NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Tabelecleucel for treating post-transplant lymphoproliferative disorder caused by the Epstein-Barr virus

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of tabelecleucel within its marketing authorisation for previously treated post-transplant lymphoproliferative disorder caused by the Epstein-Barr virus.

Background

Allogeneic haematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for a range of malignant and non-malignant blood disorders. An allogeneic HSCT involves replacing the bone marrow stem cells of a patient with stem cells from a tissue-type matched or mismatched donor. Solid organ transplants (SOTs) are used to treat a range of conditions affecting organs including the heart, kidneys, lungs, liver and pancreas. Before either an allogeneic HSCT or a SOT, the body's immune system is weakened by chemotherapy and immunosuppressants to prepare the body to receive the transplant.

Post-transplant lymphoproliferative disorders (PTLDs) are characterised by the over production of lymphoid cells in people who have had an allogeneic HSCT or a SOT. Approximately two-thirds of cases of PTLD are associated with Epstein-Barr Virus (EBV).[2] EBV is a very common human herpes virus which causes infectious mononucleosis (glandular fever). Children are often infected from an early age and the virus is carried by approximately 95% of healthy adults.[1] Post-transplant immunosuppression can result in reactivation of EBV in donor or host cells and can limit the immune response needed to clear the infection.[2] The 4 categories of PTLD are non-destructive, polymorphic, monomorphic and classical Hodgkin lymphoma. Monomorphic PTLD is the most common type of PTLD and includes diffuse large B-cell lymphoma and Burkitt lymphoma.[3]

Common signs and symptoms of PTLD include painless lumps in the neck, armpit or groin, fever, fatigue, weight loss and night sweats.[3] The prognosis of PTLD depends on its morphological subtype, whether it follows an HSCT or SOT and the time it develops after transplant. For example, around 80% of people who have PTLD within 1 year of a SOT are cured with current treatments, whereas outcomes for people in whom PTLD develops later after a SOT are poorer. The prognosis is worse for people with PTLD after HSCT, who have an expected 3-year survival of 20%.[2]

Across the UK, 1,726 allogeneic HSCTs were completed in 2019 and 1,476 were completed in 2020.[4,5] In England, 4,055 SOTs were completed between 2019 and 2020 and 3,565 were completed between 2021 and 2022.[6] Around 2% of people who have had an HSCT develop PTLD compared with around 20% of people who have had a SOT.[7] The incidence of PTLD varies by type of organ transplant and in adults is highest among people who have had multiple organ and intestinal transplants.[8]

For people with PTLD after a SOT, British Society for Haematology guidelines recommend an immediate reduction in immunosuppression where possible.[8] If the disease does not respond, rituximab monotherapy is recommended for people with CD20-positive PTLD.[8] Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) is recommended for people who do not have complete remission with rituximab alone or who have clinically aggressive disease.[8] There are no established treatments for PTLD after a SOT that is relapsed or refractory to R-CHOP.[2] Radiotherapy may be offered for localised disease or specific histological subtypes alongside a reduction in immunosuppression.[8]

For people with PTLD after an HSCT, a reduction in immunosuppression is not usually feasible because of the risk of graph versus host disease and graft rejection.[2] Rituximab monotherapy is a first-line treatment option for people with CD20-positive PTLD.[2] Chemotherapy is not usually effective but can be offered as salvage therapy given the limited treatment options available.[2]

The technology

Tabelecleucel (brand name unknown, Pierre Fabre) is an allogeneic T-cell therapy that specifically targets EBV proteins. Volunteer donor-derived T-cells are stimulated with EBV antigen presenting cells, resulting in expansion of T-cells active against EBV-infected targets. It is administered intravenously.

Tabelecleucel does not currently have a marketing authorisation in the UK for treating PTLD caused by EBV. It is being studied in a phase 3 single-arm clinical trial in people with EBV-positive PTLD:

- after a SOT, for whom rituximab alone or in combination with chemotherapy was not effective, and
- after an allogeneic HSCT, for whom rituximab alone was not effective.

Intervention(s)	Tabelecleucel
Population(s)	People with previously treated EBV-positive post-transplant lymphoproliferative disorder
Subgroups	If the evidence allows the following subgroups will be considered: • people who have EBV-positive PTLD after SOT(s) • people who have EBV-positive PTLD after allogeneic HSCT(s). • people who have had more than one previous treatment

Comparators	For people who have EBV-positive PTLD after SOT who have had rituximab monotherapy: • rituximab with chemotherapy • radiotherapy • best supportive care For people who have EBV-positive PTLD after SOT who have had rituximab in combination with chemotherapy: • radiotherapy • best supportive care For people who have EBV-positive PTLD after allogeneic HSCT who have had rituximab monotherapy: • chemotherapy • best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • response rate • duration of response • rate of allograft loss or transplant rejection • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should taken into account. The costs of diagnostic testing for EBV-positive PTLD should be included.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	None
Related National Policy	NHS England (2019) The NHS long term plan NHS England (2017) Second allogenic haematopoietic stem cell transplant for relapsed disease (all ages). Clinical commissioning Policy. Reference NHS England 16068/P NHS England (January 2015) Haematopoietic stem cell transplantation (HSCT) (All Ages): Revised. Clinical commissioning policy. Reference: NHSCB/B04/P/a NHS England (June 2013) NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). Reference B04/S/a NHS England (June 2013) NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Children). Reference B04/S/b NHS England (June 2013) NHS Standard Contract for Liver Transplantation Service (Children). Reference E03/S(HSS)/a NHS England (2020) Allogeneic Haematopoietic Stem Cell Transplantation for adults with sickle cell disease. Clinical commissioning policy. Reference no: 190138/P NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapters 15, 22, 29, 56A, 57, 68, 69, 85, 100, 103, 105, 127, 138, 139B

Questions for consultation

Where do you consider tabelecleucel will fit into the existing care pathway for PTLD caused by EBV?

Would tabelecleucel treatment be suitable for people whose disease has not responded to more than one prior therapy?

What proportion of people have CD20-positive PTLD? What is the treatment pathway for people who are not eligible for rituximab?

Have all relevant comparators for tabelecleucel been included in the scope? In particular, would any treatments recommended by NICE for lymphomas be used to treat this condition?

Are the outcomes listed appropriate?

Is this progressive condition? Is progression-free survival a relevant outcome?

Are the subgroups suggested appropriate? Are there any other subgroups in whom tabelecleucel is expected to be more clinically effective or cost effective, or other groups that should be examined separately?

Is EBV routinely tested for in people who have PTLD in the NHS?

Would tabelecleucel be a candidate for managed access?

Do you consider tabelecleucel to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of tabelecleucel can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which tabelecleucel will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

References

1. Kuri A, Jacobs BM, Vickaryous N et al. (2020) Epidemiology of Epstein-Barr virus infection and infectious mononucleosis in the United Kingdom. BMC Public Health 20, 912.

2. DeStefano C, Desai S, Shenoy A, et al. (2018) Management of post-transplant lymphoproliferative disorders. British Journal of Haematology 182: 330-343.

3. Lymphoma Action (2021) Post-transplant lymphoproliferative disorder (PTLD). Accessed May 2022.

4. British Society of Blood and Marrow Transplantation (2020) BSBMTCT Registry Annual Activity 2019. Accessed May 2022.

5. British Society of Blood and Marrow Transplantation (2020) BSBMTCT Registry Annual Activity 2020. Accessed May 2022.

6. NHS Blood and Transplant (2022) Organ Donation and Transplantation Activity Data: England. Accessed May 2022.

7. Gupta D, Mendonca S, Chakraborty S et al. (2019) Post Transplant Lymphoproliferative Disorder. Indian Journal of Hematology & Blood Transfusion 36(2): 229-237.

8. Shah N, Eyre T, Tucker D et al. (2021) Front-line management of post-transplantation lymphoproliferative disorder in adult solid organ recipient patients — A British Society for Haematology Guideline. British Journal of Haematology 193: 727-740.