New drugs

Axicabtagene ciloleucel

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Approved indication: B-cell lymphoma

Yescarta (Gilead)
cryostorage bag containing 1 x 10^6 – 2.4 x 10^6 cells/kg suspension for infusion.

The large B-cell lymphomas are a common type of non-Hodgkin lymphoma. Although treatment can cure many patients, those with refractory or relapsed disease have a poor prognosis. The median survival is approximately six months. Current salvage regimens are not very effective so other therapies are being investigated.

Many B-cell cancers express the CD19 antigen, so this has become a target for immunotherapy. Chimeric antigen receptor (CAR) T-cell therapy is one approach. The patient's own T cells are collected by leukapheresis. They are then genetically engineered to recognise the CD19 antigen. Large numbers of these anti-CD19 CAR T cells are produced then infused back into the patient.

Axicabtagene ciloleucel is a CAR T-cell therapy that, on binding to the CD19 antigen, has cytolytic activity and stimulates T-cell proliferation and the release of cytokines. The concentration of T cells peaks within 7–14 days of infusion. Cytokines and chemokines also peak within 14 days with concentrations returning to normal within 28 days.

The efficacy of axicabtagene ciloleucel was assessed in a phase II trial involving patients with refractory disease. Most had diffuse large B-cell lymphoma, but patients with primary mediastinal B-cell lymphoma or transformed follicular lymphoma were also included. All the patients were given chemotherapy a few days before the infusion of axicabtagene ciloleucel. A total of 101 patients were treated. When evaluated at least six months after the infusion, the objective response rate was 82% with 54% being complete responses. After a median follow-up of 15.4 months there was still a response in 42% of the patients. The median duration of the response was 8.1 months.[1]

The 101 patients were evaluated again after a median follow-up of 27.1 months. By then 61 patients had died or had progressive disease. The objective response rate was 83% with 58% having had a complete response. The median duration of the response was 11.1 months, with the median progression-free survival being 5.9 months. While median overall survival could not be calculated, the estimated two-year survival was 50.5%.[2]

The patients in the phase II trial had already received at least two treatments and were given lymphodepleting chemotherapy before being infused with axicabtagene ciloleucel. They all experienced adverse events which were at least grade 3 (severe) in 95%. The most frequent adverse events were fever, neutropenia, anaemia, thrombocytopenia and hypotension.[1] As axicabtagene ciloleucel causes cytokine secretion, most patients will develop a cytokine-release syndrome. This emerged in a median of two days and persisted for a median of eight days after the infusion. The deaths of two of the 101 patients were associated with the cytokine-release syndrome.

Axicabtagene ciloleucel should not be given to patients with active inflammation or infection. The therapy is also neurotoxic. Many patients will experience toxicities, such as encephalopathy, within a week of the infusion. Common presentations include confusion, tremor and aphasia.[1] CAR T-cell therapy places patients at risk of infection. As CD19 is found on normal B cells, some patients develop B-cell aplasia and hypogammaglobulinaemia. During the phase II trial 35% of the patients developed febrile neutropenia.[1]

It is still early days in the evolution of CAR T-cell therapy. On the data available so far, the response rate of 82% for axicabtagene ciloleucel in refractory disease is higher than the response rate of 20% seen in historical controls.[1] A favourable response is more likely in patients with high numbers of anti-CD19 CAR T cells, but it is not yet known if this will result in longer overall survival or improve the quality of life.[2]

T manufacturer provided the product information

REFERENCES

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2. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet Oncol 2019; 20: 31–42. https://doi.org/10.1016/S1470-2045(18)30864-7

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.

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