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Iomab-B for active, relapsed or refractory acute myeloid leukaemia in older patients (aged 55 years and older)

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LAY SUMMARY

Acute myeloid leukaemia (AML) is a type of cancer that causes the bone marrow to produce lots of immature white blood cells. It is diagnosed in around 2,400 people in England each year, and is 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 first stage of treatment is chemotherapy, to kill the leukaemia cells and many of the bone marrow cells. This may be followed by more chemotherapy and a bone marrow transplant to achieve a cure.

Iomab-B is a drug being developed to prepare patients for bone marrow transplant in a safer way, reducing the side-effects of radiation. The drug acts in two ways, firstly by delivering the radioactive component of the drug directly to the cancer growth within the bone marrow, and secondly, by killing the cancer and bone marrow cells while avoiding the effects of radiation on most healthy tissues. Iomab-B has the potential to reduce the time needed to prepare AML patients for transplant and may also increase the number of patients considered eligible for transplant. The drug is administered intravenously.

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TARGET GROUP

Active, relapsed or refractory acute myeloid leukaemia (AML) in patients aged 55 years and older – prior to haematopoietic stem cell transplantation (HCT)

TECHNOLOGY

DESCRIPTION

Iomab-B (BC8-I-131 construct) consists of BC8 labelled with iodine 131 (I-131). It is a radio-iodinated (131I) anti-CD45 murine monoclonal antibody. Iomab-B targets CD45, a pan-leukocytic antigen widely expressed on white blood cells. BC8 carries radioactivity directly to the site of cancerous growth while avoiding effects of radiation on most healthy tissues. BC8 targets and eradicate cancerous and other white blood cells in preparation for HCT. BC8 delivers I131 isotope directly to the target cells and avoids effects of radiation on most healthy tissues.[1]

Iomab-B is intended to prepare and condition patients for HCT in a potentially safer and more efficacious manner than intensive chemotherapy conditioning that is the current standard of care in HCT conditioning.[2]

In the phase III SIERRA trial[3] (NCT02665065) Iomab-B is administered intravenously at 30 mg/m2/day on days -4, -3, and -2 prior to transplantation in conjunction with a reduced intensity conditioning (RIC) regimen containing fludarabine and low-dose total body irradiation (TBI) prior to allogeneic HCT.[1]

Iomab-B has Phase III trials planned for myelodysplastic syndrome and acute myelocytic leukaemia.[1]

Phase II trials have been completed for:

- Advanced acute myeloid leukaemia (prior to stem cell transplantation)
- Advanced recurrent acute lymphocytic leukaemia (prior to stem cell transplantation)
- Myelodysplastic Syndrome (prior to stem cell transplantation)
- Acute myelogenous leukaemia in first remission (prior to stem cell transplantation)[1]

Iomab-B does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

By carrying iodine-131 directly to the bone marrow in a targeted manner, Iomab-B has the potential to minimise the side-effects of radiation on most healthy tissues while effectively killing the patient's cancer and marrow cells.[2]

HCT is the main curative option for AML patients, but as this treatment is associated with significant morbidities and high transplant-related mortality, it generally remains an option for only younger, fitter AML patients. Elimination of unwanted side-effects of transplantation could make HCT a potentially safer option for the elderly and relapsing subgroups of AML patients, and the number of patients considered eligible for HCT could increase.[4]

Iomab-B works simultaneously as an induction and conditioning regimen, enabling a relapsed/refractory patient with an active disease (in the absence of CR) to receive a transplant as a result of the cytotoxic effect of Iomab-B on tumour cells as well as the bone marrow. Use of Iomab-B in the conditioning regimen is expected to significantly cut down the time needed to prepare the patient for a transplant. Currently this period lasts from a month to six weeks. It is estimated that using Iomab-B will shorten the pre-transplant period to 10 days (Actinium, 2017).[4]

DEVELOPER

Actinium Pharmaceuticals

AVAILABILITY, LAUNCH or MARKETING

Iomab-B is a designated orphan drug in the EU/USA for relapsed/refractory AML in patients aged 55 years and older.

Phase III trial is ongoing and recruiting, with an estimated end date of June 2019.[3]

PATIENT GROUP

BACKGROUND

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 hematopoietic stem cells. Hematopoietic stem cells are specialized cells that are formed in the bone marrow, the soft, spongy material found in the centre of long bones. Hematopoietic 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.[5]

Most patients achieve a remission (an absence of signs and symptoms) after initial treatment for AML. However, some patients have residual leukaemia cells in their bone marrow even after intensive treatment: this is referred to as refractory AML. Treatment options for refractory AML may include drugs not already used during the first course of treatment. Stem cell transplantation may be used when remission is achieved, which may result in a more durable remission.[6]

Some patients reach remission and then have a return of leukaemia cells in the bone marrow and a decrease in normal blood cells: this is referred to as relapsed AML. In patients who relapse, the duration of the remission, the patient's age and the cytogenetic findings in the leukaemia cells

influence the approach to therapy. Drugs similar to those administered initially, different drugs or stem cell transplantation may be used to treat the leukaemia.[6]

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.[6] Some blood disorders (including myelodysplastic syndrome) and some auto immune conditions (including rheumatoid arthritis and ulcerative colitis) may also increase the risk of getting AML.[7]

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.[5]

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.[8] The incidence rate for England (based on 2014 data) was 5.2 per 100,000 population (European age-standardised rate).[9] Five-year relative survival for adults with AML in England (2000-2007) was 14% for men and 16% for women.[10]

Many elderly patients with AML cannot tolerate standard treatment and need attenuated treatment or supportive care only. Poor outcome is related to concomitant comorbidities (which make chemotherapy and transplantation more toxic or impossible to give), the increased incidence of adverse biological features such as unfavourable cytogenetics, and AML after a previously-diagnosed blood disorder.[11]

In 2015/16 there were 42,809 hospital admissions with primary diagnosis AML (ICD-10 code C92.0), and 45,599 finished consultant episodes (FCEs), resulting in 122,696 FCE bed days. Of these FCEs, 35,155 were for patients aged 55 years and older.[12]

The number of AML patients in the population likely to be eligible to receive Iomab-B could not be estimated from available published sources.

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. 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. 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.

CURRENT TREATMENT OPTIONS

Conventional treatment for AML has two phases - induction and consolidation.

Induction: the aim of induction is to achieve complete remission (CR). The standard induction chemotherapy regimen is the combination of an anthracycline, usually daunorubicin, given for 3 days with continuous infusion of cytarabine for 7 days (3+7).[11] British Society for Haematology guidelines state that for patients aged 60-74 years with performance status less than 2 and no comorbidities, standard induction therapy is often a plausible option, resulting in CR rates averaging 50%. Patients in this age group known to have adverse cytogenetics (even with good performance status and lacking comorbidities) may be considered for investigational therapies or mild cytoreductive therapy only. Recent data suggests delays in initiating therapy may not be harmful in older patients, thus allowing individualized approaches. An alternative to standard-dose induction should be sought for patients aged 75 years and older (and probably >=65 years) with a performance status of 2 or 3, comorbidities, or organ dysfunction. The choice of therapy should depend on the patient's wishes. Any discussion of choice of therapy must refer to observations that 74% of older patients estimated that their chances of cure with 3+7 were 50% or more; in contrast, 85% of physicians estimated this chance to be less than 10%.[13]

Consolidation: consolidation is designed to eliminate residual leukaemia cells that persist after induction. After achievement of CR, all patients will eventually relapse without further treatment, and therefore consolidation treatment is essential provided that patients have adequate organ function.[11] An international expert panel was unable to provide clear recommendations of consolidation therapy

for patients aged 60-74 years, although for patients without adverse cytogenetics, good performance status and no significant comorbidity, repetitive cycles of modest dose consolidation may be an acceptable norm. The panel noted that HCT in older patients has become an active and promising field of investigation, but current data are difficult to interpret due to small patient cohorts and inherent patient selection bias. The panel therefore concluded that HCT should be performed within clinical trials.[13]

EFFICACY and SAFETY

Trial	SIERRA, NCT02665065, GDCT0182944, GDC40000465, NCI-2016-01853, CDR785644; Iomab-B vs conventional care; phase III
Sponsor	Actinium Pharmaceuticals Inc
Status	Ongoing
Source of Information	Trial registry,[3] GlobalData[1]
Location	USA, Canada
Design	Randomised, active-controlled, crossover assignment, parallel assignment study
Participants	n=150 (planned); aged 55 years and older; acute myeloid leukaemia; active, relapsed or refractory; prior to hematopoietic cell transplantation
Schedule	Subjects are randomized in the ratio of 1:1 into two arms: Arm I - Iomab-B. Subjects receive Iomab-B at a dose of 30 mg/m^2/day on days -4, -3, and -2 prior to transplantation in conjunction with a reduced intensity conditioning (RIC) regimen containing fludarabine and low-dose total body irradiation (TBI) prior to allogeneic HCT. On day 0 through day 28 (15 mg/kg every 12 hours) for related donor and day 40 (15 mg/kg every 8 hours) for unrelated donor (taper to day 96 in absence of GVHD). Immunosuppression with either CSP or TAC starting 3 days prior to transplantation and continuing with taper through 180 days post-transplantation Arm II - Physician's choice of chemotherapy. Subjects receive azacitidine (not allowed as a single agent), cladribine, clofarabine, cyclophosphamide, cytarabine, daunorubicin, Decitabine (not allowed as a single agent with the exception of patients with documented TP53 mutations who have not previously received 10-day regimens of single agent decitabine), Doxorubicin, Etoposide, Fludarabine, Hydroxyurea (not allowed as a single agent), Idarubicin, L-Asparaginase, Mitoxantrone, Thioguanine. Subjects in the control arm with no complete response are crossoverly assigned to Iomab-B arm and are evaluated for durable complete response after six months.

Follow-up	Bone marrow aspirate and biopsy are performed in all subjects at nearly one and/or two mths after the last day of intervention to determine response and at six mths after complete response (CR) has been established to confirm CR duration.
Primary Outcomes	To assess durable complete remission (dCR) defined as CR or CRp lasting 180 days or more from time of initial CR or CRp is documented with evidence of subsequent relapse - 6 months from time of initial CR or CRp.
Secondary Outcomes	To assess the overall survival (OS) at 1 year from randomization.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as June 2019.

ESTIMATED COST and IMPACT

COST

The cost of Iomab-B 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: *more patients may be eligible for HCT treatment*

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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