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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2020

Liposomal cytarabine-daunorubicin for treating relapsed or refractory acute myeloid leukaemia in paediatric patients.

NIHRIO ID	29863	**NICE ID**	10475
Developer/Company	Jazz Pharmaceuticals UK Limited	**UKPS ID**	657859

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

Liposomal cytarabine-daunorubicin is currently being developed for paediatric patients with relapsed or refractory acute myeloid leukaemia (AML). AML is an aggressive type of blood cancer that starts from certain types of white blood cells in the bone marrow. AML results in abnormal white blood cells being produced too quickly, resulting in them accumulating in the bone marrow and spreading to other parts of the body. Relapsed AML is when the leukaemia has returned following initial successful treatment and refractory AML is leukaemia that is resistant to the initial treatment. The prognosis for children with relapsed or refractory AML is poor and associated with significant side effects so new therapies are needed.

Liposomal cytarabine-daunorubicin is made up of the chemotherapy drugs daunorubicin and cytarabine contained within fat-based particles called liposomes. Liposomal cytarabine-daunorubicin is delivered by intravenous infusion and provides controlled release of daunorubicin and cytarabine. Daunorubicin works by interrupting the copying of DNA which is necessary for cancer cell growth and cytarabine works by inhibiting DNA production to kill cancerous cells. If licenced, liposomal cytarabine-daunorubicin may offer an additional treatment option for paediatric patients with relapsed or refractory AML.

PROPOSED INDICATION

Treatment of relapsed or refractory AML in paediatrics and young adults aged between 1 and 21 years.[1]

TECHNOLOGY

DESCRIPTION

Liposomal cytarabine-daunorubicin (CPX-351, Vyxeos) is a liposomal combination of daunorubicin, an anthracycline topoisomerase inhibitor, and cytarabine, a nucleoside metabolic inhibitor in a 1:5 molar ratio.[2,3] Liposomal cytarabine-daunorubicin liposomes accumulate and persist in high concentration in the bone marrow, where they are preferentially taken up intact by leukaemia cells in an active engulfment process. Daunorubicin has antimitotic and cytotoxic activity which is achieved by forming complexes with DNA, inhibiting topoisomerase II activity; inhibiting DNA polymerase activity; affecting regulation of gene expression and producing DNA-damaging free radicals. Cytarabine is a cell cycle phase-specific antineoplastic agent, affecting cells only during the S-phase of cell division. Intracellularly, cytarabine is converted into the active metabolite cytarabine-5-triphosphate (ara-CTP). The mechanism of action is not fully understood but it appears that ara-CTP acts primarily through inhibition of DNA synthesis. Incorporation into DNA and RNA may also contribute to cytarabine cytotoxicity.[3]

Liposomal cytarabine-daunorubicin is currently in clinical development for the treatment of relapsed or refractory AML in children and young adults aged between 1 and 21 years. In the phase I/II clinical trial, NCT02642965, participants received cytarabine by intrathecal injection on day 0 and at day 28-30 or up to 7 days prior to day 1 of course 2, and they received liposomal cytarabine-daunorubicin by intravenous infusion over 90 minutes on days 1, 3 and 5. Patients without evidence of central nervous system disease (CNS1) received no further CNS-directed therapy in course 1. Patients with <5 white blood cells per microliter of blood with blast cells (CNS2) disease received additional 4-6 doses of cytarabine twice weekly starting 48 hours after the third dose of liposomal cytarabine-daunorubicin until CNS is clear at the discretion of the investigator. Patients meeting criteria for response rate proceeded to course 2. In course 2, patients received filgrastim on days 1-5 and then on day 15 until blood count recovery, and fludarabine phosphate IV over 30 minutes and high dose cytarabine IV over 1-3 hours once daily on days 1-5.[1]

INNOVATION AND/OR ADVANTAGES

The current prognosis in paediatric patients with relapsed of refractory AML is generally poor with a long-term survival from relapse of about 35%. This can only be achieved with intensive chemotherapy and, usually, allogeneic stem cell transplantation leading to very significant toxicity and even treatment-related mortality. Therefore, new therapies are needed to improve outcomes and reduce treatment related toxicity.[4]

The pharmacological advantages of liposomal cytarabine-daunorubicin are a direct consequence of the encapsulating liposome. It was designed to improve the efficacy over the traditional 7+3 cytarabine/daunorubicin chemotherapy regimen for patients with AML by maintaining a synergistic 5:1 molar ratio of cytarabine and daunorubicin within the liposome after intravenous injection.[5] The liposome remains in a gel phase at body temperature, provides stability, controls release of cytarabine and daunorubicin, limits systemic drug distribution and is preferentially taken up by leukaemia cells. This suggests that relatively large amounts of cytarabine and daunorubicin enter malignant cells via liposomes.[5] In the absence of encapsulation, conventional drug administration will result in constantly changing drug ratios after dosing, thus preventing the maintenance of any particular drug ratio that could potentially optimise anti-tumour activity.[6] In clinical studies, the elimination half-life of liposomal cytarabine-daunorubicin was much greater than free cytarabine and daunorubicin and a synergistic drug ratio was maintained for over 24 hours after administration.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Liposomal cytarabine-daunorubicin has Marketing Authorisation in the EU/UK for the treatment of adults with newly diagnosed, therapy-related AML or AML with myelodysplasia-related changes.[3]

The very common (≥10%) adverse events associated with liposomal cytarabine-daunorubicin include: infection, febrile neutropenia, hypersensitivity, sleep disorders, anxiety, delirium, headache, dizziness, cardiotoxicity, arrhythmia, chest pain, haemorrhage, hypotension, hypertension, dyspnoea, cough, pleural effusion, nausea, diarrhoea/colitis, mucositis, constipation, abdominal pain, decreased appetite, vomiting, pruritus, hyperhidrosis, musculoskeletal pain, renal insufficiency, oedema, fatigue, chills and pyrexia.[3]

Liposomal cytarabine-daunorubicin is currently in phase II/III clinical development for the treatment of myelodysplastic syndrome and several leukaemia indications such as lymphoid leukaemia, lymphoblastic leukaemia and erythroid leukaemia.[7]

In January 2012, liposomal cytarabine-daunorubicin was granted orphan drug designation by the EMA for the treatment of AML.[8]

In June 2018, liposomal cytarabine-daunorubicin was recommended for approval by the EMA's Committee for Medicinal Products for Human Use (CHMP) for the treatment of AML.[9]

In November 2017, liposomal cytarabine-daunorubicin received promising innovative medicine (PIM) designation for the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK for the treatment of AML.[10,11]

PATIENT GROUP

DISEASE BACKGROUND

AML is a type of blood cancer that affects the white blood cells, specifically myeloid cells. AML causes white blood cells to be produced more quickly than normal and as a result the cells become abnormal because they grow and divide too quickly. The abnormal myeloid cells build-up in the blood and bone marrow and eventually can spread to other parts of the body.[12] Refractory AML is defined as when a patient has not achieved complete remission (remaining blast count of 5% or more following 1-2 cycles of intense induction therapy).[13] Relapsed AML is when the leukaemia has returned following successful treatment in patients who initially achieved remission.[14] The prognosis for children with relapsed AML is relatively poor.[4]

The symptoms of AML usually develop over a few weeks and become increasingly more severe. Symptoms can include: pale skin, tiredness, breathlessness, frequent infections, unusual and frequent bleeding, such as bleeding gums or nosebleeds. In more advanced cases, AML can make the patient extremely vulnerable to life-threatening infections or serious internal bleeding.[15]

AML patients may experience a number of complications. These can be caused by the condition itself, although they can also occur as a side effect of treatment. Some of the main complications associated with AML are:[16]

- Weakened immune system: this is a common complication of AML. Even if a patient's blood is restored to normal working order with treatment, many of the medications that are used to treat AML can temporarily weaken the immune system.
- Bleeding: patients may bleed and bruise more easily or bleeding may be excessive due to the low levels of platelets in the blood. Serious bleeding can occur inside the skull, inside the lungs or inside the stomach.
- Infertility: many of the treatments that are used to treat AML can cause infertility. This is often temporary, but in some cases can be permanent.

The causes of AML are unknown. There are a number of factors that may increase a person's risk of developing AML. The following are known risk factors of AML:[17]

- Exposure to radiation
- Smoking
- Exposure to benzene and other chemical solvents
- Cancer treatments: rarely, some anti-cancer treatments such as chemotherapy or radiotherapy can cause leukaemia
- Blood disorders: such as myelodysplasia or myeloproliferative disorders
- Genetic disorders: such as Down's syndrome and Fanconi anaemia
- Family history of blood cancer.

CLINICAL NEED AND BURDEN OF DISEASE

In the UK, leukaemia is the most commonly diagnosed cancer in children, accounting for around a third (30%) of all cases. Around 70 new cases of childhood AML are diagnosed every year in the UK, which accounts for 15% of children's leukaemia cancer cases. The incidence of AML varies with age. The highest risk is in children aged less than two years; the risk in children aged two to nine years is lower and it then increases in the adolescent years. More boys than girls develop AML, by a ratio of 5:4. The reason for this difference between the sexes is not yet known.[18]

Five-year survival for AML is affected by age. The five-year survival rate for children with AML in the UK is around 70%. Infants below the age of one year and children aged 10-14 years with AML have lower survival than children diagnosed at intermediate ages (65%). In people aged between 15 and 24, around 60% will survive their leukaemia for 5 years of more after diagnosis.[18] AML relapse affects about 50% of patients who achieve remission after initial treatment and 10% to 40% of patients are refractory to treatment.[14,13] The prognosis for paediatric AML patients who have relapsed is relatively poor with a long term survival probability of about 35%.[4]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for paediatric patients AML is usually divided into two phases – induction and consolidation.[19] The aim of the induction phase is to kill as many leukaemia cells in the blood and bone marrow to treat any symptoms and induce remission. The aim of the consolidation phase is to prevent the cancer coming back (relapsing) by killing any remaining leukaemia cells in the body.[12,20]

Chemotherapy is the main treatment for AML in patients fit enough to tolerate intensive treatment.[12,20] Most intensive chemotherapy treatment courses are based on cytarabine and anthracycline, however, the incidence of cardiomyopathy correlates strongly with the cumulative dose of anthracyclines.[21,22] Some patients may not be fit enough to withstand the effects of intensive chemotherapy so they may be offered non-intensive treatments which include: radiotherapy, growth factors, and targeted cancer drugs.[20,23] For children who have relapsed, a repeat of remission induction followed by a stem cell transplant is recommended.[24]

The intensity of treatment needed to treat AML causes severe bone marrow suppression. Expert supportive care is therefore necessary and paediatric patients will usually remain in the hospital throughout the treatment. Patients will be monitored following completion of treatment in order to detect relapse or treatment related complications.[25]

CURRENT TREATMENT OPTIONS

There are currently no licenced nor NICE-recommended therapies for treatment of relapsed or refractory AML in paediatrics and young adults ≤21 years.

PLACE OF TECHNOLOGY

If licensed, liposomal cytarabine-daunorubicin will offer a licenced treatment option for paediatric patients aged 21 years or younger with relapsed or refractory AML.[1]

CLINICAL TRIAL INFORMATION

Trial	NCT02642965; A Phase 1/2 Study of CPX-351 (NSC# 775341) Alone Followed by Fludarabine, Cytarabine, and G-CSF (FLAG) for Children With Relapsed Acute Myeloid Leukemia (AML)

	Phase I/II - Active, not recruiting **Locations:** United States and Canada **Primary completion date:** 31 December 2018
Trial design	Single group assignment, open-label
Population	N=38; children and adults aged 1 year to 21 years; diagnosed with acute myeloid leukaemia (AML) that is relapsed or refractory
Intervention(s)	• cytarabine (intrathecal administration) • CPX-351 (intravenous administration) • filgrastim (subcutaneous or intravenous administration • fludarabine phosphate (intravenous administration)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Number of participants with a dose-limiting toxicity [Time frame: 28 days] • Percentage of responders (complete response or complete remission with partial platelet recovery) after up to 2 cycles [Time frame: up to 8 weeks] See trial record for full list of outcomes
Results (efficacy)	In total, 20 patients (54%) achieved complete response, 5 patients (14%) achieved complete response without platelet recovery and 5 patients (14%) achieved complete response with incomplete haematologic recovery.[26]
Results (safety)	Dose-limiting toxicity occurred in 1/6 patients enrolled in the dose finding study and was a grade 3 decrease in ejection fraction. This was the only Grade 3 cardiac toxicity. The most common ≥ Grade 3 toxicities in Cycle 1 included fever/neutropenia (45%), infection (47%), and rash (40%). There was no toxic mortality.[26]

ESTIMATED COST

CPX-351 is already marketed in the UK. 1 vial containing 100mg cytarabine and 44mg daunorubicin has a list price of £4581.[27]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Clofarabine for refractory or relapsed acute myeloid leukaemia (AML) as a bridge to stem cell transplantation (all ages). November 2018
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (all Ages). B01/S/a.

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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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