NEW DRUGS

New drugs

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Brexucabtagene autoleucel

Approved indication: mantle cell lymphoma, B-cell precursor acute lymphoblastic leukaemia

Tecartus (Gilead)
infusion bag containing 1 x 10^6 – 2 x 10^6 cells/kg suspension

Chimeric antigen receptor T-cell (CAR-T) therapy is a new anticancer treatment. The patient's T cells are harvested then genetically engineered to express chimeric antigen receptors that will bind to a protein expressed on cancer cells. Patients are given lymphodepleting chemotherapy before they are infused with their modified T cells. The first CAR-T therapies approved for use in Australia were tisagenlecleucel in 2019 and axicabtagene ciloleucel in 2020. Brexucabtagene autoleucel is another CAR-T therapy, which has been approved for adults with relapsed or refractory mantle cell lymphoma who have received at least two other treatments, and for adults with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia.

The target for the autologous T cells contained in brexucabtagene autoleucel is a transmembrane protein called CD19 located on neoplastic B cells or precursor B cells. The reinfused T cells bind to CD19, leading to T-cell activation and proliferation, and the secretion of cytokines such as interleukins. These effects lead to the death of cells expressing CD19. The anti-CD19 CAR T cells peak within two weeks of the infusion then decline over three to six months. Cytokine concentrations peak within the first eight days after infusion and return to baseline within one month.

Mantle cell lymphoma is an aggressive non-Hodgkin lymphoma. The approval of brexucabtagene autoleucel for this indication appears to be mainly based on an uncontrolled, open-label, phase II trial – ZUMA-2. The trial involved 74 patients with relapsed or refractory mantle cell lymphoma despite a median of three previous therapies, including a Bruton's tyrosine kinase inhibitor. Brexucabtagene autoleucel was successfully manufactured and administered to 68 patients. A primary efficacy analysis took place after 60 patients had been treated and followed for at least seven months.[1]

An independent radiology review committee reported that 93% of patients had an objective response to brexucabtagene autoleucel with 67% having a complete response. These responses were related to the number of anti-CD19 CAR T cells in the blood. The median time to a complete response was three months. After a median follow-up of 12.3 months, 57% of patients were in remission. The estimated progression-free survival at one year was 61%.[1]

The ZUMA-3 trial studied the use of brexucabtagene autoleucel in patients with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia. In this uncontrolled, open-label, phase II trial, brexucabtagene autoleucel was successfully manufactured and reinfused into 55 patients. After a median follow-up of 16.4 months, 56% of patients had a complete remission and 15% had a complete remission but with incomplete haematological recovery. These remissions had a median duration of 12.8 months.[2]

Patients receiving CAR-T therapy are at risk of adverse effects from the lymphodepleting chemotherapy as well as brexucabtagene autoleucel. The CD19 protein is found on normal B cells as well as cancer cells. In the ZUMA-2 trial, 99% of patients had an adverse event of grade 3 or higher and two patients died from adverse events.[1] In ZUMA-3, 95% of patients had an adverse event of grade 3 or higher and six patients died from adverse events.[2] The frequent serious adverse events include anaemia, neutropenia and thrombocytopenia. Patients are also at risk of severe infections.

The release of cytokines is to be expected because of brexucabtagene autoleucel's mechanism of action and approximately 90% of patients will develop the potentially fatal cytokine release syndrome within a few days of the infusion. Symptoms of cytokine release syndrome include fever, hypotension and tachycardia. The severity of the syndrome guides its management. In the trials, approximately 60% of patients treated with brexucabtagene autoleucel also had neurological adverse effects including encephalopathy. Other adverse effects include hypokalaemia, hypophosphataemia and hypogammaglobulinaemia. The major long-term complication of CAR-T therapy is persistent cytopenia.

For patients with relapsed or refractory cancers, the median overall survival is usually less than a year. Although it has many serious adverse effects and the data to support its use are from uncontrolled trials, brexucabtagene autoleucel may improve patient outcomes. In mantle cell lymphoma, a later

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analysis of the ZUMA-2 trial reported a median overall survival of 46.6 months after a median follow-up of 35.6 months.[3] For patients with eligible forms of acute lymphoblastic leukaemia, treatment resulted in a median overall survival of 18.2 months.[2]

T manufacturer provided the product information

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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, the European Medicines Agency and the Therapeutic Goods Administration.