EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Chimeric antigen receptor T-cell therapy

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SUMMARY

Chimeric antigen receptor T-cell therapies are promising new options for patients with relapsed or refractory diffuse large B-cell lymphoma or acute lymphoblastic leukaemia. They increase complete response rates and the chances of achieving prolonged remission.

Chimeric antigen receptor T cells are specially modified lymphocytes designed to stimulate the body's own immune system to target malignant cells. The process involves an initial harvest of the patient's own T cells, genetic modification, T-cell expansion and then reinfusion.

Cytokine release syndrome is a major short-term complication of chimeric antigen receptor T-cell therapy. The presentation typically resembles septic shock and can be fatal.

Immune effector cell-associated neurotoxicity syndrome is another major short-term complication. It presents with a spectrum of neurological deficits ranging from headache, delirium and anxiety to seizures and coma.

There are early promising results with chimeric antigen receptor T-cell therapies in other cancers. These include mantle cell lymphoma, multiple myeloma and some solid organ tumours such as glioblastoma multiforme.

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapies are a new form of immunotherapy for certain haematological malignancies. T-lymphocytes taken from the patient are modified to recognise cancer cells and then returned to the patient to raise an immune response.

Tisagenlecleucel was approved by the Australian Therapeutic Goods Administration (TGA) for children and young adults with relapsed or refractory acute lymphoblastic leukaemia and for adults with relapsed or refractory diffuse large B-cell lymphoma in 2019. Axicabtagene ciloleucel was approved for adults with relapsed or refractory diffuse large B-cell lymphoma in 2020. Currently CAR-T therapy is offered in highly specialised centres in most states of Australia.

Production and delivery

The production of CAR T cells begins with harvesting T-lymphocytes by leukapheresis of the patient's blood over several hours. Patients may then undergo bridging chemotherapy or radiotherapy to control the cancer during the manufacturing process (range 22–40 days).

After harvesting, the cells are genetically modified using viral vectors to trigger expression of receptors targeted against specific tumour antigens, such as CD19.[1,2] The numbers of modified T cells are expanded in the laboratory before the product is delivered to the treatment site. Patients undergo lymphodepletion chemotherapy with fludarabine and cyclophosphamide before infusion of the CAR-T product.

After infusion into the patient, the CAR T cells must reach tumour cells to interact with the target antigen. The CAR T cells must increase in number and persist over time to result in durable remissions.[2]

Acute lymphoblastic leukaemia

In children and young adults with relapsed or refractory acute lymphoblastic leukaemia, the 'traditional' treatment is cytotoxic chemotherapy. This has poor efficacy with complete response rates of 30–40% after the first salvage treatment and 10–20% after the second salvage treatment.[3]

In contrast, CAR-T therapy has excellent efficacy. In one trial involving 75 patients treated with tisagenlecleucel, the overall remission rate within three months was 81% and, at 12 months, overall survival was 76% (95% confidence interval (CI) 63–86%).[4] Long-term follow-up (5.9 years) found that 82% of patients experienced complete remission within three months of the infusion. For patients in remission, the median relapse-free survival was 43 months.[5]

Currently, tisagenlecleucel is approved and publicly funded for children and young adults up to and including age 25 years with primary or secondary CD19-positive relapsed or refractory acute lymphoblastic leukaemia.

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B-cell lymphoma

Due to the combination of aggressive disease and the requirement for intensive chemotherapy, the median survival for patients with refractory diffuse large B-cell lymphoma is normally six months. Response rates to salvage chemotherapy are often poor, with a pooled response rate of 20%.[6]

In a trial of tisagenlecleucel for relapsed or refractory aggressive B-cell lymphomas, 115 patients had an overall response rate of 53%, with a median follow-up of 40.3 months.[7] The estimated probability of survival after a year was 49% (95% CI 39–59%) for all patients and 90% (95% CI 74–96%) for patients with a complete response at three months.

A trial of axicabtagene ciloleucel studied 101 patients with refractory large B-cell lymphoma. After a median follow-up of 27.1 months, 83% of patients had an objective response with a median duration of 11.1 months. The median overall survival was not reached.[8]

Axicabtagene ciloleucel and tisagenlecleucel have both been approved and publicly funded for adults with relapsed or refractory primary or secondary diffuse large B-cell lymphoma after at least two other treatments or a stem cell transplant.

Patient selection

Currently, CAR-T therapy is only offered in specialist CAR-T centres within one or two hospitals per state. Patients are evaluated and discussed by local and national committees regarding their eligibility and management. All patients must have manageable disease trajectory with bridging therapy (if needed) and no significant organ dysfunction including renal, hepatic, cardiac or pulmonary impairment. Many patients will not be eligible for CAR-T therapy.

Adverse effects

CAR-T therapy shares some adverse effects with other leukaemia and lymphoma treatments. There are broad risks such as tumour lysis syndrome and febrile neutropenia secondary to the lead-in chemotherapy, the CAR-T therapy or the disease itself (especially in acute lymphoblastic leukaemia) resulting in vulnerability to opportunistic infections. There are two common major short-term complications unique to CAR-T therapy. These are cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.[9]

Cytokine release syndrome

The widespread activation of the CAR T cells can result in the release of excessive amounts of pro-inflammatory cytokines. Clinical manifestations typically resemble septic shock, with fever, hypotension, tachycardia and hypoxia the most reported symptoms.[9] This reaction can be life-threatening, frequently necessitating intensive care, and clinicians need a high index of suspicion.

The rates of cytokine release syndrome differ according to the disease and product used. Up to 80% of patients experience some level of cytokine release syndrome. The median time to onset is three days with a median duration of eight days.

The mainstay of treatment for cytokine release syndrome is the anti-IL-6 monoclonal antibody, tocilizumab. This interrupts the pro-inflammatory cascade while preserving the underlying T-cell activation. If cytokine release syndrome is refractory to tocilizumab, high-dose corticosteroids or biologic disease-modifying antirheumatic drugs, such as anakinra, have been used to suppress the cascade. While there have been concerns that these may inhibit the T-cell activation and maturation required for treatment efficacy,[9] adequate control of the syndrome is a priority. There are no definitive data showing that these drugs reduce the efficacy of CAR-T therapy.

In general, it is thought that the more severe the disease, the more severe the cytokine release syndrome. However, the lack of a cytokine release syndrome does not indicate a lack of response, nor does the presence of cytokine release syndrome imply there is a response to CAR-T therapy.[9]

Neurotoxicity

Immune effector cell-associated neurotoxicity syndrome is the second major short-term complication of CAR-T therapy. It may occur concurrently with cytokine release syndrome, and severe cytokine release syndrome is a predictive marker for the development of severe immune effector cell-associated neurotoxicity syndrome. Like cytokine release syndrome, a high tumour burden increases the risk of immune effector cell-associated neurotoxicity syndrome.[10]

The most common manifestations include headache, encephalopathy, delirium, anxiety, sleep disorders, dizziness, tremor and peripheral neuropathy. Severe manifestations include seizures, aphasia, coma and death from fatal cerebral haemorrhage or malignant cerebral oedema.[10,11]

Immune effector cell-associated neurotoxicity syndrome is common, with rates of up to 70–80% depending on the product. Severe toxicities occur in around 20% of cases.[12]

The onset of immune effector cell-associated neurotoxicity syndrome may be delayed, but nearly all cases present within eight weeks of the infusion. By then the patients are often back in the community so ongoing vigilance for symptoms is essential. Due to the potentially delayed onset, patients must have

a carer available full-time for the first month after infusion. Patients should not drive for the first eight weeks after treatment.

To treat immune effector cell-associated neurotoxicity syndrome in hospital, early high-dose corticosteroids are used, usually dexamethasone for its increased central nervous system penetration.[13] Whether corticosteroids lower the efficacy of CAR-T treatment is currently unknown.[14] Anakinra has also been used with good effect.[15]

Long-term complications

CAR T cells are not conventional pharmaceuticals. They can expand and proliferate, leading to both the desired response and potential long-term complications.

The major long-term complication of CAR-T therapy is persistent cytopenia. A grade 3 or higher cytopenia lasting more than one month after infusion affects 20–40% of patients. This can persist beyond 90 days in around a third of patients, particularly with neutropenia and thrombocytopenia. Cytopenia, combined with possible hypogammaglobinaemia and B-cell aplasia, can lead to prolonged susceptibility to infection, including by atypical organisms. This is of significant concern.[12]

Immune-related adverse effects are a potential concern for CAR-T therapy, similar to that seen with the immune checkpoint inhibitors. Possible late reactions, including persistent skin rashes, pneumonitis and lymphocytic alveolitis, have been reported in 8% of patients at a median of 234 days. However, attributing these toxicities specifically to the CAR-T therapy is difficult given that most patients have been heavily pre-treated.[16]

It is unclear whether CAR-T therapy leads to an increased rate of secondary malignancies. There have been cases of myelodysplastic syndrome as well as solid tumours including skin and bladder cancers. However, given the extensive exposure of patients to other cytotoxic therapies, attribution is difficult. There is a need for ongoing vigilance with a low threshold for bone marrow examination in patients with unexplained or worsening cytopenia.

Killed or inactivated vaccines can be given six months after therapy. The recommendation is to defer live vaccines for up to two years.

Future directions

Earlier use of axicabtagene ciloleucel in the treatment of large B-cell lymphoma has demonstrated significant overall survival benefit and it has been approved internationally for use as second-line therapy in patients with early relapsed or refractory primary large B-cell lymphoma.[17]

The potential for CAR-T therapy in treating other malignancies is encouraging. These include mantle cell lymphoma,[18] adult acute lymphoblastic leukaemia[19] and multiple myeloma.[20] Brexucabtagene autoleucel was approved for adults with relapsed or refractory mantle cell lymphoma in July 2021 and for adults with relapsed or refractory acute lymphoblastic leukaemia in September 2022. Most recently, in June 2023, ciltacabtagene autoleucel was approved for adults with relapsed or refractory multiple myeloma. These products are currently under review by the Medical Services Advisory Committee (MSAC) for public funding in Australia. There are also clinical trials targeting peripheral T-cell lymphoma and other haematological malignancies.

Recently released data around CAR natural killer cells are suggestive of good efficacy with lower rates of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome in diseases including acute lymphoblastic leukaemia, acute myeloid leukaemia and CD19-positive lymphomas.[21] Future directions may also involve earlier use of CAR-T therapy rather than waiting for the failure of two previous therapies.[14,22]

Allogeneic CAR-T therapy offers the possibility of treatment with an off-the-shelf product without the need to harvest autologous cells. This may prove to be more efficient, but will need to be balanced against the risk of graft versus host disease from the introduced T-cell population. Preliminary studies have shown favourable results for treatment of solid organ tumours such as glioblastoma multiforme and certain breast cancer targets.[23]

Conclusion

CAR-T products increase complete responses to therapy, representing a new chance at achieving prolonged remission for patients who had previously exhausted almost all other treatments. Since the initial trials, the development of protocols for managing cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome has resulted in reduced rates of complications while preserving efficacy.

CAR-based technology may offer a genuine transformation in managing haematological malignancies, potentially augmenting or replacing courses of non- specific chemotherapy to provide superior outcomes with lower morbidity and mortality. It may become more accessible in the future. ◀

Conflicts of interest: Vinay Vanguru participates in advisory boards and educational talks for Novartis, Gilead and Janssen. Phoebe Ho participates in an advisory board, with no honorarium, for Gilead.

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