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Guadecitabine for treatment naïve acute myeloid leukaemia

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LAY SUMMARY

Acute myeloid leukaemia (AML) is a type of cancer in which lots of immature white blood cells are produced in the bone marrow (the soft inner part of the bones where new blood cells are made). AML usually develops over a few weeks and becomes increasingly more severe. If left untreated it would cause death within a few weeks or months. AML incidence is strongly related to age and most common in people aged 65 years and over. Risk factors for AML include repeated exposure to benzene (usually through smoking or in the workplace), certain genetic disorders and some auto immune conditions (including rheumatoid arthritis and ulcerative colitis).

The most common treatment option for AML is chemotherapy to kill the cancerous cells. Guadecitabine is a new treatment being developed for patients who have not received prior treatment (treatment naïve) and are ineligible to undergo intensive chemotherapy. If licenced, guadecitabine would offer a new treatment option for patients that cannot tolerate the standard of care chemotherapy treatments.

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TARGET GROUP

Acute myeloid leukaemia (treatment naïve, ineligible for intensive chemotherapy) – first line

TECHNOLOGY

DESCRIPTION

Guadecitabine (SGI-110)[1] is a dinucleotide incorporating decitabine with deoxyguanosine via a 3'→5' phosphodiester bond, with potential antineoplastic activity. Guadecitabine is cleaved by intra- and extracellular phosphorylases and other enzymes, releasing decitabine. Guadecitabine (and decitabine) reverses DNA hypermethylation by inhibiting DNA methyl transferase (DNMT) enzymes leading to re-expression of specific genes that are silenced in cancer cells due to an altered methylation status of their DNA sequence.[2]

In the phase I/II clinical trial, subjects were randomly assigned to receive 5-day schedules of guadecitabine administered via subcutaneous injection 60 mg/m2 or 90 mg/m2 and a 10-day schedule of guadecitabine 60 mg/m2.[3]

The most frequently reported grade 3/4 adverse events (AE) were febrile neutropenia, thrombocytopenia, neutropenia, pneumonia, anaemia, and sepsis.[3]

Guadecitabine does not currently have Marketing Authorisation in the EU for any indication. In the EU and globally it is at late stage (Phase II and III) clinical trial development for the following indications:[1]

- Fallopian tube cancer
- Epithelial ovarian cancer
- Myelodysplastic syndrome
- Peritoneal cancer
- Chronic myelocytic leukaemia
- Metastatic colorectal cancer.

INNOVATION and/or ADVANTAGES

Guadecitabine was designed to prolong the exposure of tumour cells to the active metabolite, decitabine, which aims at ensuring greater uptake of decitabine into the DNA of rapidly dividing cancer cells.[4] Guadecitabine will therefore, if licensed, offer an additional treatment option for patients with treatment naïve acute myeloid leukaemia.

DEVELOPER

Otsuka Pharmaceutical Co Ltd and Astex Pharmaceuticcals

AVAILABILITY, LAUNCH or MARKETING

Guadecitabine was granted EU and US Orphan Drug Designation for acute myeloid leukaemia (AML) in 2015.[5,6]

PATIENT GROUP

BACKGROUND

Acute myeloid leukaemia (AML) is a group of blood and bone marrow cancers. This disorder is characterized by incomplete maturation of blood cells and reduced production of other normal haematopoietic stem cells. Haematopoietic stem cells are specialized cells that are formed in the bone marrow, the soft, spongy material found in the centre of long bones. Haematopoietic stem cells develop, or mature, into the three main blood cells – red blood cells, white blood cells and platelets.

In AML, a change in the genetic material (DNA) of a single immature cell, called a blast cell or a myeloblast cell causes the altered cell to continually reproduce itself. Eventually, these altered cells crowd out normal, healthy cells in the marrow. They also cause damage and scarring in the marrow, further disrupting the production of red cells, white cells, and platelets. These altered blast cells can be released into the bloodstream where they travel to other areas or organs in the body, potentially damaging these organs or interfering with their normal function.

Without treatment, AML progresses rapidly (acute disease). AML is the most common acute form of leukaemia in adults. Most people who develop this form of cancer are older adults; more than half of the affected individuals are 65 years old or older.[7]

Risk factors for AML include repeated exposure to benzene (usually through smoking or in the workplace), certain genetic disorders, past chemotherapy or radiation treatments for other cancers.[8] Some blood disorders (including myelodysplastic syndrome) and some auto immune conditions (including rheumatoid arthritis and ulcerative colitis) may also increase the risk of developing AML.[9]

Symptoms of AML include weakness, fatigue, shortness of breath (dyspnoea), recurrent infections (which can cause fever, body aches, and night sweats), and prolonged bleeding. Affected individuals may appear pale and they may bruise easily (including with minor injury or without a reason). There may be a loss in appetite and unintended weight loss. Inflammation of tissue in the mouth can cause pain, swollen/bleeding gums and sores.[7]

CLINICAL NEED and BURDEN OF DISEASE

In England in 2015 there were 2,471 registrations of newly diagnosed AML (ICD-10 code C92.0), of which 2,013 (82%) were persons aged 55 years and over.[10] The incidence rate for England (based on 2014 data) was 5.2 per 100,000 population (European age-standardised rate).[11] Five-year relative survival for adults with AML in England (2000-2007) was 14% for men and 16% for women.[12]

Many elderly patients with AML cannot tolerate standard chemotherapy treatment and need attenuated treatment or best supportive care only. Poor outcome is related to comorbidities (which make chemotherapy and transplantation more toxic or impossible to administer), the increased incidence of adverse biological features such as unfavourable cytogenetics, and AML after a previously-diagnosed blood disorder.[13]

In 2016/17 there were 53,881 hospital admissions with primary diagnosis AML (ICD-10 code C92.0), and 57,378 finished consultant episodes (FCEs), resulting in 135,248 FCE bed days.[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Leukaemia (acute myeloid, relapsed, refractory) - vosaroxin (GID-TA10070). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Gemtuzumab ozogamicin for untreated de novo acute myeloid leukaemia (GID-TA10142). Expected July 2018.
- NICE technology appraisal in development. Midostaurin for untreated acute myeloid leukaemia (GID-TA10124). Expected April 2018.
- NICE technology appraisal in development. Decitabine for acute myeloid leukaemia (GID-TA10146). Expected February 2018.
- NICE technology appraisal in development. Talacotuzumab for untreated acute myeloid leukaemia (GID-TA10249). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia (GID-TA10230). Expected date of issue to be confirmed.
- NICE technology appraisal. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts (TA399). July 2016.
- NICE technology appraisal. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218). March 2011.
- NICE quality standard. Haematological cancers (QS150). June 2017.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.

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 Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 16068/P. February 2017.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) All ages): Revised. B04/P/a. January 2015.

OTHER GUIDANCE

- British Society for Haematology. Diagnosis and Management of Acute Myeloid Leukaemia in Adults. January 2010.
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- Fey MF, Buske C and the ESMO Guidelines Working Group. Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2013; 24 (S6): vi138-vi143.

CURRENT TREATMENT OPTIONS

AML is a complex condition, which usually has to be treated by a multidisciplinary team and carried out in two stages, induction and consolidation. The initial induction stage of treatment is to kill as many leukaemia cells in the blood and bone marrow as possible, restore the blood to proper working order and treat any symptoms. This stage is not always successful and might have to be repeated before consolidation begins. The consolidation stage aims to prevent the cancer returning by killing any remaining leukaemia cells that may be present in the body.[15]

However, patients might not be fit enough to withstand the effects of intensive chemotherapy due to aggressive medication and side effects. Non-intensive chemotherapy may hereby be an alternative, which is designed to control the leukaemia rather than cure it.[15]

Current treatment options for those patients who are not eligible for intensive chemotherapy are low dose cytaribine and azacitidine. The choice of therapy is dependent on the blast level (less than or greater than 30% blasts). The assessment of patients should also be made on biological age when considering which patients may benefit from intensive or non-intensive chemotherapy. Treatment alternatives for unfit patients are limited to best supportive care (BSC), low intensity treatment, or clinical trials with investigational drugs. Low-intensity options are either low-dose cytarabine (LDAC) or therapy with hypermethylating agents.[16,17,18,19]

EFFICACY and SAFETY

Trial	NCT02348489, EudraCT-2014-001233-89, SGI-110-04; Phase III; not considered candidates for intensive remission induction
Sponsor	Astex Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[20], Global Data[21], Company[22]
Location	15 EU countries (incl UK), Canada, Japan, USA and other countries
Design	Randomised, parallel assignment, active-controlled
Participants	N=815; aged >= 18 years; Cytologically or histologically confirmed diagnosis of AML (except M3 acute promyelocytic leukaemia) according to WHO classification. Performance status (ECOG) of 0-3. Adults with previously untreated AML except for hydroxyurea or corticosteroids. Prior hydroxyurea or lenalidomide treatment for myelodysplastic syndrome (MDS) is allowed. Not considered candidates for intensive remission induction chemotherapy at time of enrollment based on EITHER: 1.≥75 years of age OR 2.<75 years of age with at least 1 of the following: i. Poor performance status (ECOG) score of 2-3. ii. Clinically significant heart or lung comorbidities, as reflected by at least 1 of: 1. Left ventricular ejection fraction (LVEF) ≤50%. 2. Lung diffusing capacity for carbon monoxide (DLCO) ≤65% of expected. 3. Forced expiratory volume in 1 second (FEV1) ≤65% of expected. 4. Chronic stable angina or congestive heart failure controlled with medication. iii. Liver transaminases >3 × upper limit of normal (ULN).

	iv. Other contraindication(s) to anthracycline therapy (must be documented). v. Other comorbidity the investigator judges incompatible with intensive remission induction chemotherapy, which must be documented and approved by the study medical monitor before randomization. Creatinine clearance as estimated by the Cockroft-Gault (C-G) or other medically acceptable formulas ≥30 mL/min.
Schedule	60 mg/m2 given SC daily on Days 1-5 in 28-day cycles (delayed as needed to allow blood count recovery)
Follow-up	Not reported
Primary Outcomes	Complete response (CR), Overall survival
Secondary Outcomes	Composite CR, Number of days alive and out of the hospital, Progression-free survival (PFS), Number of red blood cell or platelet transfusions, Health-related quality of life (QOL), Duration of CR
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date January 2018

ESTIMATED COST and IMPACT

COST

The cost of guadecitabine is not yet known.

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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