NEW DRUGS

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Tisagenlecleucel

Approved indication: B-cell cancers

Kymriah (Novartis)
infusion bag containing modified autologous T cells

Tisagenlecleucel is a genetically modified cell therapy developed for relapsed and refractory B-cell cancers. It is specifically approved for children and young adults (≤25 years old) with B-cell precursor acute lymphoblastic leukaemia, and for adults with diffuse large B-cell lymphoma (the most common form of non-Hodgkin lymphoma).

This product is prepared using the patient's own T cells. These are harvested from blood, then, in the laboratory, a transgene is introduced which encodes a protein called chimeric antigen receptor (CAR). This receptor is expressed on the surface of the T cells and allows them to bind to the CD19 antigen on B cells and precursor B cells. This binding activates inflammatory cytokines and destroys the CD19-positive cells.

Before the modified T cells are administered, the patient is given a short course of chemotherapy (2–4 days) to deplete their lymphocytes. To reduce the risk of an infusion reaction to tisagenlecleucel, patients are given paracetamol and an antihistamine 30–60 minutes beforehand.

The approval of tisagenlecleucel is based on two open-label, phase II trials – one in B-cell precursor acute lymphoblastic leukaemia[1] and the other in diffuse large B-cell lymphoma.[2] Both trials were single-arm studies.

One of the trials enrolled 75 patients with B-cell lymphoblastic leukaemia.[1] They were aged 3–23 years at baseline and had at least 5% lymphoblasts in their bone marrow at screening. Participants had received a median of three previous therapies and 46 of them had had an allogeneic stem cell transplant (using cells from another person).

Following lymphodepleting chemotherapy, participants were given a single infusion of tisagenlecleucel (median dose of 3.1×10^6 T cells/kg). The primary end point of the trial was an overall remission rate of more than 20%. This was defined as complete remission or complete remission with incomplete blood count recovery that lasted for at least 28 days.

In patients with at least three months follow-up, the remission rate was 81%. The event-free survival rate was 73% at six months and 50% at 12 months. The overall survival rate was 90% at six months and 76% at 12 months.[1]

In the other trial, tisagenlecleucel was assessed in 93 adults with relapsed or refractory diffuse large B-cell lymphoma.[2] The participants had previously received at least two lines of therapy.

After lymphodepleting therapy, patients were given a median of 3.0×10^8 cells by infusion. The best overall response was 52% (40% had a complete response and 12% had a partial response). The estimated probability of overall survival at 12 months was 49%. In those who had a complete response, this was 90%.[2]

Tisagenlecleucel has several serious and sometimes fatal adverse effects. Patients need to be closely monitored in the first week after infusion and need to stay within two hours of the facility where they received the infusion for the first month.

Cytokine release syndrome is very common with tisagenlecleucel. This is an inflammatory reaction that can cause hypotension, pulmonary oedema and coagulopathy and result in multiorgan failure. In the leukaemia trial, 81% of patients in the safety cohort developed cytokine release syndrome – 44% of these cases were severe. In the lymphoma trial, 58% of patients were affected including 22% who were severely affected. The median onset of these reactions was three days and their duration was 7–8 days. The anti-interleukin-6 antibody, tocilizumab, can be used to treat moderate to severe cases. A minimum of four doses of the drug should be kept on hand before the infusion is started. Corticosteroids may be used in life-threatening cases. Emergency equipment should also be available. Risk factors for severe cytokine release syndrome in leukaemia patients include high tumour burden, progressive disease following lymphodepleting therapy, infection and fever.

Febrile neutropenia was very common, as were infections (67% of the leukaemia cohort and 54% of the lymphoma cohort). These were fatal in some cases.

Encephalopathy and confusion or delirium were frequently reported – 38% in the leukaemia trial and 21% in the lymphoma trial. Headache was also very common in both trials (35% and 23%), as were nausea, diarrhoea, hypotension, tachycardia, acute kidney injury and hypokalaemia. A third of children and young adults with leukaemia had elevated liver enzymes.

In the leukaemia study, there were seven deaths that were not related to disease progression. Two of them occurred within 30 days of the infusion. Causes included embolic stroke related to mycosis, cerebral haemorrhage (in the context of coagulopathy and resolving cytokine release syndrome), encephalitis after prolonged neutropenia and lymphopenia, and mycosis.

There were eight deaths in the lymphoma trial that were not related to disease progression. They all occurred at least 30 days after the infusion. Causes included multiple organ failure, cerebral haemorrhage,

haemorrhage of a duodenal ulcer, pulmonary haemorrhage, chronic kidney disease, neuroendocrine carcinoma and sepsis.

Treatment with tisagenlecleucel should be delayed if someone has unresolved adverse effects from chemotherapy, uncontrolled infection, graft versus host disease, or rapidly progressing leukaemia or lymphoma. There is limited experience with this drug in patients who have active leukaemia or lymphoma in the CNS.

Treatment is not recommended in people with HIV or hepatitis B or C. Live vaccines should not be given for at least six weeks before tisagenlecleucel therapy and until the patient's immune system has recovered following treatment.

After administration of tisagenlecleucel, the modified T cells undergo clonal expansion followed by a slow decline. The tisagenlecleucel transgene has been shown to persist in blood and bone marrow for up to two years after the infusion in some patients.

Tisagenlecleucel is the first chimeric antigen receptor therapy to be approved in Australia. Although response rates seemed high (81% in acute lymphoblastic leukaemia and 52% in lymphoma), it is hard to quantify efficacy as there were no comparators in the trials. Doctors and their patients also need to consider the serious and life-threatening toxicities that can occur with this therapy.

T T manufacturer provided additional useful information

REFERENCES

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2. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45-56. https://doi.org/10.1056/NEJMoa1804980

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 website of the European Medicines Agency.