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Dasatinib (Sprycel) tablets for children with type II variation, philadelphia positive acute lymphoblastic leukaemia

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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, resulting in frequent infections. ALL develops quickly over days and weeks and most commonly occurs in children aged 2 to 5 years old, however it is generally a rare condition. Some children with ALL will also have a genetic mutation called 'the philadelphia chromosome' where part of chromosome 9 wrongly attaches to chromosome 22, creating a new gene which causes the cell to make too much of an abnormal protein called tyrosine kinase. This protein then causes abnormal production of lymphocytes.

Dasatinib is a tablet which works by blocking the signals in these abnormal lymphocytes which causes them to grow and divide, causing these cancer cells to die. As children with philadelphia chromosome positive ALL are less likely to be cured by chemotherapy alone, adding dasatinib to the treatment programme, this may slow the progress of ALL and relieve symptoms.

TARGET GROUP

Acute lymphoblastic leukaemia (ALL) (Paediatric; Type II variation; philadelphia positive) – first line

TECHNOLOGY

DESCRIPTION

Dasatinib (Sprycel; BMS 354825) is a tyrosine kinase inhibitor which works by inhibiting the signals within leukaemia cells which allows them to grow and divide, thus inducing death of the cell.[1] The reduction in leukaemia cells may allow more normal cells to be subsequently produced.[2] It is intended for use in type II variation philadelphia positive (Ph+) acute lymphoblastic leukaemia (ALL) in children. In the phase II clinical trial, dasatinib is administered orally at 60mg/m2 once daily for 2 years or until unacceptable toxicity.

Dasatinib is also licenced in the EU for the treatment of chronic myeloid leukaemia in those who have resistance to or intolerance of previous therapy (including imatinib), newly diagnosed Ph+ chronic myeloid leukaemia in the chronic phase and for Ph+ acute lymphoblastic leukaemia in those who have resistance to or intolerance of previous therapy.[3] Recognised very common (>10%) adverse effects (AEs) of dasatinib include: infections (bacterial, viral and fungal), shortness of breath, diarrhoea, nausea, vomiting, skin rash, fever, swelling around the face, hands and feet, headache, feeling tired or weak, bleeding, muscle pain, abdominal pain, low platelet count, neutropenia, anaemia, fluid around the lungs.[4]

Dasatinib is currently in phase II trials for:

- Oligodendroglioma
- Myelofibrosis
- Gliosarcoma
- Acute Myelocytic Leukaemia (AML)
- Myelodysplastic Syndrome
- Polycythaemia Vera
- Hypereosinophilic Syndrome
- Myeloid Metaplasia
- Recurrent Glioblastoma Multiforme (GBM)
- Systemic Mastocytosis
- Bile duct cancer (Cholangiocarcinoma) – second line
- Non-small cell lung cancer – second line
- Metastatic breast cancer – first line and second line

INNOVATION and/or ADVANTAGES

If licensed, dasatinib will offer an additional treatment option for children with philadelphia positive acute lymphoblastic leukaemia who currently have poor clinical outcomes on chemotherapy alone. Dasatinib, by its mechanism of action, has the potential to slow the progress of ALL and relieve symptoms.[21]

DEVELOPER

Bristol-Myers Squibb Pharmaceuticals Ltd (BMS)

AVAILABILITY, LAUNCH or MARKETING

Dasatinib was designated orphan drug status in the EU for acute lymphocytic leukaemia and chronic myelocytic leukaemia in December 2005.[5,6]

Dasatinib was designated orphan drug status in the USA for acute lymphocytic leukaemia and chronic myelocytic leukaemia in November 2005.[7,8]

Dasatinib was designated accelerated approval and fast track status in the USA for chronic myelocytic leukaemia in December 2005 and priority review in the USA for chronic myelocytic leukaemia in March 2006.[9]

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). ALL 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 and can spread to other parts of the body (commonly the lymph nodes, liver, spleen, CNS and testicles) causing swelling.[10, 11] There are two types of ALL; B- lymphoblastic leukaemia and T-lymphoblastic leukaemia. Some people with ALL will have a specific genetic change called the philadelphia chromosome. The philadelphia chromosome develops when part of chromosome 9 attaches to part of chromosome 22 (translocation), creating a new gene called BCR-ABL which causes the cell to make too much tyrosine kinase protein resulting in the production of abnormal lymphocytes.[12] The philadelphia chromosome is the most common genetic change in adult ALL at 20 to 30% of cases, however it is relatively rare in paediatric cases at 3 to 5% of cases.[13]

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).[14] 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.[14, 15] 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.[16]

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.[17]

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:[18]

- 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.[19]

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. [20]

Presence of the philadelphia chromosome is generally associated with higher risk of mortality and poorer response to treatments, with 20-30% children with Ph+ ALL cured by chemotherapy alone.[13] Further data on the exact population, children (below 18 years) with Ph+ ALL, likely to be eligible to receive dasatinib could not be estimated from the available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guideline in development. Blinatumomab for treating philadelphia-chromosome- positive relapsed or refractory acute lymphoblastic leukaemia (ID1008). Expected publication June 2018.
- NICE Technology appraisal guideline. Clofarabine for treating acute lymphoblastic leukaemia in children after 2 therapies (ID1033). In development - TBC.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.

OTHER GUIDANCE

No other guidance was identified.

CURRENT TREATMENT OPTIONS

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 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).

Alternative treatments offered in a case dependant basis include dasatinib to treat Ph+ ALL when all other treatment has failed, however this is not currently approved by NICE for use in the NHS.

Radiotherapy is also used for patients with advanced ALL that has spread to the central nervous system (CNS) or to prepare patients for bone marrow transplant. Stem cell and bone marrow transplant can be offered to patients who do not respond to chemotherapy (usually carried out in children and young people due to the physical strain of transplantation). [21, 22, 23]

EFFICACY and SAFETY

Trial	CA180226, CHUK10000362; children (aged 1 to 18 years), philadelphia chromosome positive ALL, treatment naive or unresponsive to imatinib, dasatinib tablets alone, phase II clinical trial.
Sponsor	Cancer Research UK and Bristol- Myers Squibb
Status	Ongoing
Source of Information	trial registry[24]
Location	UK
Design	Non-randomised, uncontrolled, single intervention study.
Participants	N=139 (planned); aged 1-18 years; diagnosed with ALL; philadelphia chromosome positive; participants previously untreated or non-responsive to imatinib.
Schedule	All participants were assigned to receive dasatinib tablet or liquid (unspecified dose) for at least 2 years.
Follow-up	Active treatment for at least 2 years. Study visits every week for the first 6 weeks then monthly over the next 6 months, every 3 months over the next 2 years and every 6 months after that.
Primary Outcomes	Efficacy and Safety (identification of side effects)
Secondary Outcomes	Not reported
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Not reported

ESTIMATED COST and IMPACT

COST

Dasatinib (Sprycel) is already marketed in the UK for the treatment of chronic myeloid leukaemia (resistant/intolerant to previous therapy including imatinib), newly diagnosed philadelphia positive chronic myeloid leukaemia (in the chronic phase) and for philadelphia positive acute lymphoblastic leukaemia (resistant/intolerant to previous therapy). The current costs are as follows:[25]

Tablet pack (quantity x dose)	Cost per pack
60 x 20mg	£1,252
60 x 50mg	£2,505
30 x 80mg	£2,505
30 x 100mg	£2,505
30 x 140mg	£2,505

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☒ No impact identified: *Cannot determine impact due to lack of available information*

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: *Cannot determine impact due to lack of available information*

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: *Cannot determine impact due to lack of available information*

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified: *Cannot determine impact due to lack of available information*

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