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Axicabtagene ciloleucel IV for relapsed/refractory acute lymphoblastic leukaemia in children and adolecents (aged 2-21 years) – second line

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LAY SUMMARY

Acute Lymphoblastic Leukaemia (ALL) is a type of cancer affecting lymphocytes (a type of white blood cell), which results in overproduction of faulty lymphocytes. This means there are not enough healthy lymphocytes available to fight infection, increasing the risk of infections and bleeding. ALL most commonly occurs in children aged 2 to 5 years old. However it is considered a rare condition, affecting around 650 people per year in the UK. Some people will not respond to treatment (refractory) or some will respond to treatment but develop ALL again (relapsed). For those with relapsed or refractory ALL, there are limited treatments available.

Axicabtagene ciloleucel (KTE-C19) is new type of therapy where T cells (a type of immune cell) are altered to display receptors which recognise molecules on the surface of cancer cells and trigger the T cells to attack and kill the cancer cells. Axicabtagene ciloleucel is given to patients by a single infusion. If axicabtagene ciloleucel was licenced for use in children and adolescents with refractory/relapsed acute lymphoblastic leukaemia it would provide an additional, cancer specific treatment option for this population.

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TARGET GROUP

Acute Lymphoblastic Leukaemia (ALL); B-precursor; primary refractory/relapsed disease after second or later therapy, or relapse after transplant; paediatric and adolescent (2-21 years) patients – second line

TECHNOLOGY

DESCRIPTION

Axicabtagene ciloleucel (anti-CD19 CAR T cell therapy; KTE-C19 CAR; KTEC-19) is a therapy comprised of genetically engineered autologous T cells with anti-CD19 Chimeric Antigen Receptors (CARs). The CAR consists of an antibody fragment (or target binding domain) which allows the CAR to recognise CD19, which is present on the surface of cancer cells, and signalling domains which activates the T cells to attack and kill the cancer cells.[1] Axicabtagene ciloleucel is intended for use in the treatment of various cancers.

In the phase I/II study, axicabtagene ciloleucel is administered intravenously by a single infusion 0.5 x 10*6 – 2 x 10*6 anti-CD19 CAR T cells/kg following a chemotherapy regimen of fludarabine and cyclophosphamide.[16]

Axicabtagene ciloleucel does not currently have Marketing Authorisation in the EU for any indication.

Axicabtagene ciloleucel, manufactured by a slightly different process, is currently in pre-registration in the EU for use in Diffuse Large B-cell Lymphoma, Primary Mediastinal B-cell Lymphoma, and transformed Follicular Lymphoma.

Axicabtagene ciloleucel is currently in phase II trials for Mantle cell Lymphoma (second line therapy) and phase III trials for Acute Lymphoblastic Leukaemia in adults.

INNOVATION and/or ADVANTAGES

If licensed, axicabtagene ciloleucel will offer an additional treatment option for children and adolescents with relapsed/refractory Acute Lymphoblastic Leukaemia, for which there are few available treatments. As a targeted immunotherapy, axicabtagene ciloleucel may have the potential to improve remission rates in children and adults with relapsed/refractory B-precursor ALL after second of later therapy or after transplant.[2]

DEVELOPER

Kite Pharma

AVAILABILITY, LAUNCH or MARKETING

Axicabtagene ciloleucel is designated EU Orphan drug status for:

- Diffuse large B-cell lymphoma (December 2014)
- Mantle cell lymphoma (September 2015)
- Follicular lymphoma (November 2015)
- Acute lymphoblastic leukaemia (November 2015)

- Chronic Lymphoblastic Leukaemia (November 2015)

Axicabtagene ciloleucel was awarded PRIME status for diffuse large B-cell lymphoma by the European Medicines Agency (EMA) in June 2016.

Axicabtagene ciloleucel is designated US Orphan drug status for:

- Diffuse large B-cell lymphoma (March 2014)
- Mantle cell lymphoma (May 2016)
- Follicular lymphoma (May 2016)
- Acute lymphoblastic leukaemia (April 2016)
- Chronic Lymphoblastic Leukaemia (April 2016)
- Primary Mediastinal B-cell Lymphoma (April 2016)

Axicabtagene ciloleucel was designated Breakthrough Therapy for Follicular lymphoma, Diffuse Large B-cell lymphoma and Primary Mediastinal B-cell lymphoma by the Food and Drugs Administration (FDA) in the US in December 2015.

PATIENT GROUP

BACKGROUND

Acute Lymphocytic Leukaemia (ALL) is a form of white blood cell cancer in which lymphoblast cells are overproduced and, as the name suggests, the disease develops acutely over days to weeks. As these cancerous lymphoblast cells do not mature they cannot fight infections (as normal white blood cells do). Overproduction of cancerous ALL cells also mean the cells fill space within the bone marrow, meaning there is inadequate space in the bone marrow to produce healthy platelets, white and red blood cells. ALL can spread to other parts of the body (commonly the lymph nodes, liver, spleen, CNS and testicles) causing swelling and dysfunction of those organs.[3, 4] There are two types of ALL; B-lymphoblastic leukaemia and T-lymphoblastic leukaemia, named after the white blood cell which has become cancerous. B-precursor ALL affect the Precursor cells and is the most common type of ALL in adults. ALL of the mature B cells is characterised by genetic changes and is known as Burkitt type ALL. T-precursor ALL affect the precursor T cells and is more likely to occur in young adults and men.[5]

ALL is a rare condition, affecting approximately 650 people per year in the UK. It is more common in adult females and children, with 85% of cases affecting those <15 years old (most commonly between 2 to 5 years old). Most symptoms in ALL are caused by lack of available healthy blood cells and include; pale skin, tiredness, breathlessness, frequent infections, unusual and frequent bleeding (e.g. bleeding gums and nose bleeds), high temperature, night sweats, bone and joint pain, swollen lymph nodes, liver and spleen, weight loss and purple skin rash (purpura).[6] It is unclear what causes the genetic mutations which result in ALL, but several risk factors to the development of ALL have been identified, which include; presence of certain genetic disorder (Down's syndrome, Fanconi anaemia and ataxia telangiectasia), previous chemotherapy (related the amount of treatment received and types of chemotherapy medicines – etoposide, mitoxantrone, amsacrine and idarubicin), being obese or overweight, having a weakened immune system (e.g. from HIV/AIDS), exposure to radiation and benzene and prenatal exposure to smoking and caffeine.[6, 7]

ALL can cause numerous physical complications which can all impact on general health and quality of life including increase frequency and severity of infections and potential for serious bleeding (although

this is rare) including intracranial, pulmonary and gastrointestinal haemorrhages. Treatments used in ALL can also cause temporary and sometimes permanent infertility, particularly in those receiving high doses of chemotherapy and radiotherapy in preparation for stem cell and bone marrow transplants. Being diagnosed with leukaemia can be very psychologically distressing and stressful for children with ALL and their parents and could trigger anxiety and depression.[8]

CLINICAL NEED and BURDEN OF DISEASE

In 2014 in the UK there was 758 new cases of ALL which equates to 1 per 100,000 people. 449 cases were in males (59%) and 309 (41%) in females, equating to a male: female incidence ratio of 15:10. ALL incidence is highest in children aged 0 to 4 years old at a rate of 6.4 per 100,000 in males (132 cases) and 5.6 per 100,000 in females (109 cases) in 2012-2014. Incidence rates then decrease as age increases with incidence rates of 3.6 and 2.9 per 100,000 for males and females aged 5 to 9 years, 2.2 and 1.4 per 100,000 for males and females aged 10 to 14 years and 1.6 and 0.9 per 100,000 for males and females aged 15 to 19 years in 2012 to 2014.[9]

ALL survival depends on age at diagnosis (with younger people having a better prognosis), and stage of ALL at diagnosis (with a poorer prognosis associated with presence of leukaemia cells in the CNS). There are no UK wide statistics for ALL survival. Data from the National Cancer Intelligence Network (NCIN) of ALL survival in England from 2008 to 2010 concluded:[10]

- 70% of all people with ALL will survive five years or more after diagnosis
- 90% people below 14 years with ALL will survive five years or more after diagnosis
- 70% people between 15 and 24 years old with ALL will survive five years or more after diagnosis
- 40% people aged between 25 and 64 years old with ALL will survive five years or more after diagnosis
- 15% people above 65 years old with ALL will survive five years or more after diagnosis

ALL accounts for less than 1% of cancer deaths in the UK (based on 2014 data) at a total of 238 deaths. Of these, 52% (n=123) of deaths were in males and 48% (n= 115) of deaths were in females (ratio of 11:10). Age standardised rates of ALL mortality in the UK in 2014 were 0.4 per 100,000 people. Mortality is strongly associated with age, with mortality rates increasing as age increases. ALL mortality is generally lowest in children, with mortality (between 2012 to 2014) at a rate of 0.2 and 0.3 per 100,000 in males and females respectively in children aged 0 to 4 years old, 0.2 per 100,000 in male and female children aged 5 to 14 years old and 0.4 and 0.1 per 100,000 in male and female children aged 15 to 19 years respectively.[11]

In 2015 to 2016, there were 60,087 admissions (21,003 aged 0 to 18 years) for lymphoid leukaemia (ICD-10: C91) in England, resulting in 68,028 bed days and 62,290 finished consultant episodes.[12]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Leukaemia (acute lymphoblastic) – dasatinib (ID386). Expected date of issue to be confirmed.

- NICE technology appraisal guidance in development. Clofarabine for treating acute lymphoblastic leukaemia in children after 2 therapies (ID1033). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Leukaemia (acute lymphoblastic) – erythrocyte encapsulated asparaginase (ID864). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Blinatumomab for treating Philadelphia chromosome positive relapsed or refractory acute lymphoblastic leukaemia (ID1008). Expected 24 October 2018.
- NICE technology appraisal guidance in development. Blinatumomab for acute lymphoblastic leukaemia (ID1036). Expected 18 July 2018.
- NICE technology appraisal guidance in development. Nelarabine for treating acute lymphoblastic leukaemia after two therapies (ID1034). Expected 27 December 2017.
- NICE Technology appraisal guidance in development. Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia (ID893). Expected 27 September 2017.
- NICE technology appraisal guidance. Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (TA451). June 2017.
- NICE technology appraisal guidance. Blinatumomab for previously treated Philadelphia chromosome negative acute lymphoblastic leukaemia (TA450). June 2017.
- NICE technology appraisal guidance. Pegaspargase for treating acute lymphoblastic leukaemia (TA408). September 2016.

- NICE guidance. Haematological cancers: improving outcomes (NG47). May 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (adult). B04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Medical Genetics (all ages). E01/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.
- NHS England. Clinical Commissioning Policy: Second allogenic haematopoietic stem cell transplant for relapsed disease (all ages). NHSE 16068/P. February 2017.

OTHER GUIDANCE

- *D. Hoelzer, R. Bassan, H. Dombret, A. Fielding, J. M. Ribera and C. Buske.* Acute Lymphoblastic Leukaemia: ESMO Clinical Practice Guidelines. *Ann Oncol* (2016) 27 (suppl 5): v69-v82.
- The National Comprehensive Cancer Network. Acute Lymphoblastic Leukaemia. V1. 2017. Available from: https://www.nccn.org/patients/guidelines/all/#1.

CURRENT TREATMENT OPTIONS

As ALL is a rapidly progressing disease, treatment usually commences days after diagnosis. In general, the treatment for ALL is carried out in three main stages:[13, 14, 15]

- Induction stage (weeks to months) - the aim of this stage is to kill leukaemia cells in the bone marrow and restore the balance of healthy cells in the blood:
    - Chemotherapy:

        - Oral and IV administration
        - Methotrexate administered into the cerebrospinal fluid by lumbar puncture
    - Targeted therapies – which include drugs designed to identify and attack cancer cells by targeting specific proteins on the cancer cell.
        - Imatinib (oral tablet). Only efficacious in subset of ALL patients who have the Philadelphia chromosome abnormality.
        - Monoclonal antibodies (e.g. rituximab). Inotuzumab and blinotumumab have also been used but are not currently recommended by NICE.
    - Steroid therapy – oral or intramuscular/venous administration
    - Blood transfusions – as not enough healthy blood cells are produced
    - Antibiotics – to prevent further infection
    - Pegaspargase – as part of antineoplastic combination therapy in children and adults
- Consolidation stage (months) – the aim of this stage is to ensure any remaining cancer cells are killed by administering chemotherapy injections.
- Maintenance stage (two years) – the aim of this stage is to prevent the leukaemia returning by administering oral chemotherapy and monitoring (by regular check-ups).

Alternative treatments can include radiotherapy in patients with advanced ALL that has spread to the central nervous system (CNS) or to prepare patients for bone marrow transplant, and stem cell and bone marrow transplant for patients who do not respond to chemotherapy (usually carried out in children and young people due to the physical strain of transplantation). [13, 14, 15]

EFFICACY and SAFETY

Trial	ZUMA-4, NCT02625480, NCI-2016-00087, CDR778554, KTE-C19-104; children and adolescents with relapsed/refractory B-precursor acute lymphoblastic leukaemia; Axicabtagene ciloleucel only; phase I/II trial
Sponsor	Kite Pharmaceuticals
Status	Ongoing - recruiting
Source of Information	trial registry[16]
Location	USA
Design	Non-randomised, open-label trial
Participants	N=75 planned; aged 2-21 years; B-precursor ALL; relapsed or refractory to first or subsequent therapy.
Schedule	Single IV infusion of CAR transduced autologous T cells (axicabtagene ciloleucel) at a targeted dose of 0.5 x 10*6 – 2 x 10*6 anti-CD19 CAR+ T cells/kg following conditioning chemotherapy regime (fludarabine and cyclophosphamide).
Follow-up	Single IV infusion
Primary Outcomes	Phase I: Safety (Incidence of adverse events defined as dose limiting toxicities) Phase II: Overall complete remission rate
Secondary Outcomes	Duration of remission, minimum residual disease negative remission rate, allogeneic stem cell transplant rate, overall survival.
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	June 2019

ESTIMATED COST and IMPACT

COST

The cost of axicabtagene ciloleucel is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☒ Other: *improved patient convenience (reduced frequency of therapies)*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☒ Other: *new staff training requirements, requirement for new facilities*

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified:

☒ None identified

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