Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING MARCH 2019

Histamine dihydrochloride (Ceplene) in combination with low dose interleukin-2 as maintenance treatment for acute myeloid leukaemia

NIHRIO ID	26838	**NICE ID**	10138
Developer/Company	Vector Therapeutics	**UKPS ID**	Not available

Licensing and market availability plans	Histamine dihydrochloride received an unconditional Marketing Authorisation from the EMA in July 2018.

SUMMARY

Histamine dihydrochloride, in combination with low dose interleukin-2 (IL-2), is indicated for the maintenance of first complete remission in patients with acute myeloid leukaemia (AML). AML is a rare and aggressive cancer of the blood and bone marrow. AML first develops in the bone marrow, where leukaemia cells accumulate and ultimately block the way for healthy blood cells to develop. They can also spill out into the bloodstream and circulate around the body. Due to their immaturity they are unable to function properly to prevent or fight infection. Most patients with AML are treated with standard chemotherapy. A period without symptoms of the disease after treatment is known as 'remission'.

Histamine dihydrochloride is an immunostimulant. This means that it changes the activity of the immune system (the body's natural defences). Histamine is a substance occurring naturally in the body that is involved in many processes. In the treatment of AML, it is thought to work by protecting immune system cells from damage. This improves the effectiveness of IL-2, a medicine that stimulates the immune system to attack cancerous cells. When histamine dihydrochloride is given with IL-2, it helps the immune system to kill the leukaemia cells that may remain in the body during remission. This may increase the likelihood for patients to remain in long-term remission.

PROPOSED INDICATION

Histamine dihydrochloride maintenance therapy is indicated for adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with low-dose interleukin-2 (IL-2) [a,1]

TECHNOLOGY

DESCRIPTION

Histamine dihydrochloride (Ceplene) is a synthetic derivative of histamine that suppresses or inhibits the formation of immunosuppressive oxygen radicals in mononuclear and polymorphonuclear myeloid cells. The inhibition is transduced by cell surface H2-type histamine receptors, and histamine dihydrochloride acts by targeting the key enzyme in oxygen radical formation by myeloid cells, the NADPH oxidase 2 (NOX2). By inhibiting the production of oxygen radicals, histamine dihydrochloride protects T-cells and Natural Killer (NK) cells from the oxidative inhibition and apoptosis that is induced by myeloid cells in-vitro.[2]

The biological activities of aldesleukin and native human IL-2, a naturally occurring lymphokine, are comparable. The in-vivo administration of aldesleukin in animals and humans produces multiple immunological effects in a dose dependent manner. The administration of aldesleukin in murine tumour models has been shown to reduce both tumour growth and spread. The mechanisms by which aldesleukin-mediated immunostimulation leads to antitumour activity are not entirely known but likely comprises activation of anti-tumour function of NK cells and cytotoxic T cells.[3,4]

Histamine dihydrochloride in combination with low-dose IL-2 is an immunotherapy which aims to induce immune-mediated destruction of residual myeloid leukaemic cells and thereby to prevent relapse of leukaemia. The role of histamine dihydrochloride is to protect lymphocytes, in particular NK cells and T cells, which have the capacity to attack and destroy leukaemic cells. The role of IL-2 is to promote the functions of NK cells and T cells by activating the anti-leukaemic properties of these cells and by expanding these cell populations by inducing cell cycle proliferation.[4]

Histamine dihydrochloride maintenance therapy is administered following completion of consolidation chemotherapy. Patients are concomitantly treated with IL-2 and are under the supervision of a physician experienced in the management of AML. IL-2 is administered twice daily as a subcutaneous injection 1 to 3 minutes prior to the administration of histamine dihydrochloride; each dose of IL-2 is 16,400 IU/kg (1 µg/kg). IL-2 is commercially available as a recombinant IL-2, aldesleukin. Histamine dihydrochloride is administered as subcutaneous injection 1 to 3 minutes after each injection of IL-2. Each 0.5 mL histamine dihydrochloride dose is injected slowly, over 5-15 minutes.[4]

Histamine dihydrochloride and IL-2 are administered for 10 treatment cycles: each cycle consists of a treatment period of 21 days (3 weeks) followed by a three-week or six-week treatment-free period. For cycles 1-3, each cycle consists of 3 weeks of treatment, followed by a 3-week treatment free period. For cycles 4-10, each cycle consists of 3 weeks of treatment, followed by a 6-week treatment free period. The recommended dosing regimen is further outlined in the summary of product characteristics (SmPC).[4]

[a] Information provided by Vector Therapeutics

INNOVATION AND/OR ADVANTAGES

Histamine dihydrochloride is a first-in-class immunotherapy that harnesses the immune system to effectively maintain remission in patients with AML. Histamine dihydrochloride unlocks activity of IL-2 in patients with AML by activating the immune system's T cells and NK cells. The combination therapy of histamine dihydrochloride and IL-2 meets a material, unmet need for effective treatment in AML care.[5]

The clinical relevance of histamine dihydrochloride in combination with low dose subcutaneous IL-2 was demonstrated in a phase III clinical study with 320 US and global AML patients. The study successfully met its primary endpoint of determining the efficacy of histamine dihydrochloride and IL-2 on patients' Leukaemia-Free Survival (LFS), defined as the time from study entry to relapse or death. Histamine dihydrochloride was proven to prevent relapse in AML patients in first remission and to prolong LFS while preserving quality of life during treatment. Three years after first remission, 40% of patients were leukaemia free, as opposed to only 26% of control patients.[b,5,6] Additionally, a European phase IV study provided evidence of clinical benefits of histamine dihydrochloride in combination with IL-2 and helped to define biomarkers predictive of survival. [5,7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Histamine dihydrochloride was initially authorised under exceptional circumstances by the European Medicines Agency (EMA).[1] In July 2018, based on a review of the data on quality, safety and efficacy, the Committee for Medicinal Products for Human Use (CHMP) considered that the benefit-risk balance of histamine dihydrochloride in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.[8]

Histamine dihydrochloride was granted an orphan drug designation in the EU in April 2005 for the treatment of AML.[9] Histamine dihydrochloride was withdrawn from the community register of orphan medicinal products in October 2018 at the end of the 10-year period of market exclusivity.[1]

PATIENT GROUP

DISEASE BACKGROUND

Leukaemia is a cancer of the white blood cells. AML is a rare and aggressive cancer of the blood and bone marrow. Acute leukaemia means it progresses quickly and aggressively, and usually requires immediate treatment. [10] AML first develops in the bone marrow, where leukaemia cells accumulate and ultimately block the way for healthy blood cells to develop. Leukaemia cells may spread outside of the bloodstream into other parts of the body, including the central nervous system (affecting the brain and spinal cord), skin, and gums. [11,12]

There are different subtypes of AML, based on how mature the cancer cells are at the time of diagnosis and how different they are from normal cells. [13] The symptoms of AML usually develop over a few weeks, becoming more severe as the number of immature white blood cells (blast cells) in the blood increases. Symptoms of AML may include: pale skin, tiredness, breathlessness, a high temperature, excessive sweating, weight loss, frequent infections, unusual and frequent bleeding, easily bruised skin, petechiae, bone and joint pain, and a feeling of fullness or discomfort in the abdomen.[14]

[b] Information provided by Vector Therapeutics

Due to the rapid progression of the disease, if AML is not treated quickly it can result in death within months.[11,12] The causes of AML are unknown and in most cases it is unclear why leukaemia develops. Factors that increase a person's risk of developing AML may include: exposure to radiation, smoking, exposure to benzene and other solvents, some anti-cancer treatments, and certain blood or genetic disorders.[15]

AML patients may experience a number of complications. These can be caused by the condition itself or occur as a side effect of treatment. Some of the main complications associated with AML include a weakened immune system, infection, increased risk of bleeding and/or bruising, and infertility (which may be temporary or permanent).[16] AML relapse affects >50% of all patients who achieved remission after initial treatment with chemotherapeutic drugs, and can occur several months to several years after treatment. However, every patient carries the risk of relapse, and the majority of relapses occur within two to three years of initial treatment.[17]

CLINICAL NEED AND BURDEN OF DISEASE

European age standardised incidence rates of AML in England and Wales in 2015 were 5.3 and 5.4 per 100,000 (respectively). AML accounts for less than 1% of all new cancer cases in the UK.[18]

In England in 2016, there were 3,715 registrations of newly diagnosed cases of myeloid leukaemia (ICD 10: C92).[19] AML incidence is strongly related to age, with the highest incidence rates being in older males and females. In the UK, the peak rate of AML cases is 85-89 years of age (based on 2013-2015 data). In the UK, 56% of AML cases are in males, and 44% are in females.[18]

In the UK in 2016, there were 2,601 deaths from AML.[20] Five-year relative survival for AML in men in England (14%) is similar to the average for Europe (15%). Five-year relative survival for AML in women in England (16%) is below the average for Europe (18%).[21]

In England in 2017-2018, there were 44,245 admissions of acute myeloblastic leukaemia (ICD 10: C92.0) resulting in 118,428 FCE bed days.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Patients with newly diagnosed AML who achieve a complete remission following remission induction therapy have historically been advised to receive consolidation treatment with either high-dose chemotherapy supported by an allogeneic HLA-matched sibling stem cell transplant, high-dose chemotherapy and autologous stem cell transplant, or, most commonly, high-dose chemotherapy delivered without stem cell support.[23] Post-consolidation therapy, or maintenance therapy, is not currently part of standard treatment for patients with most forms of AML.[24,25]

CURRENT TREATMENT OPTIONS

Midostaurin is recommended, within its marketing authorisation, as an option in adults for treating newly diagnosed acute FLT3-mutation-positive myeloid leukaemia with standard daunorubicin and cytarabine as induction therapy, with high-dose cytarabine as consolidation therapy, and alone after complete response as maintenance therapy.[26]

PLACE OF TECHNOLOGY

Histamine dihydrochloride is indicated for adult patients with AML in first remission concomitantly treated with IL-2.[1]

CLINICAL TRIAL INFORMATION

Trial	**Re:Mission, NCT01347996; histamine dihydrochloride and IL-2; phase IV**
Sponsor	Meda[c]
Status	Published
Source of Information	Publication[27], trial registry[7], manufacturer[28]
Location	Sweden
Design	Single group assignment, single arm, open-label
Participants	n=84; aged 18-79; AML in first complete remission (CR1)
Schedule	Subjects received histamine dihydrochloride 0.5 mg subcutaneously twice daily and IL-2 1 µg/kg [16,400 IU/kg] body weight twice daily for 10, 21 day cycles.
Follow-up	Active treatment for 18 mths or until relapse/death. Follow-up ≤ 2 yrs.
Primary Outcomes	Minimal residual disease (MRD) in AML patients receiving histamine dihydrochloride/IL-2 [Time Frame: Comparison at baseline and various time points up to 2 yrs] • A second primary objective of this study is to evaluate MRD in patients who are receiving remission maintenance therapy with histamine dihydrochloride/IL-2. MRD will be evaluated using RQ-PCR for molecular detection of genetic markers of AML. Patients' MRD status will be quantified at the time of enrollment (baseline) and within ten days after completion of Cycles 3, 5, 6, 7, 9 and 10 of histamine dihydrochloride/IL-2 therapy, corresponding to approximately every 3 months during this immunotherapy. Pharmacodynamic effects of histamine dihydrochloride plus low dose IL-2 (histamine dihydrochloride /IL-2) by monitoring T and NK cell phenotypes and their functionality after the first and third cycles of treatment [Time Frame: Baseline vs Cycle 1 and 3] • The quantitative and qualitative pharmacodynamic effects of histamine dihydrochloride /IL-2 on the immune responses of T and NK cells will be assessed as follows: 1. Changes in T and NK cell phenotypes (CD56, CD3, CD4, CD8) in peripheral blood from Day 1 (baseline) to Day 21‡ of Cycle 1 and from Day 1 (pre-treatment Cycle 3) to Day 21‡ of Cycle 3. 2. Changes in immune response markers (CD3, NKp46 [and other NCRs], CD25, CD69, and IFN-γ) in peripheral blood from Day 1 (baseline) to Day 21‡ of Cycle 1 and from Day 1 (pre-treatment Cycle 3) to Day 21‡ of Cycle 3
Secondary Outcomes	Duration of LFS [Time Frame: up to 2 yrs] • LFS will be defined as the time from achieving CR after successful induction therapy until relapse of AML (defined as 5% or more blast cells in the bone marrow).

[c] Information provided by Vector Therapeutics

Key Results	67% of patients with functional, autoreactive NK cells remained relapse-free for a pre-scheduled follow-up of 2 years vs. 11% relapse-free survival in corresponding patients devoid of active NK cells (p=0.0002, n=39).
Adverse effects (AEs)	Not reported.
Expected reporting date	Completed June 2014.

Trial	NCT00003991; **histamine dihydrochloride and IL-2; phase III**
Sponsor	Maxim Pharmaceuticals
Status	Published
Source of Information	Publication[29], trial registry[6], manufacturer
Location	EU (incl UK), USA, and other countries
Design	Randomised, open-label, parallel assignment
Participants	n=320; ≥ 18 years of age; AML in CR or subsequent CR; less than 5% blasts in normal bone marrow; less than 3 mths since last dose of chemotherapy or less than 6 mths since achieving CR
Schedule	Patients are stratified according to complete remission (first vs subsequent) and randomised to one of two treatment arms: • **Arm I:** Following consolidation chemotherapy or autologous stem cell transplantation, patients receive IL-2 subcutaneously followed by histamine dihydrochloride subcutaneously over 5-7 minutes twice daily on days 1-21. Treatment repeats every 6 weeks for 3 courses and then every 9 weeks for 7 courses in the absence of disease relapse or unacceptable toxicity. • **Arm II:** Patients receive no further therapy following consolidation chemotherapy or autologous stem cell transplantation. Quality of life is assessed prior to study, and at visits 6, 7, 10, 11, 16, 17, and 22. Treatment comprised 10, 21-day cycles with IL-2 (16,400 U/kg) plus histamine dihydrochloride (0.5 mg).
Follow-up	Treatment continued for a total of 18 mths or until the patients relapsed, died, discontinued therapy because of adverse events, withdrew consent, or became lost to follow-up. After 18 mths of treatment (histamine dihydrochloride/IL-2 arm) or observation (control arm), all patients were followed for at least 18 additional mths until the study closure date on October 31, 2003 (3 yrs after enrollment of the last patient).
Primary Outcomes	• To determine the efficacy of postconsolidation maintenance treatment with HDC/IL-2 versus control on the LFS of all patients.
Secondary Outcomes	• LFS rates at 12, 24, and 36 mths after random assignment, effects of treatment on LFS of patients in CR1 and subsequent CR, overall survival, safety, toxicity, and quality of life.
Key Results	Three yrs after enrollment of the last patient, treatment with histamine dihydrochloride/IL-2 was found to improve LFS compared to the control group in the study population (CR1 + CR > 1, n = 320; P < .01, log-rank test). 34% of patients treated with histamine dihydrochloride/IL-2 vs. 24% placebo patients were in LFS at 36 months. For patients in CR1 (n = 261), treatment significantly improved LFS (P = .01) with 3-yr LFS estimates of 40% (histamine dihydrochloride/IL-2) compared with 26% (control).

Adverse effects (AEs)	Only three Grade 3 adverse events happened in more than 5% of the patients during the trial: Thrombocytopenia (16% vs. 9.4%), neutropenia (5.7% vs. 3.1%) and headache (7% vs. 0%), histamine dihydrochloride/IL-2 vs. placebo, respectively. No Grade 4 AEs occurred in >1.3% of patients. Among Grade 1-2 AEs, the events which were significantly more prominent in the histamine dihydrochloride/IL-2 arm included IL-2-related side effects such as injection site reactions, fever, fatigue, and myalgia, along with side effects related to HDC such as palpitations, flushing, and headache. There were no cases of grade 3 or 4 hypotension, nor were there any cases of capillary leakage syndrome or renal insufficiency. The incidence of AEs resulting in dose reduction or treatment interruption was 26%, the most common reasons being local inflammatory reactions at the injection sites (7.1%) or fever (5.1%). Self-assessment of e.g. global health, fatigue and nausea using the EORTC OLQ-C30 instrument did not reveal significant differences between treated and control patients.
Expected reporting date	Completed August 2011.

ESTIMATED COST

The cost of histamine dihydrochloride in combination with IL-2 is not yet known.

The Scottish Medicines Consortium (SMC) noted the cost or relevant comparators as £3,544 for 0.5mg subcutaneous injection histamine dihydrochloride twice daily on days 1 to 21 of a cycle and £2,176 for aldesleukin (IL-2) 16,400 IU/kg subcutaneous injection twice daily on days 1 to 21 of a cycle for a total of £5,720 per cycle. Further details on cost of relevant comparators are available in SMC No. (666/10) dated 17 December 2010.[30]

ADDITIONAL INFORMATION

Vector Therapeutics did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Midostaurin for untreated acute myeloid leukaemia (TA523). June 2018.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- NHS. Clinical Guidelines for Leukaemia and other Myeloid Disorders – AML. 2016.
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