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Blinatumomab (Blincyto) for first relapsed/refractory, B-precursor, acute lymphoblastic leukaemia, in children and adolescents

LAY SUMMARY

Acute lymphoblastic leukaemia (ALL) is a type of blood 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, resulting in frequent infections. ALL is a rare condition that develops quickly over days and weeks and most commonly occurs in children aged 2 to 5 years old. B-precursor ALL is an aggressive form of the cancer in which too many B-cell lymphoblasts (a type of blood cell) are found in the bone marrow and blood. ALL is usually treated with chemotherapy drugs, however for some people, these may not work and their leukaemia continues to grow or comes back after treatment.

Blinatumomab is a type of drug called a monoclonal antibody. Monoclonal antibodies work by seeking out cancer cells by looking for particular proteins on the cells' surface. Blinatumomab is a new drug that is already used to treat ALL in adults and is currently being studied to see how well it works and whether it is safe to use in children and young people with ALL. If blinatumomab is licensed for use in the UK, it will offer a new treatment for paediatric patients with B-precursor ALL that have not responded to initial treatment (refractory) or has returned after initial successful treatment (relapsed).

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TARGET GROUP

Acute lymphoblastic leukaemia in children and adolescents (B-precursor; Philadelphia chromosome negative; high-risk relapsed/refractory)

DESCRIPTION

Blinatumomab (Blincyto) is a monoclonal antibody (a type of protein) that binds to CD19 (a protein encoded by the CD19 gene) expressed on the surface of cells of B-lineage origin and CD3 (a transmembrane protein) expressed on the surface of T-cells. Hence, it is a bispecific CD19-directed CD3 T-cell engager. It connects CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells and thereby activates endogenous T-cells. It mediates the formation of a synapse between the T-cell and the tumour cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines and proliferation of T-cells, which result in redirected lysis of CD19+ cells. Hence, by attaching to the cancer cells and the TCR/CD3 complex, the medicine is expected to stimulate the T cells to kill the cancer cells.[1,2]

In the currently ongoing phase III clinical trial (NCT02393859), subjects are randomized to receive either blinatumomab or standard consolidation chemotherapy. If the patient is enrolled in the initial phase of the study, he/she will receive one cycle of blinatumomab. If the patient is enrolled in the adaptive phase of the study, he/she will receive three cycles of blinatumomab. The patients will be followed up for up to 36 months.[3] Doses are not specified for paediatric population, however, in adults it is administered by continuous intravenous infusion with initially 9 micrograms/24 hours on days 1-7 of first cycle, followed by 28 micrograms/24 hours on days 8-28, first cycle is followed by a 2 week treatment-free interval, then 28 micrograms/24 hours for days 1–28 of second and subsequent cycles—patients who achieve complete remission after 2 treatment cycles may receive up to 3 additional cycles of consolidation treatment.[4]

Blinatumomab is licenced in the EU for the treatment of Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL) in adults.[5]

The most common reported side effects with blinatumomab (which may affect more than 1 in 10 people) are infusion-related reactions, infections, pyrexia, headache, febrile neutropenia, peripheral oedema, nausea, hypokalaemia, constipation, anaemia, cough, diarrhoea, tremor, neutropenia, abdominal pain, insomnia, fatigue and chills.[5]

Blinatumomab is also being investigated as a treatment for adult patients with diffuse large B cell lymphoma (DLBCL)[6], follicular lymphoma, extranodal marginal zone B-cell lymphoma and nodal marginal zone B-cell lymphoma.[1]

INNOVATION and/or ADVANTAGES

The current standard of care in acute lymphoblastic leukaemia (ALL) is associated with considerable toxicity and there is a lack of novel treatment options for subjects who relapse or are refractory to treatment. Therefore, innovative therapeutic approaches are urgently needed.[3] Monoclonal antibody-based therapies have the potential of increased response rates without excessive toxicity. Blinatumomab has demonstrated results in both the minimal residual disease setting and the relapsed/refractory setting.[7] If licensed, blinatumomab will offer an additional treatment option for

children or adolescence with B-precursor, Philadelphia chromosome negative, relapsed or refractory ALL.

DEVELOPER

Amgen Ltd

AVAILABILITY, LAUNCH or MARKETING

Blinatumomab was designated orphan drug in the EU for the treatment of acute lymphoblastic leukaemia in July 2009.[2]

PATIENT GROUP

BACKGROUND

Acute lymphoblastic leukaemia (ALL) is a type of blood cancer that starts from young white blood cells called lymphocytes in the bone marrow (the soft inner parts of the bones, where new blood cells are made). This type of cancer usually develops quickly over days or weeks and is the most common type of leukaemia to affect children, but can also affect adults.[8]

In healthy children the bone marrow produces blood stem cells that become mature blood cells over time. A blood stem cell may become a myeloid stem cell or a lymphoid stem cell. Myeloid stem cells become either red blood cells, platelets or white blood cells. Lymphoid stem cells become lymphoblast cells and then one of three types of lymphocytes (white blood cells) – B lymphocytes, T lymphocytes or natural killer cells. In children with ALL, too many stem cells become lymphoblasts, B lymphocytes, or T lymphocytes. Hereby, the cells are not able to fight infection and as the number of leukaemia cells in the blood and bone marrow increases, the number of healthy white blood cells, red blood cells, and platelets decreases.[9] Precursor B-lymphoblastic leukaemia is an aggressive type of leukaemia in which too many B-cell lymphoblasts are found in the bone marrow and blood.[10] Approximately 80% of paediatric patients with ALL have B precursor leukaemia.[11]

Although more than 80% of children with ALL can be cured, certain subsets have a higher risk of relapse. Relapse risk can be predicted by early response to therapy, clinical and pharmacogenetics features of the host, and genetic characteristics of leukemic cells.[12] Cytogenetic changes associated with higher-risk ALL include BCR-ABL (a fusion gene produced when a segment of Abelson protooncogene, ABL, from chromosome 9, translocates to the major breakpoint cluster region, M-BCR, on chromosome 22) fusion of t, known as the Philadelphia chromosome, which is seen in approximately 3% of paediatric ALL.[11]

Exact causes of this disease remain unknown, however, children with genetic disorders such as Down's Syndrome, are known to have a higher risk of developing leukaemia. Siblings of a child with ALL have a slightly increased risk of developing ALL themselves.[13] Risk factors also include prenatal exposure to X-ray, postnatal exposure to high doses of radiation, previous treatment with chemotherapy, genetic conditions such as neurofibromatosis, blood syndrome, Fanconi anaemia, ataxia telangiectasia, Li-Fraumeni syndrome or constitutional mismatch repair deficiency.[14]

Most of the symptoms experienced in ALL are caused by the lack of healthy blood cells and may include pale skin, feeling tired and breathless, repeated infections over a short period of time, unusual

frequent bleeding, high temperature, night sweats, bone and joint pain, easily bruised skin, swollen lymph nodes, abdominal pain, unexplained weight loss, a purple skin rash.[15]

CLINICAL NEED and BURDEN OF DISEASE

In the UK, there were around 760 new cases of ALL in 2014. It accounts for less than 1% of all new cancer cases. There were around 240 ALL deaths in the UK in 2014, with a mortality rate highest in people aged 80-89.[16] ALL is the only form of leukaemia that is more common in children than in adults. More than half of all children diagnosed with ALL are under the age of five years with a peak in incidence in children aged two to three years. Boys have a greater risk of developing the disease, by a factor of 4:3.[17] In the UK, ALL incidence in children aged 0 to 4 years old was 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.[18]

ALL is the most common cancer diagnosed in children and represents approximately 25% of cancer diagnoses among children younger than 15 years. Survival is high in children with ALL with a survival rate approaching 90%. The survival rate is highest in children diagnosed between one and four years of age.[17]

In 2016 to 2017, there were 60,895 admissions for lymphoid leukaemia (ICD-10: C91) in England, resulting in 69,147 bed days and 63,352 finished consultant episodes.[19]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Blinatumomab for treating Philadelphia-chromosome-positive relapsed or refractory acute lymphoblastic leukaemia [ID1008]. Expected February 2019
- NICE technology appraisal in development. Blinatumomab for acute lymphoblastic leukaemia [ID1036]. Expected November 2018
- NICE technology appraisal in development. Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia [ID893]. Expected September 2017
- NICE technology appraisal in development. Tisagenlecleucel-T for previously treated B-cell acute lymphoblastic leukaemia in people aged 3 to 21 at initial diagnosis [ID1167]. Expected TBC
- NICE technology appraisal. Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (TA450). June 2017
- NICE technology appraisal. Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (TA451). June 2017
- NICE technology appraisal. Pegaspargase for treating acute lymphoblastic leukaemia (TA408). September 2016

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Paediatric Oncology. E04/S/a
- NHS England 2017. Clinical commissioning policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 16068/P

OTHER GUIDANCE

- ESMO Guideline Committee. Acute lymphoblastic leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up.

Guidance(s) specifically for the paediatric population was not identified.

CURRENT TREATMENT OPTIONS

The principal treatment for ALL in children is chemotherapy and some will require radiotherapy and/or a stem cell transplant.[17]

In general, the treatment for ALL is carried out in three main stages:

- 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 intravenous (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. Those with Ph+ will usually be given targeted therapy alongside chemotherapy
    - Imatinib (oral tablet)
    - 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).[20,21,22]

However, the treatment of paediatric patients with ALL usually depends on risk based stratification. Patients can be classified into groups based on risk of treatment failure. Those with favourable features can be treated with less toxic regimens, whereas more aggressive regimens are reserved for those with more high-risk disease. More aggressive disease is usually seen in infants and those older than 10 years. Despite all advances in treatment, approximately 15-20% of patients with ALL will suffer relapsed disease, the most common cause of treatment failure.

With intensive therapy that may include hematopoietic stem cell transplant (HSCT), overall survival from relapsed ALL is approximately 40%. Similar to those patients with newly diagnosed ALL, those with relapsed disease can be risk stratified. Immunotherapy is a broad and promising field that seeks to harness the power of the immune system to allow for a more targeted approach.[11]

EFFICACY and SAFETY

Trial	NCT02393859, EudraCT-2014-002476-92; paediatric subjects up to 17 years; compared to standard chemotherapy; phase III
Sponsor	Amgen Ltd
Status	Ongoing, currently recruiting
Source of Information	Trial registry[3,1]
Location	14 EU countries (incl UK), Australia, Israel
Design	Randomized, active controlled
Participants	N=320 (planned); aged <17 years old; with Philadelphia chromosome negative (Ph-) high-risk (HR) first relapse B-precursor ALL (as defined by I-BFM SG/IntReALL criteria); M1 or M2 marrow at the time of randomization, - Age > 28 days and < 18 years at the time of informed consent/assent; Availability of the following material from relapse diagnosis for central analysis of MRD by PCR: clone-specific primers and reference DNA, as well as primer sequences and analysed sequences of clonal rearrangements.
Schedule	Subjects will be randomized to receive either blinatumomab or standard consolidation chemotherapy. Subjects receive one cycle of a continuous intravenous infusion of blinatumomab at a dose of 30.3 to 38.5 µgs for four weeks.
Follow-up	Follow up for up to 36 months
Primary Outcomes	Event-free survival [Time Frame: 36 months]
Secondary Outcomes	• Overall survival [Time Frame: 36 months] • MRD response [Time Frame: 4 weeks] • Adverse events [Time Frame: 30 days after the last dose of study treatment or 90 days after alloHSCT (whichever is longer)] • Survival [Time Frame: 100 days following alloHSCT] • Anti-blinatumomab antibody [Time Frame: 4 weeks] • Relapse Incidence [Time Frame: 36 months] • Css [Time Frame: 2 weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date is January 2020. Estimated study completion date December 2022.

ESTIMATED COST and IMPACT

COST

Blinatumomab is already marketed in the UK for the treatment of adults with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia; a 38.5 microgram vial costs £2,017 (excluding VAT).[23] Blinatumomab is listed under the patient access scheme with a simple confidential discount.[24]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ 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

☒ 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

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☐ None identified

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