NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of tisagenlecleucel-T within its marketing authorisation for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years.

Background

Acute lymphoblastic leukaemia (ALL) is a cancer of lymphocyte-producing cells. Lymphocytes are white blood cells that are vital for the body's immune system. In ALL there is an excess production of immature lymphocyte-precursor cells, called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the numbers of red cells, white cells and platelets in the blood. ALL can be classified into 3 groups based on immunophenotyping: B-precursor ALL (also known as precursor-B-cell ALL), mature B-cell ALL and T-cell ALL.[1] B-precursor ALL is characterised by the presence of cytoplasmic immunoglobulins and CD10, CD19, CD22 and CD79a expression. A specific chromosomal abnormality known as the 'Philadelphia chromosome' is present in around 3-5% of ALL in children and 25% of adult ALL.[2]

ALL is most common in children, adolescents and young adults, with around 65% of cases diagnosed in people aged under 25.[3] A second increase in incidence is observed in people aged over 60 (around 13% of cases).[3] It is also more common in males (around 6 out of 10 cases) than females.[1,3] In the UK, around 440 cases of ALL are diagnosed in children each year.[4]

The aim of treatment in ALL is to achieve a cure. Treatment for newly diagnosed ALL can take up to 3 years to complete and is generally divided into 3 phases: induction, consolidation and maintenance.

During induction, newly diagnosed ALL in children and adults is generally treated with chemotherapy combinations including vincristine, an anthracycline and asparaginase. NICE technology appraisal guidance 408 recommends pegaspargase (a polyethylene glycol conjugate of E. coli-derived L-asparaginase) as part of antineoplastic combination therapy, as an option for treating ALL in children, young people and adults when they have untreated newly diagnosed disease. A tyrosine kinase inhibitor (such as imatinib or dasatinib) can be used for treating Philadelphia-chromosome-positive ALL. Consolidation treatment typically includes intensified chemotherapy, followed by low-dose chemotherapy in the maintenance phase. For high risk ALL, stem cell transplantation may also be used as consolidation therapy.[5,6]

The overall survival rate is approximately 90% for children and 60% for adolescents and young adults at 5 years.[7] Most children with ALL are cured of the disease,[1] but around 10% of ALL in children relapses and requires further treatment.[8] Recent non-

UK studies show that relapsed childhood ALL has an overall five-year survival of around 50%.[9,10] The likelihood of ALL relapse is higher in adults and is around 45%.[11] There is no universally accepted treatment approach for relapsed or refractory ALL.[6] Treatment may include conventional combination chemotherapy and for most people this would be fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG) with idarubicin. Off-label clofarabine may be used in children and young adults. People with Philadelphia-chromosome-positive relapsed or refractory disease can have a tyrosine kinase inhibitor alone or in combination with conventional chemotherapy. In adults with relapsed or refractory disease, NICE technology appraisals recommend targeted treatments:

- TA450 recommends blinatumomab as an option for Philadelphia-chromosome-negative relapsed or refractory precursor B-cell ALL in adults.
- TA451 recommends ponatinib as an option for Philadelphia-chromosome-positive ALL in adults with the T315I gene mutation or for whom dasatinib or imatinib cannot be used.
- TA541 recommends inotuzumab ozogamicin as an option for treating relapsed or refractory CD22-positive B-cell precursor ALL in adults.

NICE technology appraisals also recommend chimeric antigen receptor T-cell (CAR-T) therapies, immunotherapies that uses a patient's own immune cells that have been genetically modified to treat their cancer:

- TA554 recommends tisagenlecleucel therapy for use within the Cancer Drugs Fund as an option for treating relapsed or refractory B-cell ALL in people aged up to 25. This appraisal will update and replace technology appraisal 554.
- TA893 recommends brexucabtagene autoleucel for treating relapsed or refractory B-cell ALL in people 26 years or older.

Other treatment options may include stem cell transplantation if a suitable donor can be found, or best supportive care (including palliative care).

The technology

Tisagenlecleucel-T (Kymriah, Novartis) is administered intravenously as a single infusion. It has a marketing authorisation in the UK for for treating paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia that is refractory, in relapse post-transplant or in second or later relapse.

Intervention(s)	Tisagenlecleucel-T
Population(s)	Children and young adults up to 25 years of age with B-cell acute lymphoblastic leukaemia that is refractory, in relapse post-transplant or in second or later relapse

Comparators	Established clinical management without tisagenlecleucel-T including: • fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy • clofarabine • inotuzumab ozogamicin (CD22-positive B-precursor ALL) • blinatumomab (Philadelphia-chromosome-negative ALL) • a tyrosine kinase inhibitor such as dasatinib, imatinib or ponatinib alone or in combination with FLAG-based combination chemotherapy (Philadelphia-chromosome-positive ALL) • stem cell transplantation • best supportive care (including palliative care)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival (including relapse-free and event-free survival) • response rate (including minimal residual disease and haematologic responses and complete remission) • rate of allogeneic stem cell transplant • 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.

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	**Related technology appraisals:** Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over (2023) NICE technology appraisal guidance 893 Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (2018) NICE technology appraisal guidance 554 Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (2018) NICE technology appraisal guidance 541 Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (2017) NICE technology appraisal guidance 451 Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (2017) NICE technology appraisal guidance 450 Pegaspargase for treating acute lymphoblastic leukaemia (2016) NICE technology appraisal guidance 408 **Related technology appraisals in development:** KTE-X19 for previously treated B-precursor acute lymphoblastic leukaemia in people aged 2 to 21. NICE technology appraisal guidance. [ID1336] Publication date to be confirmed **Related NICE guidelines:** Haematological cancers: improving outcomes (2016) NICE guideline NG47. **Related quality standards:** Haematological cancers (2017) NICE quality standard 150
Related National Policy	NHS England (2021) Addition of rituximab to first-line standard chemotherapy for CD20 positive B-cell precursor acute lymphoblastic leukaemia (Adults). Clinical commissioning policy. Reference no. [P200901P] (URN: 1748) The NHS Long Term Plan (2019) NHS Long Term Plan NHS England (2018) Arsenic trioxide for the treatment of high risk acute promyelocytic leukaemia (all ages). Clinical commissioning policy. Reference no. 170072P

	NHS England (2017) NHS Medicines for Children's Policy

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7. National Comprehensive Cancer Network (2021) NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukaemia. Version 2.2021.
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10. Rheingold SR, Ji L, Xu X, et al (2019). Prognostic factors for survival after relapsed acute lymphoblastic leukemia (ALL): a Children's Oncology Group (COG) study. J Clin Oncol. 37(15).
11. Fielding AK, Richards SM, Chopra R et al. (2007) Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood 109(3):944-50.