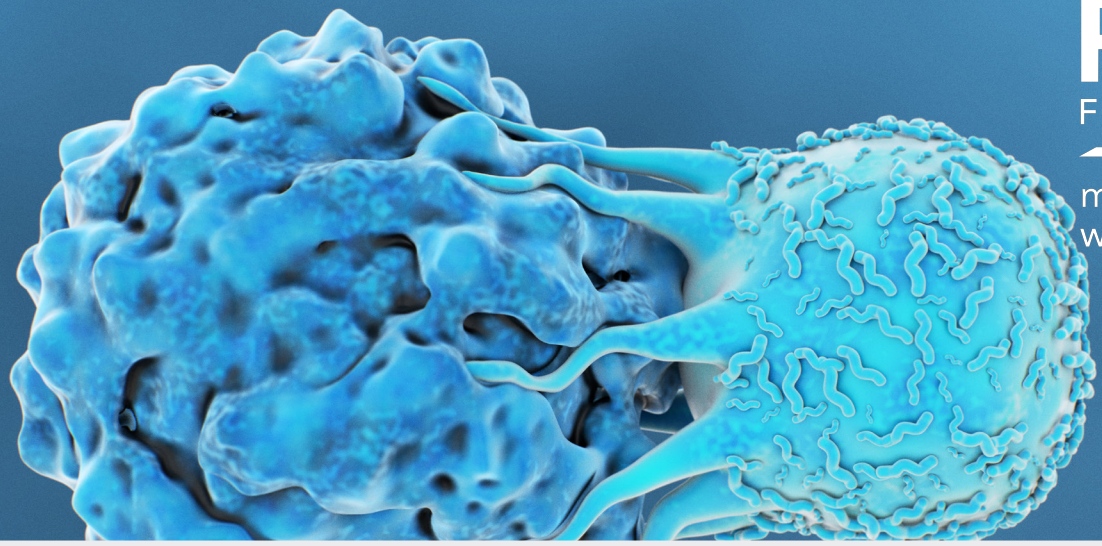

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CAR-T cell therapies

Immunotherapy primes the immune system to recognise and eliminate cancer cells, making it a promising approach for treating cancer. However, cancer cells can actively hide from or 'switch off' immune cells, and can be difficult for the immune system to identify. CAR-T cell therapies are a form of cellular immunotherapy that use genetically modified T cells, a type of white blood cell. CAR-T cells are engineered to express a chimeric antigen receptor (CAR), which is designed to recognise a predefined molecular marker (an antigen) on the surface of cancer cells. This allows CAR-T cells to help the immune system recognise and kill cancer cells. CAR-T therapies have achieved remission in cancer patients with advanced blood cancer who have failed multiple previous treatments.

Summary

- CAR-T cell therapies have been approved in some countries to treat late-stage leukaemia and lymphoma
- CAR-T cell therapies have shown success in treating patients who have failed to respond to other treatments
- The potentially life-threatening side effects and high cost associated with CAR-T therapies prevent them from being used in early disease
- Extensive planning is required to ensure the complex manufacturing process required to make CAR-T therapies can be completed without delaying treatment

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CAR-T cell therapies

What are CAR-T cell therapies?

There are two main types of CAR-T therapy:

- Allogeneic – T cells are derived from a healthy donor
- Autologous – T cells are derived from the patient's own cells

Allogeneic therapies are only at the clinical trial stage. There are issues with rejection, meaning the CAR-T cells do not survive as long in the patient, and graft-versus-host-disease (GVHD), which is a potentially life-threatening condition whereby the donor CAR-T cells attack the patient's normal, non-cancerous cells. Allogeneic CAR-T cells usually require further genetic modification to stop or minimise the impact of rejection and GVHD, making their development complicated and slowing the path to clinical implementation.

In contrast, autologous CAR-T therapies have been approved for use in patients in some countries for the treatment of leukaemia and lymphoma. Because autologous therapies are created from the patient's own cells, they are less likely to be rejected, so survive longer in the body. This results in better patient outcomes, as they have the potential to continually eliminate cancerous cells longer-term. Two patients who received CAR-T therapy in an early clinical trial have remained in remission a decade after treatment, with CAR-T cells still detectable in their bodies [1].

Current clinical use

Globally, a number of CAR-T therapies have been approved. Kymriah and Yescarta are among four CAR-T therapies approved by the European Medicines Agency (EMA) and among five approved by the US Food and Drug Administration (FDA). In China, two CAR-T therapies have been approved (Yescarta and Carteyva) for the treatment of large B cell lymphoma and Kymriah is approved in Hong Kong for patients ≤25 years of age with relapsed or refractory B cell acute lymphoblastic leukaemia.

All current CAR-T therapies are associated with significant and potentially life-threatening side effects, meaning patients are closely monitored for 28 days after treatment. These include cytokine release syndrome and neurotoxicity, both of which are primarily caused by over activation of the immune system. Treatment centres administering CAR-T therapy need experience with treating these side effects, as well as expertise in extracting and handling T cells. Treatments therefore tend to be delivered by a small number of specialist centres, in the countries where they have been approved.

CAR-T cell manufacturing

The manufacturing pipelines to produce autologous CAR-T cell therapies can be slow, complex and costly because each patient sample is part of a bespoke pipeline. T cells are collected from the patient and shipped to the manufacturing site for genetic modification to express the CAR, before quality control and safety testing. Manufacturing times vary but in the US are typically around 17 days for Yescarta and 22 days for Kymriah [2]. The cells are then shipped back to the treatment centre and given to the patient in an infusion.

Issues that can arise during this process include:

- Disease progression during manufacture – as patients have late-stage and often aggressive disease, 'bridging' chemotherapy is sometimes required to keep the cancer under control during manufacturing.
- The location of the manufacturing site – long shipping times increase the time to treatment, which increases the risk of the disease progressing in the patient while they wait for the CAR-T cells to be made. Some countries, for example China and the US, undertake manufacturing in-country; others have the CAR-T cells manufactured overseas.

As more autologous CAR-T therapies receive approval, bespoke pipelines will need to be optimised to manage costs and ensure supply meets demand. In contrast, once the development issues for allogeneic therapies are resolved, manufacturing is likely to be quicker, simpler and cheaper because a single pipeline can be run in advance for all cells, which is easier to scale-up.

Enabling access to CAR-T therapies

As novel and state of the art therapies, CAR-T cells raise issues concerning patient access, requiring strategic decision-making at the health system level to ensure they are available to those who most need them.

Patient access

The high cost of autologous CAR-T cell therapy and geographic constraints are a challenge to equitable access. Patients must attend a specialist treatment centre and stay nearby for monitoring after treatment, which may impose significant financial and social burdens, leaving some patients unable to access CAR-T therapies. Specific support for these patients may help to overcome these challenges. In addition, patients may have to be prioritised for treatment as CAR-T therapy is resource-intensive, with criteria for this requiring careful consideration.

Reimbursement

As CAR-T therapies are newly developed, there is little long-term data available. This, in combination with their high cost, can make proving cost-effectiveness difficult, resulting in delays or rejection of CAR-T therapies at the reimbursement stage. However, novel reimbursement approaches have so far proved successful for allowing initial access to CAR-T therapies [3]. These include managed access agreements, where therapies are recommended temporarily until more data is available, or outcome-based reimbursement schemes, typically involving staged payment plans based on patient outcomes at different time points. These approaches are likely to be used more widely as more bespoke and personalised medicines become available.

Research and clinical trials

While currently approved CAR-T therapies have shown success in treating patients with no other treatment options, challenges remain that prohibit more widespread use, including use earlier in the disease course. Research is focused on improving efficacy, reducing side effects, and expanding into other areas including [4]:

- Improving CAR-T cell design to increase their ability to recognise and kill cancer cells, thus increasing treatment response rates

- Reducing side effects – for example by optimising CAR design to reduce over activation, programming 'kill switches' to turn off CAR-T cells if side effects are serious or giving preventative treatment for side effects alongside treatment
- Optimising antigen selection – finding new antigens and developing dual targeting CAR-T cells, which target two antigens simultaneously, to enable use in new cancer types and to overcome resistance to treatment
- Combination treatment, for example with other immunomodulatory agents, to improve immune response, potentially increasing treatment success rates
- Developing effective allogeneic CAR-T therapies that can be manufactured in advance in bulk to reduce time to treatment and manufacturing costs
- Use in solid tumours, including identifying antigens, improving CAR-T cell access to the tumour, and overcoming the ability of the tumour to 'switch off' the immune response
- Use of CAR-T therapy in other disease areas, such as infectious disease, autoimmune disease, and heart disease

China is undertaking the largest number of clinical trials for CAR-T cell therapy globally after overtaking the United States in 2017. Most trials are investigating use of CAR-T cells for treating blood cancers, although many are exploring use in solid tumours and a few are looking at non-cancers, including infectious disease and autoimmune disease [5].

Conclusion

CAR-T therapies have great potential for providing a novel approach to treating a range of cancers in the future. With currently available therapies, patients who previously failed multiple treatments for blood cancers can achieve remission following treatment with CAR-T cells. However, their potential for life-threatening side effects, high cost, and complex manufacturing processes must be overcome before CAR-T therapies can be scaled-up. Development of allogeneic CAR-T therapies may address some of these issues, however safety and efficacy need to be demonstrated in clinical trials before wider clinical use.

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