Delivering on the Promise of CAR-T Cell Therapy: Optimising the Clinical Trial Process

CAR-T cell therapy has brought great hope to patients suffering from blood cancers. However, bringing such cutting-edge technology to market has its own set of challenges. How can we anticipate and mitigate risks in CAR-T cell therapy clinical trials to ensure this revolutionary therapy is appropriately trialled and can benefit a larger group of patients?

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When people talk about cancer treatment, mainstream treatment options such as surgery, chemotherapy, and radiation therapy often come to mind. In the past decade, a novel class of cancer therapeutics has brought great hope to cancer patients worldwide. Collectively known as immunotherapy, such treatment entails mobilising patients' own immune systems to attack cancer cells.[1] One such immunotherapy that has generated a huge amount of interest and has been hailed as a game-changer is Chimeric Antigen Receptor T-Cell (CAR-T) therapy.[2]

Introduction to Autologous CAR-T Therapy

As its name suggests, CAR-T therapy utilises genetically modified T-lymphocyte cells (also known as T-cells), fitted with specific receptors, to recognise and kill cancer cells. Such T-cells are typically obtained from patients and then transported to a laboratory where they are genetically modified and left to mature and proliferate. Once these cells are ready, the genetically modified T-cells are infused into patients with the hope that they will continuously proliferate in their host. Thanks to the receptors these T-cells have been fitted with, they will then recognise and kill any cancer cells that have the target antigen on their cell surface.[2,3,4]

Life cycle of CAR-T Therapy

At the time of writing, all of the approved CAR-T products are autologous CAR-T therapies, with the Asia-Pacific having five such FDA-approved products.[5,6,7,8,9,10] In autologous CAR-T therapy, a patient's own T-cells are used to manufacture their own unique drug. The currently approved CAR-T therapies target either CD-19, which is present on all B-cells, or B-cell maturation antigen (BCMA), which is present on the surface of mature B-cells. Presently, CAR-T therapy is only approved to treat a limited set of B-cell cancers such as Non-Hodgkin lymphoma (NHL), B-cell acute lymphoblastic leukaemia (ALL), and multiple myeloma (MM).[11,12]

Though it has been shown to be highly effective in treating patients with B-cell cancers, CAR-T therapy is not without side effects. As opposed to mainstream therapies, the extraction and use of a patient's own cells to manufacture a therapy presents huge logistical demands. These harvested cells require transportation under carefully controlled cryogenic conditions to the laboratory (often across national borders). They then need to be transported back to the patient post-modification in an uninterrupted cold chain, ensuring adherence to strict quality control standards at every step so that these modified T-cells remain viable ahead of their infusion back into the patient.

Navigating the Complexity of CAR-T Cell Therapy Clinical Trials: Key Considerations for Risk Management

The number of CAR-T clinical trials is steadily increasing as refinements are made to CAR-T structures to enhance their efficacy whilst reducing undesirable effects. Moreover, researchers are also looking at expanding CAR-T targets and clinical indications in hopes of bringing this revolutionary drug to a broader patient population. As of February 2023, there are 685 active CAR-T clinical trials globally,[13] despite the impact of the COVID-19 pandemic.

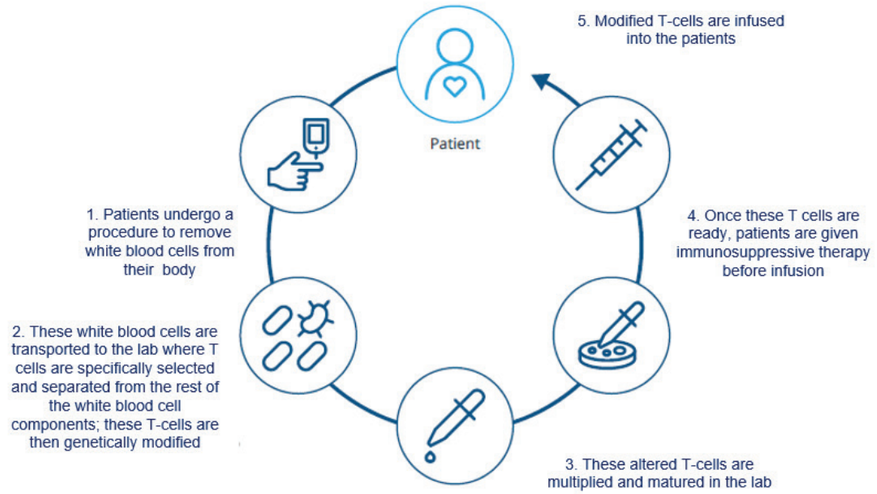
Recipients of this cutting-edge treatment also face several potential undesirable effects post-infusion. Some of the common side effects, which unsurprisingly are related to the patient's own immune processes, include an over-activation of the immune system, a lower white blood cell count, and a higher risk of infections (ranging from bacterial to viral to fungal infections) – all of which are manageable with clinical intervention.

As highlighted in the recent Cell and Gene Therapy (CAGT) Hot Button Series published by IQVIA, so far, CAR-T clinical trials have demonstrated some helpful predictability to the timing and type of side effects associated with CAR-T therapies. This provides researchers with a reliable roadmap to monitor patients' well-being post-infusion. Furthermore, researchers need to account for the complexities of autologous CAR-T therapy clinical trials (e.g., logistics, choosing the right patients, etc.) to ensure that recipients are not burdened with additional risks beyond those they face from the therapy. So, what are some of the risk management considerations autologous CAR-T therapy clinical trial sites need to be employing as a priority?

For starters, clinical trial sites looking at the possibility of outpatient administration of CAR-T therapies should analyse and be familiar with the risks associated with such study designs. Experience from the use of currently registered products and ongoing clinical trials has shown that, with appropriate controls, it is achievable to maintain patient safety when administering CAR-T therapy in an outpatient setting. Nevertheless, this is often dependent on the selected CAR-T product and its target patient population. To manage the risks associated with outpatient treatment, it is imperative for clinical trial sites to have the necessary infrastructure for rapid assessment and hospital admission in the event of suspected CAR-T treatment side effects.[14,15]

On top of that, clinical trial sites also need to consider the logistical demands associated with CAR-T therapy. A robust contamination-prevention strategy needs to be in place to ensure that CAR-T products remain sterile before

Figure 1: Life cycle of CAR-T therapy



infusion into the recipient. This will protect the recipients from any unnecessary infections. Moreover, all product-handling and infusion procedures need to be precisely recorded to ensure patient safety and that trial quality management is traceable.

The Important Role of the Caregiver Ecosystem

As outlined above, recipients of CAR-T therapies face several potential side effects post-infusion. Hence, it is often required for recipients to have a caregiver present with them post-CAR-T infusion, independent of the age of the patient, to ensure the necessary intervention is provided in the event of a problem. The risk of post-infusion side effects should also be taken into consideration during CAR-T therapy clinical trial patient selection. The selected CAR-T therapy recipient must thus have a designated caregiver available for the duration of the clinical trial and both parties must be willing to comply with the follow-up trial procedures.

Such clinical trial follow-ups are typically intensive during the first few weeks of infusion as that is when the risks of experiencing side effects are the greatest. CAR-T therapy recipients are therefore required to stay near a treatment facility in the early post-infusion period so that they can receive rapid medical attention should problems arise.

Long-term clinical trials such as those involving CAR-T therapies are often at risk of having a high dropout rate which threatens the validity of the trial.[16] The follow-up intensity will decrease with time and as risks of severe early side effects resolve, so the frequency of site contact and follow-up procedures and visits will decline too. Having said that, the longevity and burden of such follow-ups can get operationally heavy and as aforementioned may lead to high dropout rates. Collaboration with third parties, such as IQVIA nurse teams, can alleviate the burden on site, whilst ensuring patient safety is not compromised.

The advent of virtual trial technologies can help support patients and site investigators by providing a convenient way to keep up with their scheduled follow-ups. The IQVIA Decentralized Trials (DCT) model (virtual trials model) is particularly useful for long-term follow-up of CAR-T therapy clinical trial recipients. This virtual trial model provides greater flexibility in the clinical trial study design while allowing clinical trial investigators to remotely monitor patients in real time. For this to be successfully implemented, it is vital that patients and their caregivers are provided with the necessary training on how to use the provided equipment and when to seek help to ensure patient safety is not compromised.

Moreover, the use of such virtual technologies will enable clinical trial sites to engage a more diverse patient group, beyond those traditionally able to participate in clinical trials. Greater diversity and inclusion in clinical trials provide greater confidence in novel and revolutionary therapies.

By keeping these considerations in mind, CAR-T clinical trial researchers could potentially mitigate the additional risks beyond those CAR-T therapy recipients face from the treatment.

Delivering on the Promise of CAR-T Cell Therapy

The advent of CAR-T therapies has the potential to revolutionise the way many cancers are treated, as it has been shown to lead to remarkable therapeutic successes in some clinical applications for cancer patients with advanced tumour disease. It is widely believed that CAR-T therapy has the potential to become one of the mainstream cancer treatments alongside surgery, chemotherapy, radiation therapy, and other well-established immunotherapies. The early promise of CAR-T therapy has spurred researchers to actively develop improved processes and approaches in hopes of developing new and improved CAR-T products that can benefit a broader patient population.

It is important for pharmaceutical companies and clinical trial investigators to adopt a strategic, highly organised and coordinated approach when designing CAR-T clinical trials. And, whenever possible, be deliberate in mitigating and managing the risks associated with each clinical trial step. Incorporating virtual trial technologies may also be the secret to bringing more of these revolutionary drugs to life, whilst limiting undesirable effects and simplifying the logistical burden on site and patient. APBN

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References

1. National Cancer Institute (n.d) Immunotherapy to treat cancer. Retrieved February 2023, from: https://www.cancer.gov/about-cancer/treatment/types/immunotherapy
2. Almåsbak H, Aarvak T, Vemuri MC. CAR T Cell Therapy: A Game Changer in Cancer Treatment. J Immunol Res. 2016; 2016: 5474602.
3. Yakoub-Agha I, Chabannon C, Bader P et al. Management of adults and children undergoing chimeric antigen receptor T-Cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). Haematologica 105(2) February 2020.
4. Selim AG, Minson A, Blombery P, et al. CAR-T cell therapy: practical guide to routine laboratory monitoring Pathology (April 2021); 53(3); 408-415.
5. ASGCT Q3 regulatory approvals: The American Society of Gene + Cell Therapy. Retrieved February 2023, from: https://asgct.org/global/documents/asgct-pharma-intelligence-quarterly-report-q3-2021.aspx
6. Abecma USPI. Retrieved February 2023, from: https://www.fda.gov/media/147055/download
7. Breyanzi USPI. Retrieved February 2023, from: https://www.fda.gov/media/145711/download
8. Kymriah USPI. Retrieved February 2023, from: https://www.fda.gov/media/107296/download
9. Tecartus USPI. Retrieved February 2023, from: https://www.fda.gov/media/140409/download
10. Yescarta USPI. Retrieved February 2023, from: https://www.fda.gov/media/108377/download
11. Liu A. FiercePharma: With approval for China's 2nd CAR-T therapy, Juno, WuXi joint venture goes up against Gilead and Fosun's Yescarta. Retrieved February 2023, from: https://www.fiercepharma.com/pharma-asia/juno-wuxi-jv-goes-up-against-yescarta-china-nod-for-cart-therapy
12. FDA approval brings first gene therapy to the United States. Retrieved February 2023, from: https://www.fda.gov/news-events/pressannouncements/fda-approval-brings-first-gene-therapy-united-states
13. NIH Clinical Trials.gov (31 Jan 2023) CAR-T active clinical trials. Retrieved February 2023, from: https://clinicaltrials.gov/ct2/results?term=CART&Search=Apply&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=
14. Hayden PJ, Roddie C, Bader P, Basak GW, Bonig H, Bonini C, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol Off J Eur Soc Med Oncol. 2022 Mar;33(3):259–75.
15. Myers GD, Verneris MR, Goy A, Maziarz RT. Perspectives on outpatient administration of CAR-T cell therapy in aggressive B-cell lymphoma and acute lymphoblastic leukemia. Open Access. 10. Retrieved from: https://jitc.bmj.com/content/jitc/9/4/e002056.full.pdf
16. Bell ML, Kenward MG, Fairclough DL, Horton NJ. Differential dropout and bias in randomised controlled trials: when it matters and when it may not. The BMJ. 2013 Jan 21;346:e8668.

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