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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Treosulfan in combination with fludarabine for paediatric non-malignant disease before allogeneic stem cell transplant

NIHRIO ID	26772	**NICE ID**	10128
Developer/Company	Medac GmbH	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase II clinical trial

SUMMARY

Treosulfan in addition to fludarabine is in clinical development for paediatric non-malignant disease prior to allogeneic stem cell transplant. Treosulfan is a medicine given to patients before they have a bone marrow transplant from a donor known as 'allogeneic haematopoietic stem cell transplantation'. It is used as a 'conditioning' treatment to clear the patient's bone marrow and make room for the transplanted bone marrow cells, which can then produce healthy blood cells. Treosulfan is used together with another medicine called fludarabine for the treatment of a variety of disorders that require a bone marrow transplant.

In the body, treosulfan is converted into compounds called epoxides which kill cells, especially those that develop rapidly such as bone marrow cells, by attaching to their DNA while they are dividing. If licensed, treosulfan in addition to fludarabine will offer an additional option for conditioning therapy prior to allogeneic haematopoietic stem cell transplantation (HSCT) in paediatric patients with non-malignant diseases. This combination has the potential to reduce toxicity and improve treatment-related outcomes compared to other conditioning regimens.

PROPOSED INDICATION

Conditioning therapy prior to first allogeneic haematopoietic stem cell transplantation (HSCT) in paediatric patients with non-malignant diseases.[1]

TECHNOLOGY

DESCRIPTION

Treosulfan is a bifunctional alkylating agent which has been shown to possess antineoplastic activity in animal tumour screen and in clinical trials. The activity of treosulfan is due to the formation of epoxide compounds in vivo. The epoxides formed react with nucleophilic centres of the DNA and are responsible via secondary biological mechanisms for the antineoplastic effect. It is important that in vivo the monoepoxide first formed can already alkylate a nucleophilic centre of the DNA. This fixes the compound to this centre by chemical reaction before the second epoxide ring is formed.[2]

Fludarabine is a water-soluble fluorinated nucleotide analogue of the antiviral agent vidarabine, 9-ß-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase. Fludarabine phosphate is rapidly dephosphorylated to 2F-ara-A which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2F-ara-ATP. This metabolite has been shown to inhibit ribonucleotide reductase, DNA polymerase α/δ and ε, DNA primase and DNA ligase thereby inhibiting DNA synthesis. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occur.[3] While some aspects of the mechanism of action of 2F-ara-ATP are as yet unclear, it is assumed that effects on DNA, RNA and protein synthesis all contribute to inhibition of cell growth with inhibition of DNA synthesis being the dominant factor. In addition, in vitro studies have shown that exposure of CLL lymphocytes to 2F-ara-A triggers extensive DNA fragmentation and cell death characteristic of apoptosis.[3]

Treosulfan in combination with fludarabine conditioning regimen is currently in clinical development for the treatment of paediatric patients with non-malignant disease. In the phase II clinical trial (NCT02349906), participants randomised to the treosulfan based conditioning regimen will receive treosulfan intravenously at a dosage (based on body surface area) of 10, 12 or 14 g/m^2/day on three consecutive days (-6, -5 and -4). Treosulfan will be given over 2 hours as part of background conditioning regimen prior to allogeneic stem cell transplantation.[1]

INNOVATION AND/OR ADVANTAGES

The novel combination of treosulfan and fludarabine has shown to be a favourable combination for conditioning with respect to toxicity, the achievement of complete donor chimerism, and low Graft Versus Host Disease (GVHD) rate and with a low treatment-related mortality and relapse rate. Consequently, the overall and disease-free survival rates are promising in a poor-risk patient population.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, treosulfan is licensed in the EU/UK for the palliative treatment of epithelial ovarian cancer. The most commonly reported adverse events are myelosuppression and gastrointestinal complaints.[2]

Furthermore, treosulfan in combination with fludarabine is licenced in the EU as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non malignant diseases, and in paediatric patients older than one month with malignant diseases.[5]

Fludarabine is licensed in the EU/UK for the treatment of B-cell chronic lymphocytic leukaemia (CLL) in adult patients with sufficient bone marrow reserves. The most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anaemia), infection including pneumonia, cough, fever, fatigue, weakness, nausea, vomiting and diarrhoea. Other commonly reported events include chills, oedema, malaise, peripheral neuropathy, visual disturbance, anorexia, mucositis, stomatitis and skin rash. Serious opportunistic infections have occurred in patients treated with fludarabine. Fatalities as a consequence of serious adverse events have been reported.[3]

Treosulfan was granted orphan drug designation in the EU by the EMA for the conditioning treatment prior to haematopoietic progenitor cell transplantation in February 2004.[6]

PATIENT GROUP

DISEASE BACKGROUND

An allogeneic haematopoietic stem cell transplantation (HSCT) involves replacing the bone marrow stem cells of a patient (after high-dose conditioning treatment), with stem cells from a tissue-type matched or mismatched donor. Before a patient receives HSCT they need to have a type of treatment called a 'conditioning treatment' which prepares the body by eradicating the abnormal bone marrow to minimise the chance of the body rejecting the healthy donor cells. HSCT is a potentially curative treatment for various non-malignant diseases such as inborn errors of metabolism (metabolic disorders), primary immunodeficiencies, haemoglobinopathies and bone marrow failure syndromes.[7]

Primary immune deficiency disorders are a rare group of genetic diseases that are classified according to the nature of the deficiency (for example severe combined immunodeficiency, combined immune deficiency with or without associated disorders, antibody deficiency, phagocytic disorders, immune regulatory disorders and innate immune defects). Although the treatments vary according to the disorder and its complications, common treatments include immunoglobulin infusions, anti-microbial drugs and biological (monoclonal antibody) therapies.[7]

CLINICAL NEED AND BURDEN OF DISEASE

In England, the Hospital Episodes Statistics procedures for admitted children between 0 and 17 years old in 2017-18 recorded 154 admissions as main procedure for allogeneic peripheral blood stem cell transplant (OPCS-4 code X33.6) ; 41 admissions for allograft of bone marrow from sibling donor (OPCS-4 code W34.3); 37 admissions for allograft of bone marrow from

matched unrelated donor (OPCS-4 code W34.4); and, 13 admissions for allograft of cord blood stem cells to bone marrow (OPCS-4 code W99.1).[8]

The paediatric population eligible to receive treosulfan based conditioning regimen prior to HSCT for non-malignant diseases could not be estimated from available sources.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aim of allogeneic HSCT is to correct the hematopoietic or immunological dysfunction or enzymatic deficiency causing the underlying disease.[9]
Allogeneic HSCT can cure a number of non-malignant diseases in children. Among non-malignant diseases, aplastic anaemia, sickle cell disease and, autoimmune diseases can also be effectively treated with HSCT.[10]

CURRENT TREATMENT OPTIONS

Before a patient receives HSCT they need to have a type of treatment called a 'conditioning treatment' which prepares the body by eradicating the abnormal bone marrow to minimise the chance of the body rejecting the healthy donor cells.[11]

Currently the standard high-dose intensity (myeloablative) conditioning regimens include:[11]
- cyclophosphamide and total body irradiation
- cyclophosphamide and busulfan
- cyclophosphamide and thiotepa
- high-dose busulfan with fludarabine with or without thiotepa

Reduced intensity conditioning regimens include:[11]
- low-dose busulfan with fludarabine
- melphalan and fludarabine

PLACE OF TECHNOLOGY

If licensed, conditioning treatment with treosulfan in combination with fludarabine will offer an additional option prior to allogeneic haematopoietic stem cell transplantation (HSCT) in paediatric patients with non-malignant diseases, with the potential to reduce toxicity and improve treatment-related mortality compared to other conditioning regimens.

CLINICAL TRIAL INFORMATION

Trial	NCT02349906, MC-FludT.16/NM; children up to 17 years; treosulfan vs. busulfan, each administered as part of a standardised fludarabine-containing treatment; phase II
Sponsor	Medac GmbH
Status	Ongoing

Source of Information	Trial registry[1]
Location	EU (not inc UK)
Design	Randomised, active comparator-controlled, open-label study
Participants	n=100 (planned); children aged up to 17 years; non-malignant disease indicated for first myeloablative allogeneic HSCT, including inborn errors of metabolism, primary immunodeficiencies, haemoglobinopathies and bone marrow failure syndromes; first allogeneic HSCT; available matched sibling donor (MSD), matched family donor (MFD) or matched unrelated donor (MUD). For bone marrow (BM) and peripheral blood (PB) match is defined as at least 9/10 allele matches after four digit typing in human leucocyte antigen (HLA)-A, -B, -C, -DRB1 and DQB1 antigens. For umbilical cord blood (UCB) match is defined as at least 5/6 matches after two digit typing in HLA-A and -B and four digit typing in DRB1 antigens.
Schedule	Participants will be randomised to one of the treatment arms: • Arm 1: Subjects will receive one treosulfan dose per day (10, 12 or 14 g/m^2/day, based on body surface area) administered i.v. on three consecutive days (-6, -5 and -4); given over 2 hours as part of background conditioning regimen prior to allogeneic stem cell transplantation. • Arm 2: Subjects will receive total daily busilvex dose (3.2 to 4.8 mg/kg/day, based on body weight) according to authorised dosage for children and adolescents administered i.v. as part of the background conditioning regimen on four consecutive days (days -7, -6, -5 and -4); given in 1, 2, or 4 portions per day according to the respective hospital's standard.
Follow-up	day -7 to day +100
Primary Outcomes	Comparative evaluation of freedom from transplant (treatment)-related mortality (TRM), defined as death from any transplant-related cause from the day of first administration of study medication (day -7) until day +100 after HSCT. [Time frame: day -7 to day +100]
Secondary Outcomes	Engraftment; donor-type chimerism, overall survival, graft failure, evaluation of rescue therapies, pharmacokinetics
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date in July 2020.

ESTIMATED COST

Treosulfan is already marketed in the UK. The NHS indicative price for treosulfan is:[12]

- A pack of 5 x 1 mg powder for solution for injection vials costs £494.40
- A pack of 5 x 5 mg powder for solution for injection vials costs £2,434.25

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE health technology appraisal in development. Rivogenlecleucel for treating haematological non-malignant diseases in children and young people undergoing haploidentical haematopoietic stem cell transplant (GID-TA10405). Expected publication date to be confirmed.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Children). B04/S/b

OTHER GUIDANCE

- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All ages); Revised. B04/P/a. 2015.[13]

ADDITIONAL INFORMATION

Medac GmbH 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.

REFERENCES

1 ClinicalTrials.gov. *Treosulfan-based Versus Busulfan-based Conditioning in Paediatric Patients With Non-malignant Diseases*. *Trial ID: NCT02349906*. Available from: https://clinicaltrials.gov/ct2/show/NCT02349906 [Accessed 18 October 2019].

2 electronic Medicines Compendium (eMC). *Treosulfan Injection (medac UK).* Available from: https://www.medicines.org.uk/emc/product/1414/smpc [Accessed 18 October 2019].

3 electronic Medicines Compendium (eMC). *Fludara 50mg powder for solution for injection or infusion.* Available from: https://www.medicines.org.uk/emc/product/1125/smpc [Accessed 18 October 2019].

4 Casper J, Knauf W, Kiefer T, Wolff D, Steiner B, Hammer U, et al. Treosulfan and fludarabine: a new toxicity-reduced conditioning regimen for allogeneic hematopoietic stem cell transplantation. *Blood*. 2004 Jan 15;103(2):725-31. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12947008 10.1182/blood-2002-11-3615.

5 European Medicines Agency (EMA). *Trecondi* Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/trecondi [Accessed 19 November 2019].

6 European Medicines Agency (EMA). *Public summary of positive opinion for orphan designation of treosulfan for the conditioning treatment prior to haematopoietic progenitor cell transplantation* Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/04/186-public-summary-positive-opinion-orphan-designation-treosulfan-conditioning-treatment-prior_en.pdf [Accessed 21 October 2019].

7 National Institute for Health and Care Excellence (NICE). *Treosulfan with fludarabine for non-malignant disease before allogeneic stem cell transplant [ID1540].* Available from: https://www.nice.org.uk/guidance/gid-ta10453/documents/draft-scope-pre-referral [Accessed 18 October 2019].

8 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 [Accessed 21 October 2019].

9 Faraci M, Bagnasco F, Leoni M, Giardino S, Terranova P, Subissi L, et al. Evaluation of Chimerism Dynamics after Allogeneic Hematopoietic Stem Cell Transplantation in Children with Nonmalignant Diseases. *Biol Blood Marrow Transplant*. 2018 May;24(5):1088-93. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29292059 10.1016/j.bbmt.2017.12.801.

10 Galgano L, Hutt D. HSCT: How Does It Work? In: Kenyon M, Babic A, eds. *The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT*. Cham (CH) 2018:23-36.

11 National Institute for Health and Care Excellence (NICE). *Treosulfan with fludarabine for non-malignant disease before allogeneic stem cell transplant - Draft scope.* Available from: https://www.nice.org.uk/guidance/gid-ta10453/documents/draft-scope-pre-referral [Accessed 21 November 2019].

12 British National Formulary (BNF). *Treosulfan.* Available from: https://bnf.nice.org.uk/medicinal-forms/treosulfan.html [Accessed 21 October 2019].

13 National Health Service (NHS). *Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised.* Available from: https://www.england.nhs.uk/wp-content/uploads/2018/07/Haematopoietic-stem-cell-transplantation-All-Ages.pdf [Accessed 29 October 2019].

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