>
<td>Requiring positive pressure (eg. CPAP, BiPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

Organic toxicities associated with cytokine release syndrome (CRS) may be graded according to Common Terminology Criteria for Adverse Events v5.0, but they do not influence CRS grading.

*Fever is defined as temperature ≥38 °C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. 1CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5 °C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

Low-flow nasal cannula is defined as oxygen delivered at 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at ≥16 L/minute.

CPAP=continuous positive airway pressure, BiPAP=bilevel positive airway pressure

Table 3 | American Society for Transplantation and Cellular Therapy consensus grading for immune effector cell associated neurotoxicity syndrome

<table>
<thead>
<tr>
<th>Neurotoxicity domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed level of consciousness*</td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens only to tactile stimulus</td>
<td>Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma</td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td>Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention</td>
<td>Life-threatening prolonged seizure (&gt;5 min); or repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td>Motor findings§</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Deep focal motor weakness such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Elevated ICP/ cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/local edema on neuroimaging†</td>
<td>Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad</td>
</tr>
</tbody>
</table>

Immune effector cell associated neurotoxicity syndrome (ICANS) grade is determined by the most severe event [ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema] not attributable to any other cause, for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

*Patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Intracranial hemorrhage or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

§Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

†Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

EEG=electroencephalogram; IEE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; N/A=not applicable
insults was to be expected. However, some of these cytopenias were biphasic, signaling that the bone marrow’s regenerative ability was intact and that other confounding factors might have been at play. Moreover, patients were referred earlier in their course, and clinical trials using CAR-T therapy for first and second line therapies also reported prolonged cytopenias, suggesting that this might be specific to CAR-T therapy. At present, reports are limited, retrospective, and variable in their definitions of severity and time of onset of prolonged cytopenias.

No evidence based guidelines for management and prevention exist, but the consensus between these retrospective reports and expert opinion is that risk factors include higher grade and prolonged CRS. A risk stratification tool for predicting hematological toxicity after CAR-T (CAR-HEMATOTOX) has also recently been developed, which incorporates baseline blood counts and inflammatory markers as risk factors. Management generally focuses on ruling out myelodysplastic syndrome and supportive care with growth factors and transfusions. These cytopenias are largely reversible, although, very rarely, more aggressive intervention is needed to rescue patients from persistent cytopenias. Presence of cytopenias might also have prognostic significance, as one retrospective study found that longer duration of cytopenias following CAR-T infusion was associated with improved progression free survival (PFS).

**Clinical experience**

The CAR-T field has grown in recent years, and there are now six FDA approved commercial CAR-T products with eight indications (tables 2, 3fig 2). The antigen target varies by disease type, but in general, CD19 has been the main target of interest in ALL and non-Hodgkin’s B cell lymphoma, and B cell maturation antigen (BCMA) has been the main target of interest in multiple myeloma. Other targets that are currently being explored include CD22, CD30, CD33, CD70, and CD123 for various hematologic malignancies, and B7H3 and EGFR for solid tumors. Here, we review the clinical experience of all the FDA approved CAR-T products, as well as some products in development.

**Acute lymphoblastic leukemia**

ALL is the most common malignancy in childhood and the second most common acute leukemia in adults. Prognosis varies by disease characteristics, but relapsed and refractory disease invariably carries a poor prognosis. Tisagenlecleucel (tisa-cel) was the first CAR-T therapy to be approved in August 2017 by the FDA for patients up to 25 years with B cell acute lymphoblastic leukemia (B-ALL) that is refractory or in second or later relapse. Approval was based on the ELIANA trial, a phase 2 multicenter, single-cohort study of tisa-cel in pediatric/young adult patients with CD19+ relapsed and/or refractory (R/R) B-ALL. In the updated analysis of 75 patients who received tisa-cel infusion, the overall remission rate—complete remission or complete remission with incomplete hematologic recovery (CRi)—within three months was 81%. All patients who achieved a response were negative for minimal residual disease (MRD) by flow cytometry, and median duration of response was also not reached at a median follow-up of 13.1 months. CRS and neurotoxicity of any grade occurred in 77% and 40% of patients, respectively, with 47% of patients requiring ICU management. The median persistence of tisa-cel in the blood was 168 days, with persistence up to 20 months in some patients; this is thought to be mediated by the 4-1BB costimulatory domain.

Until very recently, commercial CAR-T therapy for ALL was only available for the pediatric/young adult population. However, in October 2021, brexucabtagene autoleucel (brexu-cel) received FDA approval for adult patients (≥18 years) with R/R B-ALL based on the ZUMA-3 trial. Brexu-cel had previously been approved for R/R MCL and consists of a CD19 antigen binding domain with a CD28 costimulatory domain. It is like axi-cel, but includes an extra step during manufacturing that removes circulating CD19-expressing malignant cells to prevent possible activation and exhaustion of the CAR-Ts during the ex vivo manufacturing process. ZUMA-3 was a phase 2, multicenter, single-arm study evaluating brexu-cel in adult patients with R/R B-ALL, 44% of whom had prior allogeneic stem cell transplant (SCT). Here, 55/71 enrolled patients received infusion with an overall complete remission/CRi rate of 71%; 97% of responders achieved MRD negativity. The median duration of remission in ZUMA-3 was 12.8 months. This compares favorably with historical data such as 4.6 months in the INO-VATE trial (inotuzumab ozogamicin) and 7.3 months in the TOWER study (blinatumomab). Grade 3 or higher CRS and neurotoxicity occurred in 24% and 25% of patients, respectively. Most patients no longer had detectable CAR-Ts by polymerase chain reaction assay at six months.

Despite these advances, approximately 30-50% of B-ALL will eventually relapse after CD-19 CAR-T therapy. Thus, some advocate for consolidative allogeneic SCT for patients who achieve an MRD-negative remission after CAR-T therapy, especially after the shorter duration CD28-based CAR-T therapy. At the discretion of their treating physician, 9% of patients in ELIANA and 18% of patients in ZUMA-3 went on to receive allogeneic SCT following CAR-T therapy. Other promising strategies include the development of CD22-directed CAR-Ts after the failure of CD19-directed or sequential CD19/CD22 CAR-T therapy. Close monitoring of MRD status by traditional multicolor flow cytometry or even higher sensitivity next generation sequencing (10^-6 level) can help predict relapse risk and allow for earlier intervention.

**Non-Hodgkin’s lymphoma**

Large B cell lymphoma (LBCL)

DLBCL is the most common subtype of NHL, comprising approximately 25% of all cases, and
30–40% of patients are refractory to or relapse after frontline chemoimmunotherapy. For those who remain refractory to salvage chemotherapy or relapse after autologous SCT, CD19-directed CAR-T therapy has revolutionized the treatment landscape. Before the advent of CAR-T therapy, patients with R/R DLBCL had limited options and continued to receive chemotherapy, preceding the eventual demise of the vast majority. Three FDA approved CD19 CAR-T therapies are available for adult patients with R/R LBCL after two or more lines of systemic therapy: axi-cel, approved in 2017 based on the ZUMA-1 trial; tisacel, approved in 2018 based on the JULIET trial; and lisocabtagene maraleucel (liso-cel), approved in 2021, based on the TRANSCEND trial. All are approved for DLBCL not otherwise specified, high grade B cell lymphoma (HGBL), and DLBCL arising from follicular lymphoma; axi-cel and liso-cel are additionally approved for primary mediastinal B cell lymphoma (PMBCL). Key differences in these products include choice of costimulatory domain, which impacts CAR-T expansion kinetics and subsequent rates of CRS/ICANS, and manufacturing time/time to infusion (table 2, 3). CD28-costimulated CAR-Ts demonstrate earlier and more rapid expansion (leading to more CRS/ICANS), while 4-1BB-costimulated CAR-Ts show longer persistence. Axi-cel utilizes a CD28 costimulatory domain while tisa-cel and liso-cel have 4-1BB costimulatory domains; liso-cel is also manufactured such that it has a constant 1:1 ratio of CD8:CD4 CAR-Ts, which improved expansion and activity in animal models.

Initial overall response rates (ORR) and complete remission rates in the three pivotal trials ranged from 52% to 82% and 40% to 54%, respectively. Notably, responses were consistent among high risk subgroups including those with HGBL with myc and bcl2 and/or bcl6 rearrangements (double/triple hit lymphomas), or those with primary refractory disease. Although cross-trial comparisons are difficult owing to the different grading criteria used, axi-cel had the highest rate of grade ≥3 neurotoxicity (28%) and tisa-cel had the highest rate of grade ≥3 CRS (22%). Several real world CAR-T studies of axi-cel and tisa-cel since then have shown similarly impressive efficacy and safety, including in patients who were older and had more comorbidities than those in the initial trials. With longer follow-up, the 1 and 2 year PFS rates for these products have plateaued at 35-44%, suggesting that a single infusion of CD19 CAR-Ts can result in durable responses for approximately 40% of patients. However, consolidative allogeneic SCT is currently not recommended for patients who respond because of the high risk of transplant related mortality and older age/increased comorbidities of patients with LBCL compared with patients with B-ALL.

More recently, these three CD19 CAR-T products were also studied in the earlier, second-line setting against standard-of-care salvage chemotherapy followed by autologous SCT–axi-cel in ZUMA-7, tisa-cel in BELINDA, and liso-cel in TRANSFORM. All three trials were multicenter phase 3 trials specifically evaluating “high risk” patients with LBCL, defined as primary refractory or relapsed within 12 months of first line chemoimmunotherapy. Key differences in these trials include type of bridging therapy permitted, whether crossover was allowed, event-free survival (EFS) definitions, and manufacturing times for the CAR-T arms. ZUMA-7 met its primary endpoint—axi-cel demonstrated superior EFS over standard care (median EFS, 8.3 v 2.0 months, respectively; hazard ratio, 0.4). Thus, axi-cel became the first CD19 CAR-T product to also receive FDA approval in the second line setting for adults with high risk LBCL. TRANSFORM also met its primary endpoint of EFS at interim analysis, with a median EFS of 10.1 months in the liso-cel group versus 2.3 months in the standard care group. This was a registrational study for FDA approval in this setting. Interestingly, BELINDA did not meet its primary endpoint, with the tisa-cel and standard care groups having similar EFS (3.0 months in both groups), overall survival, and response rates.

**Indolent NHL**

CD19 CAR-T therapy has also been studied in indolent NHL, including follicular lymphoma, marginal zone lymphoma (MZL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Axi-cel was approved by the FDA in March 2021 for adult patients with relapsed or refractory follicular lymphoma (R/R FL) after two or more lines of systemic therapy, based on the ZUMA-5 trial. This phase 2 trial included 124 patients with follicular lymphoma (grades 1–3a) and 22 patients with MZL (nodal or extranodal) who had relapsed or refractory disease after two or more lines of therapy, with a median of three prior lines of therapy. The ORR was an impressive 92% among all efficacy-evaluable patients: 94% (80% complete response) in the follicular lymphoma group and 85% (60% complete response) in the MZL group. Median duration of response has not yet been reached and the estimated one year PFS was 72%. Grade ≥3 CRS and neurotoxicity occurred in 7% and 19%, respectively. Tisa-cel was also studied in 98 adult patients with R/R FL in the phase 2 ELARA trial. At interim analysis, tisa-cel demonstrated an ORR of 86% and a complete response rate of 69%, meeting its primary endpoint of complete response rate. There were no cases of grade ≥3 CRS and only 3% grade ≥3 ICANS. An FDA approval for this indication is also anticipated.

Although CLL/SLL was one of the first B cell malignancies to be successfully treated with CD19 CAR-Ts, response rates in subsequent studies have been considerably lower than those seen with LBCLs and they have not yet been approved in this setting. A phase 2 dose optimization study of CD19 CD3/C/4-1BB CAR-Ts in 32 adult patients with R/R CLL showed an ORR of 44% and a complete response rate of 28%. Median PFS for the entire cohort was only one month, but was 40.2 months for those...
who achieved complete response. The suboptimal response rates are thought to be in part due to T cell dysfunction and immune suppression mediated by the CLL cells. A small study of CD19 CAR-Ts with concurrent ibrutinib demonstrated an ORR of 83% (CR rate, 22%) and lower CRS severity compared with patients who did not receive ibrutinib.75

Mantle cell lymphoma

MCL is a unique subtype of NHL which is usually grouped with the indolent lymphomas, but can often have a more aggressive disease course. ZUMA-2 was a phase 2 multicenter trial of brexu-cel in patients with R/R MCL who had previously received anthracycline or bendamustine containing chemotherapy, an anti-CD20 monoclonal antibody, and Bruton’s tyrosine kinase (BTK) inhibitor therapy.76 In the 68 patients who were infused, ORR was 93% with a CR rate of 67%. Estimated one year PFS was 61%. Almost all patients developed CRS of any grade, but only 15% were grade ≥3, and 31% developed grade ≥3 neurotoxicity. Although the trial required all patients to have previously been treated with BTK inhibitor therapy, the FDA approved brexu-cel in July 2020 with the broader indication of just relapsed/refractory MCL.

Multiple myeloma

Multiple myeloma is a neoplastic disorder of plasma cells which accounts for approximately 10% of all hematologic malignancies and predominantly affects older adults (median age of diagnosis, 65-74). Although multiple myeloma is still considered incurable, the number of new therapies available has increased over the past decade, which has extended the median survival of affected patients. However, a small subset of patients remains relapsed or refractory despite these new classes of drugs, for whom CAR-T therapy might be viable. BCMA is almost universally expressed in both normal and malignant plasma cells and thus has become the main antigen target of interest in CAR-T therapy.77 78 Multiple BCMA CAR-T constructs are under investigation, with just one approved thus far.

Idecabtagene vicleucel (ide-cel) became the first FDA approved CAR-T product for multiple myeloma in March 2021, with the indication of relapsed or refractory disease after four or more prior lines of therapy, including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 monoclonal antibody. Approval was based on the phase 2 multicenter KarMMA trial of adult patients with relapsed or refractory multiple myeloma, who had received a median of six prior lines of therapy (including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 monoclonal antibody).79 Among the 128 infused patients, 73% achieved the primary endpoint of overall response (partial response or better), with 33% achieving complete response or better. Responses remained high in subgroups with aggressive disease, including high risk cytogenetic abnormalities, triple- or penta- refractory disease, and extramedullary disease. Median estimated PFS was 8.8 months. Most patients (84%) developed CRS, but only 5% were grade ≥3. Neurotoxicity was uncommon.

Ciltacabtagene autoleucel (cilta-cel) is another promising BCMA-directed CAR-T therapy which expresses two BCMA-targeting single-domain antibodies to increase avidity. Cilta-cel was studied in the phase 1 LEGEND-2 trial in China80 and in the phase 1/2 multicenter CARTITUDE-1 trial in the US.81 Patients in CARTITUDE-1 were also heavily pretreated, with 88% triple-class refractory. Among the 97 infused patients, the ORR was 97% and 67% of response and PFS had not yet been reached. CRS of any grade occurred in 95% of patients, but only 5% were grade ≥3. Cilta-cel was granted FDA approval in February 2022, with a similar indication of relapsed/refractory multiple myeloma after four or more prior lines of therapy.

Other malignancies

Given the wide success of CAR-Ts in non-Hodgkin’s lymphoma and B-ALL, CAR-T therapies are also being explored with great interest in other hematologic malignancies and solid tumors (table 4). Relapsed or refractory acute myeloid leukemia (AML) represents an area of unmet need, as many patients are either not eligible for curative allogeneic SCT or still relapse following SCT. However, finding an ideal target antigen in AML has been challenging, as many of the myeloid antigens expressed on malignant leukemia cells are also expressed on normal hematopoietic stem/progenitor cells (HSPCs), which could result in profound myeloablation if targeted. Nonetheless, clinical trials that target various markers are ongoing, including CD33, CD123, and C-type lectin-like molecule-1 (CLL-1). While CD33 and CD123 are also expressed by healthy HSPCs, CLL-1 expression is more restricted to AML blasts/leukemia stem cells and monocytes.82 83 Additionally, CAR-T therapy targeting CD30 is also under investigation for CD30-expressing hematologic malignancies such as Hodgkin’s lymphoma and various T cell lymphomas. Two parallel phase 1/2 trials evaluated anti-CD30 CAR-T therapy in 41 patients with relapsed or refractory Hodgkin’s lymphoma who had received a median of seven prior lines of therapy including brentuximab vedotin and immune checkpoint inhibitors.84 The ORR was 62% with a CR rate of 51% for all patients, and even better at 79%/59% for those who received fludarabine-based rather than bendamustine-based lymphodepletion. CRS (all grade 1) was observed in 24% and no patients experienced neurotoxicity.

AML=acute myeloid lymphoma; CNS=central nervous system; NHL=non-Hodgkin’s lymphoma.

CAR-T therapy has also been studied in solid tumor malignancies during the past decade, although these efforts have been met with considerably more roadblocks and very few complete responses.85 86
The main challenges include lack of a ubiquitous target antigen within each tumor type, difficulty with CAR-T trafficking to the main tumor sites, and an immunosuppressive microenvironment induced by the tumors. Earlier trials in glioblastoma targeting epidermal growth factor receptor variant III (EGFRvIII) failed to achieve any responses better than stable disease, and although CAR-T trafficking to the tumor site was demonstrated, there was also increased expression of inhibitory molecules and regulatory T cells in the tumor microenvironment following CAR-T infusion.\(^87\)\(^88\) An earlier trial targeting carcinoembryonic antigen (CEACAM5) in gastrointestinal malignancies also highlighted potential issues with “on-target/off-tissue” toxicity, as several patients in dose cohort 4 experienced acute respiratory distress thought to be due to CAR-T trafficking to areas of CEACAM5 expression on lung epithelial cells.\(^89\) Newer generations of CAR-Ts are attempting to tackle some of these issues by modulating antigen affinity, providing additional signals for CAR-T activation/expansion, or counteracting the immunosuppressive tumor microenvironment with combination PD-1/PD-L1 blockade.\(^86\) Table 4 lists select ongoing clinical trials targeting various antigens, including B7H3, CD171, EGFR, GD2, GPC3, HER2, IL-13Rα2, mesothelin, PSCA, and PSMA.

### Guidelines

Given that this treatment encompasses a new family of “living drugs” with varying properties and indications, formulating consensus guidelines remains a challenge. Many decision points required during therapy lack high quality evidence for guidance. For assessment of candidacy, clinicians initially relied on the inclusion and exclusion criteria for each individual registrational study. However, it is now clear that most patients do not fit into those categories; a real world update showed that approximately half of the patients treated at several referral centers did not meet...
those criteria. The consensus is that most patients require adequate organ function and reserve, mainly cardiac, pulmonary, hepatic and renal, to be able to safely withstand lymphodepleting chemotherapy and survive an episode of sepsis with standard supportive measures; however, exact cut offs are still challenging and depend on the risk and benefit of each individual situation.

Guidelines for grading and treating adverse events of special interest of CAR-Ts, namely CRS and ICANS, appeared with the first approved CAR-T to guide investigators. However, with subsequent CAR-Ts, it was apparent that no one size fits all, as certain cell products have markedly different kinetics of efficacy and toxicity and thus require interventions at different time points. There was a time when it was challenging for clinicians to adhere to several different toxicity management guidelines. The ASTCT therefore sponsored consensus guidelines that function across products and disease states, address severity of symptoms, and are easy to remember and follow.

Emerging treatments and challenges
CAR-T therapy is still only in its infancy and many opportunities lie ahead in improving efficacy and reducing toxicities. Most current CAR-T models are limited by sensitivity when target antigen density is low (through mechanisms such as trogocytosis), contributing to tumor antigen escape or primary resistance. Methods being studied to improve efficacy include better transduction systems such as the Sleeping Beauty transposon/transposase system and increasing CAR-T persistence via additional costimulatory domains, “armored” CARs with constitutive cytokine secretion, deepened lymphodepletion regimens before CAR-T treatment, and combination with checkpoint blockade to reverse T cell exhaustion. Dual target CARs targeting two antigens to overcome loss or down regulation of one target antigen are also being developed, primarily targeting CD19/CD22 or CD19/CD20. Methods being studied to mitigate toxicity (primary CRS/ICANS) include switchable CAR-T platforms incorporating a small molecule “on-off switch” (CALIBR and UniCAR) and improved prophylaxis strategies (fig 4).

Additionally, given that a subset of patients has such aggressive disease that they cannot wait the three to four weeks it takes for their autologous CAR-T product to be manufactured, multiple allogeneic CAR-T products are also in development. The T cells are largely derived from peripheral blood mononuclear cells of healthy donors and engineered using gene editing (such as the CRISPR-Cas9 system) targeting the T cell receptor α constant (TRAC) locus. The allogeneic CAR approach allows the manufactured cells to be available immediately (ie, “off the shelf”) and potentially used for multiple
recipients, leading to decreased implementation and manufacturing costs. However, preventing graft-versus-host-disease or rapid clearance of the allogeneic cells by the host immune system are two ongoing challenges in this field.

Finally, cost of CAR-T infusion and equitable access to these lifesaving therapies remain ongoing issues. Many possible barriers to CAR-T referral and CAR-T access to these therapies remain ongoing challenges in this field.

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Who are the best candidates for CAR-T therapy?

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What are the mechanisms of tumor escape in patients with DLBCL are treated at community oncology centers, but CAR-T therapy can currently only be performed at specialized transplant centers with FACT accreditation owing to potential for serious toxicities. At present fewer than 100 centers in the US are FACT certified, so distance to a treatment center may limit CAR-T access for some patients. Additionally, the high cost of these products—$375 000-475 000 per dose—and reimbursement challenges are likely prohibitive for many who would otherwise be eligible.

Recognizing these disparities and specific barriers for each patient will be the first step in improving access to CAR-T therapy.

RESEARCH QUESTIONS

• What are the mechanisms of tumor escape in patients who do not respond to CAR-T therapy?

• What is the pathophysiology behind the toxicities seen with CAR-T therapy; how do we risk stratify patients and pre-empt toxicities?

• What is the pathophysiology behind prolonged cytopenias seen after CAR-T therapy?

• Who are the best candidates for CAR-T therapy?

• How can we design the “best” CAR-Ts to combine affordable, quick, and reliable mass production with excellent safety and efficacy?

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