White Paper

CAGT Hot Buttons Series

"Testing the CAR": Risk mitigation in autologous CAR-T therapy clinical trials in oncology

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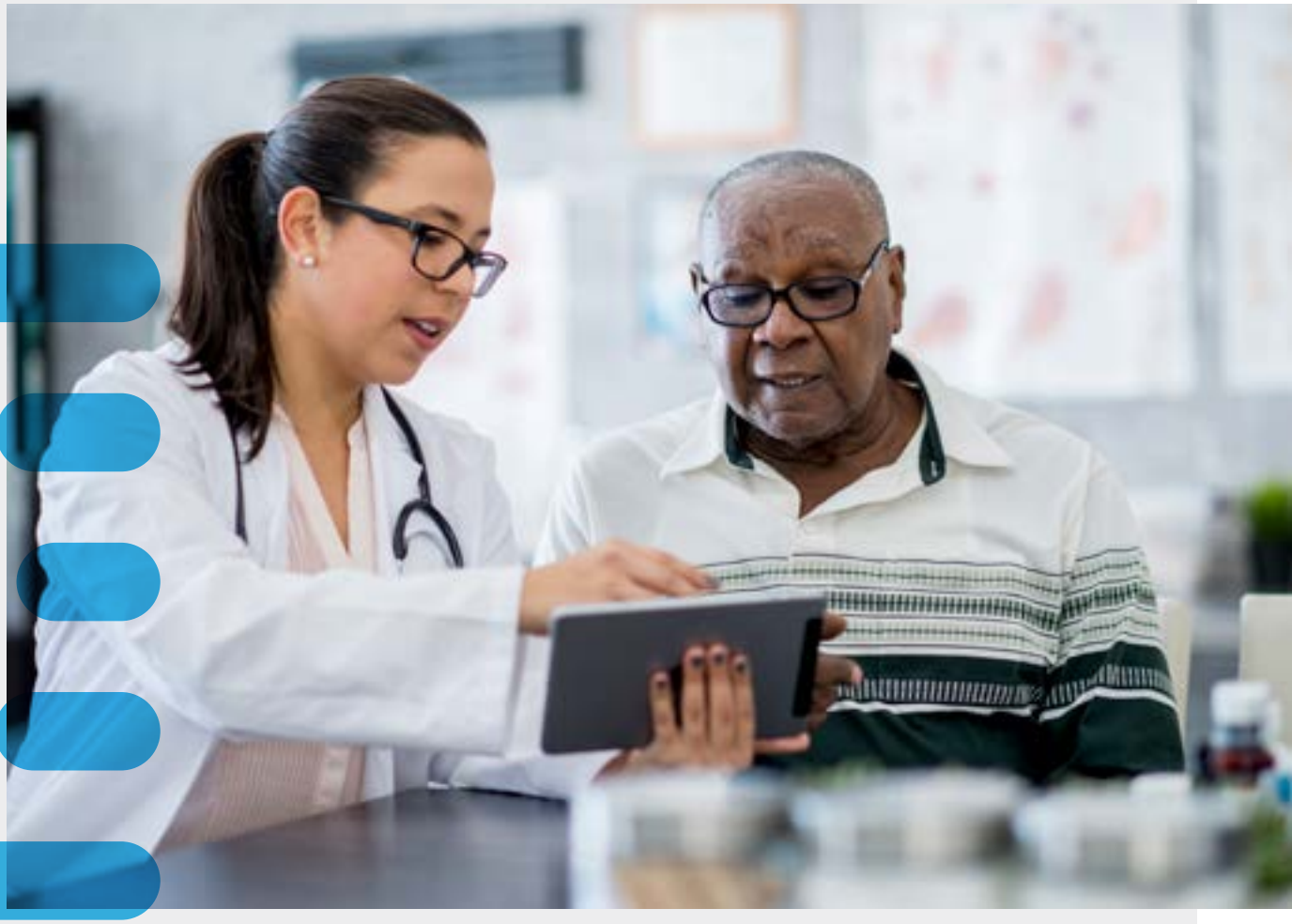

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Summary

Activity in the field of Cell and Gene Therapy (CAGT) has been steadily increasing as the techniques are refined, and patient selection and monitoring are standardized. This white paper builds on the first paper in the CAGT Hot Buttons series, "Starting the CAR: An Introduction To Autologous CAR-T Therapy". Here, we discuss frequently encountered medical hazards of the most widely available autologous Chimeric Antigen Receptor T-cell (CAR-T) therapies in the B cell hematologic malignancy patient population. These complications are cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, cardiovascular toxicity, tumor lysis syndrome, infections, hypogammaglobulinemia and cytopenia. We outline considerations for the management of these toxicities and we present some considerations from a clinical trial perspective.

Introduction

Autologous CAR-T therapy embodies the concept of 'personalized medicine' better than any other available treatment. In the first white paper in the CAGT Hot Buttons series[1], we introduced basic concepts. All of the currently marketed CAR-T therapies are registered for hematologic cancers, but as additional effective CAR-T therapy targets are identified, other indications and applications are almost inevitable[2].

We discuss some of the most commonly encountered post-infusion complications of the currently registered CAR-T therapies, and how to mitigate them. We also answer some frequently asked questions from site staff when they look after clinical trial patients who will receive these "living drugs" for treatment of their hematologic cancer.

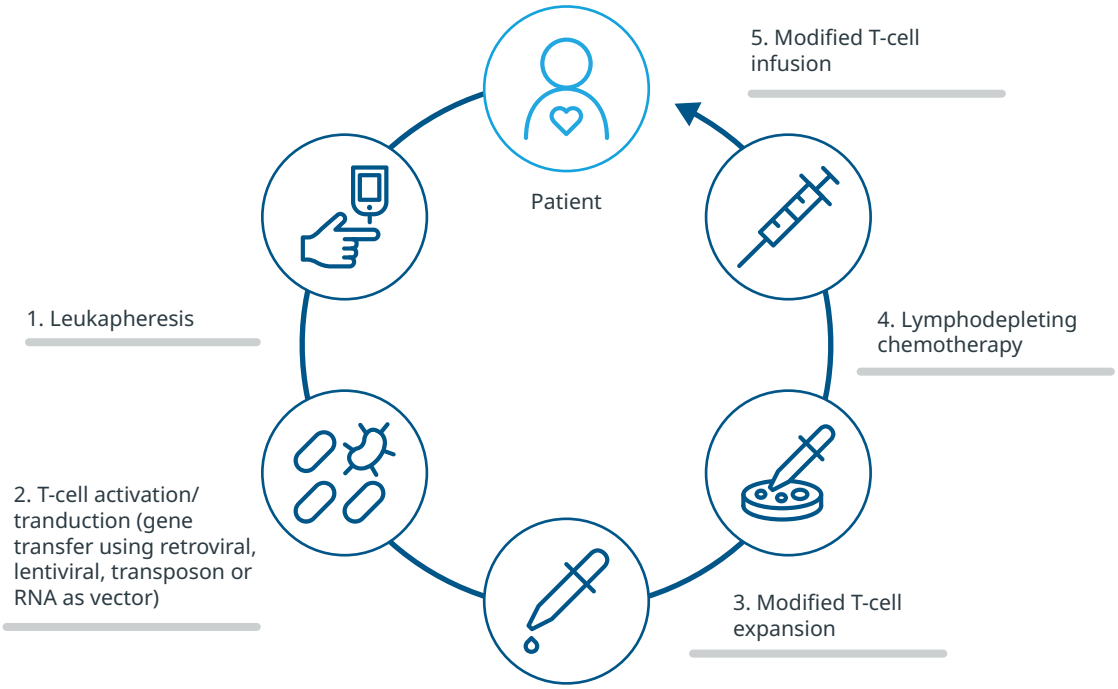
Autologous CAR-T therapy production: the product is the process

In autologous CAR-T therapy, the patient's own white blood cells are the starting material for production of their unique therapy. To begin the process, a patient undergoes a chemotherapy washout to ensure successful collection of adequate T-cells. They then proceed with leukapheresis. In this procedure, the patient is connected to an apheresis machine that removes the required type of white blood cells and returns the rest of the blood components to the patient. The extracted cells are transported to the manufacturing laboratory, where the desired lymphocyte population is selectively activated. The lymphocytes are then genetically altered (transduced). Transduction is performed usually using a virus that carries synthetic genetic material into the lymphocyte so that it will express specific T cell receptor structures

on its surface. The genetically altered lymphocytes are multiplied in the laboratory, then frozen and transported back to the treatment facility for infusion into the patient[3].

The manufacture of the patient's CAR-T product generally takes about 3–4 weeks to complete. Quality control and careful prevention of contamination are routine throughout the process.

Figure 1: Autologous CAR-T therapy manufacture and administration[1]



While patients wait for their product to be manufactured, they may require chemotherapy to control their disease (bridging therapy). The use of bridging therapy is common for those who have cancer that is aggressive, and at high risk for rapid progression. The bridging chemotherapy is given at doses lower than those used to induce remission.

After the treating facility has received the cell product, the treatment team prepares the CAR-T therapy recipient for infusion. The patient's white blood cell population is reduced using a short course of chemotherapy drugs, usually cyclophosphamide and fludarabine. This process is called lymphodepletion (LD) and can be administered either inpatient or outpatient, depending on patient characteristics and the treating facility's operating procedures. The purpose of LD is to enhance the efficacy of the infused lymphocytes. Sites should follow local guidelines for the use of medications to prevent infections after LD.

On the day of the CAR-T therapy infusion (Day 0), prior to treatment, the patient receives premedication with acetaminophen and an antihistamine to reduce the risk of an immediate allergic reaction. Corticosteroids should be avoided as premedication due to potential interference with the efficacy of the infused CAR-T product. The cell product is prepared and administered according to standard procedures at the treatment facility. Cell infusion can also be done either inpatient or outpatient.

After the lymphocyte infusion, the T cells themselves do not require further immune signaling to be active against their targets. The infused cells continue their activity against the tumor cells (persistence) until they are depleted or exhausted. Patients may therefore be able to achieve long-lasting disease control from a single CAR-T treatment infusion. Some recipients have indeed experienced prolonged remission some up to 5 years.

General safety considerations

Recipients of CAR-T therapies face several potential complications at almost any time after infusion.

Experience to date with the registered autologous CAR-T therapies has shown that there is some predictability to the timing and type of these side effects.

Table 1: Autologous CAR-T therapy toxicity timeline[5]

AUTOLOGOUS CAR-T THERAPY TOXICITY TIMELINE*				
DAY POST-INFUSION	EARLY POST-INFUSION PERIOD		MEDIUM-TERM	LONG-TERM
	DAY 0-28		DAY 28-100	DAY 100-365 AND BEYOND
	DAY 0-14	DAY 14-28		
Main clinical features	Neutropenia; anti-inflammatory treatments		Impaired cellular and humoral immunity	Persistent CD19 B-cell aplasia, hypogammaglobulinemia
CRS frequency	High risk	Medium risk	Very low risk of delayed CRS	Minimal / negligible
ICANS frequency	Ongoing high risk		Very low risk of delayed ICANS	_
Bacterial infection frequency				
Bacteremia	High	Low after D14	_	_
Gastroenteritis (C. difficile)	Medium risk		_	_
Pneumonia (encapsulated bacteria)	Medium risk		Low	Low risk ongoing beyond D365
Viral infection frequency				
HSV, VZV	Low		Ongoing low risk	Ongoing low risk
Other herpesviruses	Low		_	_
Respiratory viruses (seasonal / intermittent)	Medium risk		Persistent medium risk	Persistent medium risk
Fungal infection frequency				
Candida species	Medium risk		_	_
Molds	_	Low after D14	Persistent low risk until D56	_
Pneumocystis	_	_	Low	Low risk until D180

Abbreviations: CRS: Cytokine Release Syndrome, ICANS: Immune Effector Cell-associated Neurotoxicity Syndrome, HSV: Herpes Simplex Virus, VZV: Varicella Zoster Virus.
*Adapted from Hill & Seo[5]

The most frequently reported early (<28 days post infusion) toxicities are cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS), tumor lysis syndrome (TLS) and infections. In the medium term (>28 days to 100 days post infusion), the risks of infection and TLS predominate but delayed-onset CRS or delayed-onset ICANS may also occur in this period. During the medium term and for some time afterward, patients may experience prolonged B cell aplasia and resultant hypogammaglobulinemia. Five-year follow-up data from the use of tisagenlecleucel for non-Hodgkin lymphoma (NHL) at a single center showed no new long-term side effects[4,6].

We discuss common toxicities associated with CAR-T therapy below, in order of their frequency:

1. CYTOKINE RELEASE SYNDROME (CRS)

CRS is a systemic inflammatory response that begins with lymphocyte activation and tumor cell destruction and is perpetuated by further lymphocyte and macrophage activation. The chemical mediators secreted by immune cells for activation and communication are called cytokines. The most significant cytokine implicated in CRS development is interleukin (IL)-6, but IL-1 and macrophage signaling cytokines are also heavily involved.

CRS rates vary widely between different CAR-T products and different patient populations. Higher rates of any severity of CRS (>90%) have been described in younger patient populations with acute lymphoblastic leukemia (ALL) than in older patient populations with NHL. A subset (10-40%) of all patients with CRS is at risk of severe CRS[7].

CAR-T therapy recipients with a higher risk of developing CRS include younger patients and those with higher tumor burden (e.g., ALL with higher blast counts), especially those with active inflammation or infection at the time of infusion. Those receiving higher doses of CAR-T therapy, and those who had fludarabine in their LD regimen, are also at potentially increased risk of developing more severe CRS.

CRS varies in severity, from transient fever ≥38°C with or without flu-like symptoms, to a severe condition resembling full-blown macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH). These patients are very ill with high fever, very high ferritin levels and widespread organ dysfunction. MAS and HLH has a high mortality rate if the 'cytokine storm' is not successfully calmed.

CRS is managed according to its severity. For example, the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system uses assessment of 3 vital signs: body temperature, blood pressure and oxygen saturation as shown in Table 2 below:

Table 2: ASTCT CRS Consensus Grading[8]

CRS PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Fever*	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
WITH				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
AND/OR†				
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: BiPAP: Bilevel positive airway pressure; CPAP: continuous positive airway pressure

Organ toxicities associated with CRS may be graded according to CTCAE 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.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

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

All patients with fever should undergo testing to identify the causes of their fever, e.g., infection. Given their degree of immune suppression, they should also receive appropriate broad-spectrum antimicrobial coverage in addition to further evaluation for CRS. All patients with CRS should be evaluated for CRS severity and for changing neurological function, as this is assessed and managed separately (see ICANS section below).

In general, treatments range from nonspecific medications for fever (antipyretics), to cytokine blocking medications, e.g., tocilizumab (anti-IL-6 receptors) and immunosuppression with corticosteroids. Despite initial concerns, in practice, tocilizumab and corticosteroids used for treatment of CRS do not appear to affect efficacy of the infused cells. These drugs are now being used for moderate CRS to prevent progression to severe CRS. In addition to tocilizumab and corticosteroids, patients with severe CRS may receive additional anti-cytokine and anti-inflammatory agents such as anakinra.

The most severe CRS cases need general supportive therapy and specific therapy. These patients are also admitted to the Intensive Care Unit (ICU) and given medications to increase blood pressure, alongside respiratory support, e.g., intubation and ventilation.

2. IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME (ICANS)

ICANS is the second most common toxicity associated with CAR-T therapy. ICANS of any severity has been reported at rates approaching 70% of recipients[7]. The onset of ICANS tends to be later than that of CRS. Not all patients with CRS will develop ICANS, but severe CRS is a risk factor for severe ICANS. The risk of developing ICANS is also affected by the malignancy type and burden, the CAR-T product itself and the extent of central nervous system (CNS) involvement by the underlying disease.

ICANS is generally self-limiting in mild cases, but may cause serious complications, such as combinations of disturbances of language, brain electrical activity, motor function and consciousness in more severe cases. In the most severe form, brain swelling occurs and this may be fatal if not treated promptly.

Early detection of ICANS is essential to assess for deterioration and the need for dexamethasone treatment. Monitoring for ICANS consists of frequent assessment of the neurological status of CAR-T therapy recipients using standardized screening tools (e.g., twice daily or as per protocol) *(see Table 3 below)*.

Table 3: Immune Effector Cell-associated Encephalopathy (ICE) Score[8]

For more details on ICE score, please visit the MD Anderson Cancer Center IEC Therapy Toxicity Assessment and Management Algorithm (also known as CARTOX).

Item	Score
Orientation: (year, month, city, hospital)	4 points (1 point each)
Naming: name 3 objects	3 points (1 point each)
Following commands: follow 1 simple command	1 point
Writing: write a standard sentence	1 point
Attention: count backwards from 100 by 10	1 point

ICE Scoring: 10: no impairment, 7-9: grade 1 ICANS, 3-6: grade 2 ICANS, 0-2: grade 3 ICANS, 0 due to patient unarousable and unable to perform ICE assessment: grade 4 ICANS.

The immune effector cell-associated encephalopathy (ICE) score forms part of the ICANS assessment, together with the presence of seizures, motor dysfunction and tremors. Handwriting disturbance is one of the earliest manifestations of ICANS and is easy to detect by asking the patient to write a simple standard sentence.

The etiology of ICANS has not yet been fully clarified, so there is currently no specific antidote for it. Therapy is therefore mainly supportive. It is important to manage coexisting CRS, e.g., using tocilizumab, but IL-6 receptor blockade is not effective in the management of ICANS. Promising results have been seen with the use of the anti-IL-1 receptor therapy anakinra[9]. All patients with ICANS receive monitoring and supportive care, e.g., intravenous hydration, but more severe cases may also need antiepileptic drugs, corticosteroids and transfer to the ICU.

3. CARDIOVASCULAR TOXICITY

Early cardiovascular complications occur in 10-20% of recipients, and include tachycardia, hypotension, arrhythmias and heart muscle impairment. The most severe cases progress to left ventricular dysfunction that may worsen to cardiac failure and death. Risk factors for cardiovascular toxicity include grade ≥2 CRS, greater disease burden and pre-existing cardiac disease or toxicity from prior therapies. Prior therapy such as anthracycline chemotherapy, radiation therapy and tyrosine kinase inhibitor (TKI) targeted therapy are most frequently implicated. Patients' troponin levels should be monitored as this is a sensitive marker of cardiac toxicity[10,11].

The processes that cause cardiotoxicity are poorly understood, so treatment is mainly supportive. Worse cardiac outcomes tend to occur in patients with a longer interval between CRS onset and specific anti-IL6 treatment[11].

4. TUMOR LYSIS SYNDROME (TLS)

TLS occurs when large numbers of tumor cells are destroyed by treatment. The tumor cells release their internal contents as they burst, e.g., potassium, phosphate, and cellular nucleic acids. These cause electrolyte abnormalities and hyperuricemia that can lead to renal and cardiac damage. Resultant electrolyte disturbances contribute to dangerous cardiac arrhythmias. TLS is not a toxicity that is specific to CAR-T therapy.

CAR-T therapy recipients at the highest risk of TLS include those with pre-existing renal disease and those with hematologic malignancies, especially those with large numbers of tumor cells. These recipients may therefore require pre-hydration. The cardiac and renal function of elderly patients should be assessed before hydrating them aggressively. Patients at high risk of TLS may also receive preventive medication to reduce uric acid, e.g., allopurinol or rasburicase. Patients who develop suspected TLS should be managed according to local standards of care, which is mainly supportive. The goals of therapy are to correct electrolyte abnormalities, reduce uric acid and support renal function, e.g., hemodialysis for severe renal injury[12].

5. INFECTIONS

CAR-T therapy recipients who have had many prior lines of anticancer therapy, or corticosteroids shortly after CAR-T infusion are at a higher risk of infections. In general, the risk of bacterial infections is greatest early after LD and CAR-T treatment infusion when neutropenia is most prominent. The risk for viral infection co-exists with the risk for bacterial infection, but tends to predominate later, past resolution of neutropenia, given the important role of lymphocytes in viral host defense. Further, those patients with persistent B cell aplasia and hypogammaglobulinemia are at the highest risk of severe viral infections months after CAR-T treatment infusion.

Standard preventive medications are used around the time of LD and CAR-T infusion, depending on the patient characteristics and requirements, e.g., antifungals, anti-pneumocystis and antiviral medications. While neutropenic, treating physicians may also opt to place patients on prophylactic antibiotics in addition to the above. Any patient who develops fever after CAR-T treatment infusion should routinely undergo investigation for infection in addition to screening and monitoring for CRS. They should be given broad-spectrum antibiotics until the infection screen results are available[5].

6. HYPOGAMMAGLOBULINEMIA

Hypogammaglobulinemia is defined as low levels of gamma-type antibodies (immunoglobulin G, or IgG) in the blood. This is considered an expected on-target, off-tumor toxicity of CAR-T therapy and can persist for months to years after CAR-T infusion. It potentially puts recipients at higher risk of severe infections, especially with viruses, and may impact the immune response to vaccinations. Those patients with prolonged, severe hypogammaglobulinemia and severe infections may require immunoglobulin infusions, but these generally do not affect CAR-T treatment efficacy[6,13].

7. PROLONGED CYTOPENIA

All patients who have undergone LD have low white blood cell counts afterwards. Some cell types, e.g., neutrophils, recover more quickly from chemotherapy than others e.g., lymphocytes. Decreased B cell lymphocyte counts are an expected on-target, off-tumor toxicity of currently marketed CAR-T therapies, as the CD19 antigen target is present on both cancer cells and healthy B-lymphocytes. Post CAR-T therapy infusion, B-cell counts recover more slowly due to ongoing on-target activity of infused CAR-T treatment, but lymphocyte numbers usually improve with time[4]. Long-term data (>5 years post CAR-T treatment infusion) are now available. Severe infections also have not been reported as frequently as initially projected[6].

General considerations for clinical trial risk management

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) established guidelines for the protection of clinical trial subjects' rights, safety and wellbeing. ICH Efficacy Guideline 6 (E6) is also known as the Good Clinical Practice (GCP) guideline. GCP Principle 8 outlines clinical trial risk management considerations. It states that clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results[14].

Patients with hematologic cancers who are eligible for the currently marketed CAR-T therapies have risk factors for complications in common, e.g., the potential for poor bone marrow function from advanced malignant disease and/or prior treatment. Careful attention to protocol design and conduct is required in all clinical trials, especially in this patient population. CAR-T therapy clinical trials are therefore inherently complex in consideration of patients' eligibility and safety management.

CAR-T therapy recipients participating in clinical trials should not be burdened with additional risks beyond those they already face from the therapy.

Below, we discuss possible questions that sites could raise when they conduct autologous CAR-T therapy clinical trials in oncology:

1. CAN CAR-T THERAPY BE DELIVERED IN AN OUTPATIENT SETTING?

Experience to date with the currently registered products and ongoing clinical trials has shown that, with appropriate controls, it is feasible to maintain patient safety when delivering CAR-T therapy in an outpatient setting; however, this is specific to the patient population and each individual CAR-T investigational product. General recommendations are summarized below. Treatment centers should:

- Understand fully the planned therapy, e.g., cell product dose, receptor target and co-stimulatory domain
- Understand expected toxicity details, e.g., onset and clinical features as determined by the specific CAR-T product/construct
- Select CAR-T therapy recipient and clinical trial candidates carefully
- Provide thorough caregiver training and support
- Confirm space in the infusion center or outpatient clinic and capabilities of outpatient staff in administering the LD and infusion of the CAR-T product
- Establish SOPs specific for outpatient administration and post-infusion monitoring
- Provide contacts and facilities for rapid admission in case of suspected CAR-T treatment toxicity, e.g., CRS

If facilities for rapid assessment and admission are not available, hospital admission for in-patient CAR-T therapy infusion and early follow-up is required[10,15].

Figure 2: A telehealth visit in progress

2. HOW ARE CAR-T THERAPY RECIPIENTS CHOSEN FOR CLINICAL TRIALS?

Patients enrolled in CAR-T therapy clinical trials typically have already exhausted multiple treatments before attempting CAR-T therapy. If patients are too debilitated by complications of their disease and/or prior treatment, they may not have the ability to cope with the preparation for, and receipt of, the CAR-T treatment. Further, given the risks outlined above, patients are generally asked to stay within 1 hour of the treatment center for at least 1 month following CAR-T infusion and are required to have a caregiver present with them during that time, independent of age of the patient. CAR-T therapy clinical trial selection criteria should take this into consideration.

Potential clinical trial CAR-T therapy recipients should meet study population, safety and disease-related requirements at the time of study entry. Then, as treatment preparations progress, patients should also meet stage-specific safety criteria, e.g., at white blood cell collection (leukapheresis), at LD and, finally, immediately before CAR-T treatment infusion.

Irrespective of the patient population that is to be enrolled, both CAR-T therapy recipients' and caregivers' willingness to comply with follow-up trial procedures should be a strict requirement. This is also a current European Society for Blood and Marrow Transplantation (EBMT) mandate[10].

3. ARE THERE SPECIFIC CLINICAL TRIAL CONSIDERATIONS FOR CAR-T THERAPY ADMINISTRATION?

CAR-T therapy-specific clinical trial safety management should meet standards of medical care that best protect the clinical trial subjects' rights, safety and wellbeing. The safety monitoring of clinical trial patients is therefore likely to be more extensive than in routine practice. Trial conduct according to the risk management requirements of the approved protocol is essential.

Before and during the infusion, CAR-T product should be handled gently to ensure that the planned CAR-T lymphocyte dose reaches the recipient. Rigorous prevention of contamination of the CAR-T product is practiced during all steps of administration. Patient care standards established for the delivery of currently approved CAR-T products also apply to clinical trials, e.g., pre-medication shortly before the infusion[10,15].

All product handling (e.g., cold chain) and infusion procedures should be accurately recorded to ensure that patient safety and trial quality management are safeguarded and traceable.

4. DOES CLINICAL TRIAL FOLLOW-UP DIFFER FROM US FDA CAR-T THERAPY RISK EVALUATION AND MITIGATION STRATEGIES (REMS)?

The US FDA has the longest regulatory experience with CAR-T therapy and has well-established standard requirements for product development and marketing registrations. ICH-GCP and the FDA's REMS are complementary to each other for the development of CAR-T products. Local regulations may differ, so these should be considered in conjunction with the ICH-GCP standards in partnership with local regulatory and quality experts.

Figure 3: Overview of cell therapy logistics

The FDA has made recommendations for CAR-T therapy clinical trial safety monitoring, toxicity grading, dose-limiting toxicity definitions and follow-up duration in consideration of the occurrence of complications of the autologous CAR-T therapy process[16]. The stages of the CAR-T therapy process are classified into 3 risk categories in the FDA's draft Guidance for Industry document, dated March 2022, as follows:

1. Cell procurement in an autologous setting
2. Concomitant therapy (e.g., LD)
3. CAR-T therapy

Early follow-up post infusion is intensive, when the risks of CRS, ICANS and TLS are greatest. Initially, for approximately 4 weeks after infusion and discharge from the hospital, CAR-T therapy recipients are required to remain near the treatment facility. Once they complete this early follow-up period with no major safety concerns, they may then travel further away from the treatment facility. These 'geographic limitations' also apply to clinical trial participants.

Post infusion follow-up periods are roughly divided into early, medium-term and long-term. The early period is from Day 0 through Day 28; medium-term is from Day 29 to Day 100, and long-term follow-up is from 101 days through 1 year and beyond. FDA REMS mandates that the currently registered CAR-T therapies' long-term follow-up periods continue to 15 years, because of the technology used to create the chimeric receptors in the laboratory.

Clinical trial protocol follow-up periods are also divided into the follow-up periods above, as the focus of toxicity detection changes. Sponsors may therefore split clinical trials into protocols specific to short-term and long-term follow-up according to the technology used for the gene modification and toxicity detection targets. For example, patients who undergo treatment with CAR-T under an initial "short-term" protocol (follow-up limited to months after infusion) will transition to a separate long-term follow-up protocol (follow-up for years) after they complete the early post infusion period.

Regardless of clinical trial participation, CAR-T therapy recipients may be required to enroll in their own country's cell therapy registration database, e.g., the European Union's EBMT registry[17].

Follow-up intensity generally decreases with time and resolution of early toxicities, so the frequency of site contact and follow-up procedures and visits does decrease. Continuity of care must be established early for all CAR-T therapy recipients because all patients will potentially be followed-up for years after they receive their infusion.

Figure 4: IQVIA Nurse performing clinical trial follow-up home visit

The use of virtual trial technologies, and engagement of the IQVIA Nurse team, are invaluable for success in all periods of patient follow-up. For example, during the more intensive follow-up periods, when real-time access to patient safety data is essential, wearable technology can be employed to meet this goal.

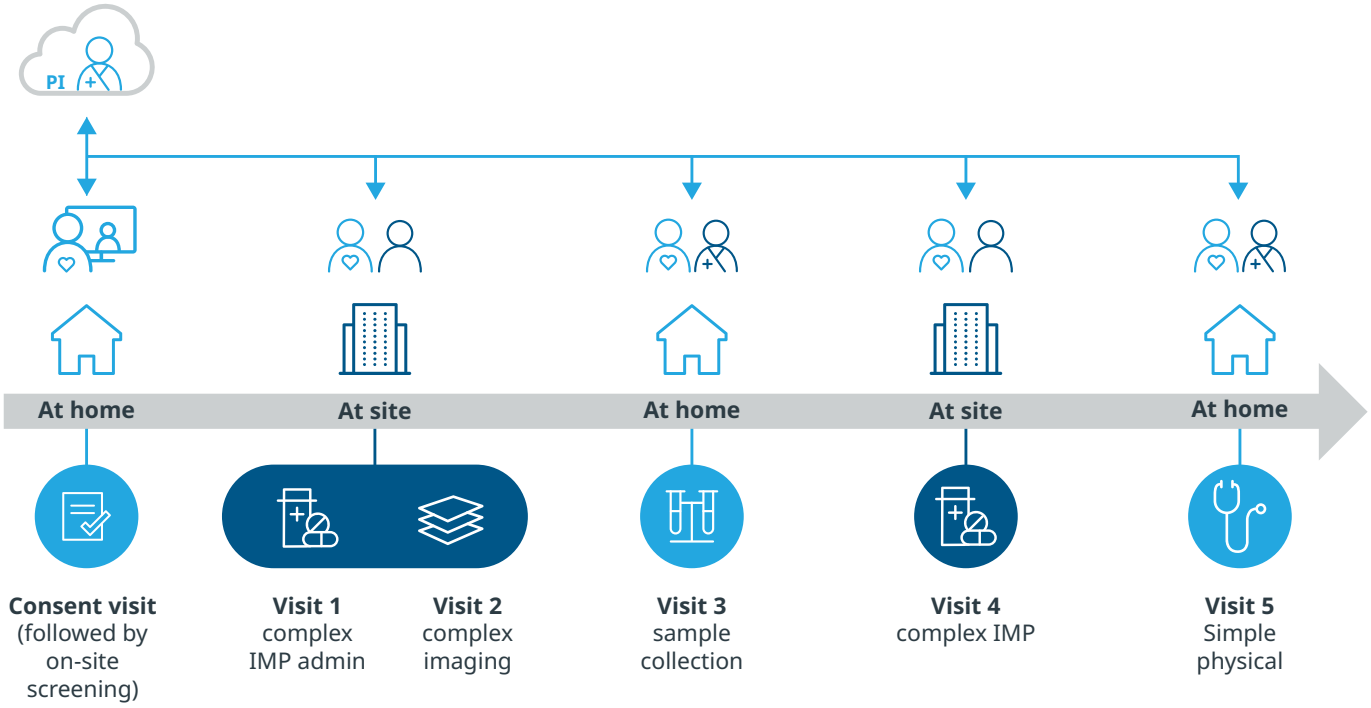
One of the toughest challenges in long-term clinical trials is the high dropout rate which threatens the validity of the trial[18]. The IQVIA Decentralized Trials (DCT) model (virtual trials model) is particularly suited to long-term follow-up of CAR-T therapy clinical trial recipients at home. The flexibility of virtual trials technologies strengthens patient participation by delivering study participation directly to participants through a digital experience. See Figure 4 for an illustration of the IQVIA DCT model in practice.

The patient and their caregiver(s) will need careful training on how to use provided equipment, e.g., electronic tablets and wearables for vital signs. They should also be counselled on reporting any concerns and when to seek medical care to ensure patient safety. Collaboration with the IQVIA Nurse Program team for clinical trial follow-up will further enhance patient safety and retention in trials. To connect with the IQVIA Nurse Program team, please contact: RNPSRequest@IQVIA.com

Figure 4: Decentralized Trials*[19]

The solution — IQVIA decentralized trials

Delivered as hybrid approaches blending remote and site-based elements or as fully remote studies, IQVIA Decentralized Trials expands research opportunities to participants, reduces overall burden and offers sponsors greater flexibility in study design. Or configurable, integrated DCT technology platform collects data in real time, engages and retains study participants, and serves as the central monitoring hub for the trial.



IMP: Investigational Medicinal Product

*This image shows a more generalized version of a decentralized trial model. DCTs are not one-size-fits-all and trial elements may vary based on participant choice and needed. Figure is for illustration of DCT capability only and not specific to CAR-T therapy.

Anticipate to mitigate

Successful clinical trial safety management starts with familiarity with the protocol, investigational product and study population. Clinical trial site staff need detailed training on the expected onset time, symptoms and signs of toxicities that the recipients may experience. Additionally, the protocol's investigational product background, handling and required safety management procedures should be highlighted during the training. Lastly, wherever possible, harness technology and connectivity to enhance patient follow-up compliance, ongoing patient safety and long-term commitment to regulatory requirements.

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