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Treosulfan in combination with fludarabine for malignant and non-malignant diseases - prior to stem cell transplantation

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LAY SUMMARY

Acute myeloid leukaemia (AML) is a type of blood cancer that starts from young white blood cells in the bone marrow. Myelodysplastic syndrome (MDS) is a similar condition, where blood cells in the bone marrow do not mature and become healthy blood cells. Both AML and MDS usually occur in older people. If a patient with these conditions has been successfully treated, there may be a significant risk of the condition developing again. These patients may be offered stem cell transplantation (SCT), which will replace the stem cells in the bone marrow. Before a patient receives SCT they need to have a type of treatment called a "conditioning therapy" to prepare the body and get rid of the existing bone marrow.

Treosulfan given with fludarabine is being developed as a new conditioning therapy for people with conditions like AML or MDS prior to SCT. Both drugs are administered by injection and clinical studies have shown that, compared to current conditioning therapies, treosulfan might increase the success of the SCT with fewer complications, allowing people to live for longer.

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TARGET GROUP

Malignant and non-malignant diseases, indicated for haematopoietic stem cell transplant (HSCT) but considered to be at increased risk for standard conditioning therapies, aged 1 month to 70 years – prior to HSCT; in combination with fludarabine

TECHNOLOGY

DESCRIPTION

Treosulfan (Ovastat) 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. Treosulfan is converted in vitro under physiological conditions (pH 7.4; 37 °C) non-enzymatically via a monoepoxide to the diepoxide (diepoxybutane) with a half-life of 2.2 hours. 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.[1]

Fludarabine is a chemotherapy drug used in the treatment of chronic lymphocytic leukaemia. It acts at DNA polymerase alpha, ribonucleotide reductase and DNA primase, results in the inhibition of DNA synthesis, and destroys cancer cells.[2]

Treosulfan in combination with fludarabine is intended for use in children aged from one month and adults aged up to 70 years with malignant and non-malignant diseases (including acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS)) as a conditioning regimen prior to haematopoietic stem cell transplant (HSCT).[3] In the phase III clinical trial (NCT00822393), treosulfan 10g/m^2/day intravenous infusion (IV) on days -4, -3, and -2 was administered to adults with AML or MDS in combination with fludarabine 30mg/m^2/day IV on days -6 to -2 prior to HSCT.[4] In the phase II paediatric clinical trial (NCT02349906) treosulfan 10, 12 or 14g/m^2/day (based on body surface area) was administered on days -6, -5 and -4 prior to HSCT.[5]

Treosulfan is licensed in the UK for palliative treatment of epithelial ovarian cancer.[1,6] Very common adverse effects (≥ 1/10) include myelosuppression (leukocytopenia, thrombocytopenia, anaemia), vomiting, nausea, alopecia (usually mild) and bronze skin pigmentation. Common adverse effects (≥ 1/100 to <1/10) include infections (mycotic, viral, bacterial).[1]

Treosulfan in combination with fludarabine does not currently have a marketing authorisation approval in the UK as a conditioning regimen prior to HSCT.

INNOVATION and/or ADVANTAGES

Treosulfan in combination with fludarabine is a myeloablative reduced-toxicity conditioning (RTC) regimen.[7] This regimen has been shown to be myeloablative (as indicated by profound, long-lasting and usually irreversible marrow aplasia), is associated with a favourable safety profile[3], and has also been shown to enable fast and sustained engraftment.[3,8]

In contrast to busulfan (a similar drug currently licensed in the UK for RIC), treosulfan does not require enzymatic activation and therefore bypasses hepatic metabolism. Pharmacokinetic studies of both single and multiple IV infusions of treosulfan have shown low inter-patient and intra-patient variability, and do not require levels to adjust the dosing, unlike busulfan.[9]

In the phase III trial, treosulfan was compared to busulfan.[4,10] Results published from this trial showed that complete donor-type chimerism was significantly higher after the treosulfan regimen. At 24 months after HSCT, event-free survival (EFS) was significantly non-inferior (64.0% vs. 50.4%) corresponding to a hazard ratio (HR) of 0.65 in favour of treosulfan (p=0.0000164; one-sided p-value for testing non-inferiority). Further, overall survival was significantly higher after the treosulfan regimen (71.3% vs. 56.4%; HR 0.61; p=0.0082), and was associated with a significant reduction in transplantation-related mortality (12.1% vs. 28.2%; HR 0.54; p=0.0201). Notably, the cumulative incidence of relapse/progression was comparable between both regimens (24.6% vs. 23.3%). Consequently, this led to a significantly superior 24-month GvHD and relapse-free survival after the treosulfan compared to the busulfan regimen (51.4% vs. 38.4%; HR 0.72; p=0.0224).[11]

DEVELOPER

Medac GmbH

REGULATORY INFORMATION/ MARKETING PLANS

Treosulfan was designated an orphan drug in the EU for conditioning treatment prior to HSCT in February 2004.[12]

Treosulfan was designated an orphan drug in the USA for conditioning treatment prior to HSCT in April 2015.[13]

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.[14]

The majority of patients with AML enter remission upon induction chemotherapy, but the risk of relapse is considerable, and varies greatly according to age and genetic subtype.[15] Haematopoietic stem cell transplant (HSCT) is a potentially curative treatment that should be offered to patients with AML with adverse risk disease at high risk of relapse.[9]

Myelodysplastic syndrome (MDS) is a group of conditions where the bone marrow produces blood cells that are not fully developed. These abnormal blood cells either stay in the bone marrow or are destroyed before they get into the bloodstream. As the condition develops, the bone marrow becomes full and the immature blood cells spill out into the bloodstream.[16] Patients with high-risk MDS have a 33%-45% change of progression to AML and a median survival of around 12 months

without intervention. Clinicians should identify patients suitable for HSCT at diagnosis, as this therapy has the greatest curative potential. Early intensive treatment and consolidation with HSCT offers a survival advantage.[17]

Treosulfan is also being developed as an RTC for other, non-malignant conditions where treatment involves HSCT, including haemoglobinopathy, primary immune deficiency or inherited bone marrow failure syndrome.[18]

CLINICAL NEED and BURDEN OF DISEASE

The latest available statistics show that in 2012 there were 1,361 first allograft transplants, including 718 for leukaemia, and 208 for MDS or mucopolysaccharide diseases (MPS), and 211 for lymphoma.[19]

The population likely to be eligible to receive treosulfan in combination with fludarabine could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adults). B04/S/a.
- 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 Adult Myelodysplastic Syndromes. December 2013.[17]

CURRENT TREATMENT OPTIONS

Haematopoietic stem cell transplant (HSCT) is a potentially curative treatment for some patients with AML or MDS. The transplant procedure begins with conditioning therapy to kill leukaemia cells, eradicate existing bone marrow tissue (in order to provide space for engraftment of transplanted donor stem cells) and to suppress the patient's immune system so as to minimise the risk of graft rejection.[19] Standard conditioning regimens are associated with substantial morbidity and mortality, and consequently are restricted to younger and fitter patients.[3] Traditionally, high-dose intensity conditioning has been the standard approach to HSCT for AML, with commonly used myeloablative

conditioning regimens (MAC-HCT) including cyclophosphamide and total body irradiation, cyclophosphamide and busulfan, or fludarabine and busulfan.[9]

Reduced intensity conditioning (RIC) has been widely introduced over the past 15 years and is now widely used for AML patients, particularly in older or heavily pre-treated patients and in those with medical comorbidities.[9] Most studies have shown that more intensive regimens control AML better, but leukaemia-free survival is not improved due to excess non-relapse mortality (NRM), and MAC-HCT should be used in patients deemed fit.[9]

For patients with MDS, studies have shown significantly increased relapse rates after RIC when compared with patients transplanted after MAC-HCT, but decreased NRM in the RIC cohorts, resulting in a comparable overall survival of both groups. As for AML, MAC-HCT should be used for higher-risk patients with good performance status and no comorbidities, whereas less fit patients or patients with comorbidities should be considered for RIC.[20]

As the incidence of AML and MDS is age-dependent and the vast majority of patients are older than 50 years, only a small minority of patients qualify for HSCT with standard conditioning regimens.[8] RIC regimens have been developed to make HSCT accessible to older and medically infirm patients. In RIC regimens, the dose intensity is reduced in an attempt to reduce transplant-related mortality (TRM) while potent immunosuppression is exerted to help with the engraftment and graft-versus leukaemia effect.[15]

EFFICACY and SAFETY

Trial	NCT00822393, EudraCT2008-002356-18, MC-FludT.14/L; treosulfan vs busulfan; phase III
Sponsor	Medac GmbH
Status	Published in abstract
Source of Information	Abstract[11], Trial Registry[4]
Location	6 EU countries, not UK
Design	Randomised, active-controlled
Participants	n=460; aged 18-70 yrs; AML in complete remission or MDS; indicated for HSCT but considered to be at increased risk for standard conditioning therapies as aged ≥50 yrs and/or HCT-CI score >2; prior to HSCT
Schedule	Randomised to treosulfan 10g/m^2/day IV on days -4, -3, and -2; or busulfan 3.2mg/kg/day IV on days -4 and -3; both in combination with fludarabine 30mg/m^2/day IV on days -6 to -2.
Follow-up	Follow-up 2 yrs
Primary Outcomes	Event-free survival (EFS) [Time Frame: within 2 yrs after transplantation]
Secondary Outcomes	Comparative evaluation of incidence of CTC grade III/IV mucositis/stomatitis between day -6 and day +28.
Key Results	At 24 months after HSCT, EFS was significantly non‑inferior (64.0% vs. 50.4%) corresponding to a hazard ratio (HR) of 0.65 in favour of treosulfan (p=0.0000164; one‑sided p‑value for testing non‑inferiority). Further, overall survival was significantly higher after the treosulfan regimen (71.3% vs. 56.4%;

	HR 0.61; p=0.0082), and was associated with a significant reduction in transplantation‑related mortality (12.1% vs. 28.2%; HR 0.54; p=0.0201). Notably, the cumulative incidence of relapse/progression was comparable between both regimens (24.6% vs. 23.3%). Consequently, this led to a significantly superior 24‑month GvHD and relapse‑free survival after the treosulfan compared to the busulfan regimen (51.4% vs. 38.4%; HR 0.72; p=0.0224).
Adverse effects (AEs)	Safety results in terms of acute adverse events (CTCAE v4.03) were well comparable between both regimens as were the incidences and severity degrees of acute and chronic GvHD.

Trial	NCT01063660, MC-FludT.7/AML; treosulfan; phase II
Sponsor	Medac GmbH
Status	Published
Source of Information	Publication[3], Trial Registry[21]
Location	4 EU countries, not UK
Design	Non-randomised, non-controlled
Participants	n=75; aged 18-60 yrs; AML with <5% myeloblast in the bone marrow; indicated for HSCT; prior to HSCT
Schedule	Treosulfan 14g/m^2/day IV on days -6, -5, and -4 and fludarabine 30mg/m^2/day IV on days -6 to -2.
Follow-up	Follow-up 1 yr
Primary Outcomes	Efficacy: Evaluation of engraftment Safety: Evaluation of the incidence of CTC grade III/IV adverse events hyperbilirubinemia and mucositis/stomatitis, veno-occlusive disease or seizures between day -6 and day +28.
Secondary Outcomes	• Evaluation of disease free survival • Evaluation of overall survival • Evaluation of relapse incidence • Donor chimerism on days +28, +56 and +100 • Evaluation of non-relapse mortality on days +28 and +100
Key Results	All patients showed primary engraftment of neutrophils after a median of 20 days. Acute GvHD grade II–IV occurred in 21% and extensive chronic GvHD occurred in 16% of the patients. After a median follow-up of 715 days, the 2-year overall and DFS estimates were 61% and 55%, respectively. The 2-year incidences of relapse and non-relapse mortality reached 34% and 11%, respectively.
Adverse effects (AEs)	Non-haematological adverse events grade III–IV in severity included mainly infections (59%) and gastrointestinal symptoms (7%).

Trial	NCT01062490, MC-FludT.8/MDS; treosulfan; phase II
Sponsor	Medac GmbH
Status	Published

Source of Information	Publication[8], Trial Registry[22]
Location	4 EU countries, not UK
Design	Non-randomised, non-controlled
Participants	n=45; aged 18-65 yrs; MDS; indicated for HSCT; prior to HSCT
Schedule	Treosulfan 14g/m^2/day IV on days -6, -5, and -4 and fludarabine 30mg/m^2/day IV on days -6 to -2.
Follow-up	Follow-up 2 yrs
Primary Outcomes	Efficacy: Evaluation of engraftment Safety: Evaluation of the incidence of CTC grade III/IV adverse events hyperbilirubinemia and mucositis/stomatitis, veno-occlusive disease or seizures between day -6 and day +28.
Secondary Outcomes	• Evaluation of disease free survival • Evaluation of overall survival • Evaluation of relapse incidence • Evaluation of non-relapse mortality on days +28, +100
Key Results	All but one patient showed primary engraftment of neutrophils after a median of 17 days. Acute GvHD grade II–IV developed in 24%, and extensive chronic GvHD in 28% of the patients. After a median follow-up of 780 days, the 2-year overall and disease-free survival estimates were 71% and 67%, respectively. The 2-year cumulative incidences of non-relapse mortality and relapse were 17% and 16%, respectively.
Adverse effects (AEs)	Non-hematologic adverse events of grade III–IV in severity included mainly infections and gastrointestinal symptoms (80% and 22% of the patients, respectively).

Trial	NCT00919503, NCI-2010-01277; treosulfan; phase II
Sponsor	Medac GmbH
Status	Published
Source of Information	Publication[23], Trial Registry[24]
Location	USA
Design	Non-randomised, non-controlled
Participants	n=31; aged 0-49 yrs; non-malignant disease; indicated for HSCT; prior to HSCT
Schedule	Treosulfan 14g/m^2/day IV on days -6, -5, and -4 and fludarabine 30mg/m^2/day IV on days -6 to -2.
Follow-up	Follow-up 2 yrs
Primary Outcomes	Preliminary efficacy [Time Frame: 1 yr following transplant]
Secondary Outcomes	• Non-relapse mortality [Time Frame: up to 1 yr following transplant] • Incidence of grade II-IV acute GvHD [Time Frame: within first yr following transplant] • Incidence of chronic GvHD [Time Frame: within two yrs following transplant] • Donor chimerism [Time Frame: up to 5 yrs] • Disease response following HSCT [Time Frame: up to 5 yrs] • Immune reconstitution following HSCT [Time Frame: up to 5 yrs]

	• Incidence of infections [Time Frame: within first yr following transplant] • Overall survival [Time Frame: within two yrs following transplant]
Key Results	All patients engrafted. Day-100 TRM was 0%. With a median follow-up of 2 years, the 2-year survival was 90%. Three patients died of GVHD, recurrent hemophagocytic lymphohistiocytosis, and a surgical complication, respectively. The cumulative incidences of grades II to IV and III to IV acute GVHD at day 100 and chronic GVHD at 2 years were 62%, 10%, and 21%, respectively.
Adverse effects (AEs)	The most common toxicities associated with treosulfan were skin rash, mild mucositis, and transient elevation of hepatic transaminases.

Trial	NCT02333058, MC-FludT.17/M; treosulfan; phase II
Sponsor	Medac GmbH
Status	Published
Source of Information	Publication[18], Trial Registry[25]
Location	5 EU countries, incl UK
Design	Non-randomised, non-controlled
Participants	n=77; aged 0-17 yrs; haematological malignant disease; indicated for HSCT; prior to HSCT
Schedule	Infants <1yr: Treosulfan 30g/m^2/day IV on days -6, -5, and -4 Children ≥1yr: Treosulfan 42g/m^2/day IV on days -6, -5, and -4 Both with Fludarabine 30 mg/m2/day IV on days from -7 to -3 prior to HSCT +/- ThioTEPA 2 x 5mg/kg/day IV on day -2.
Follow-up	Active follow-up 1 yrs
Primary Outcomes	Freedom from transplant (treatment)-related mortality (TRM) [Time Frame: from the day of first administration of study medication until day +100 after HSCT]
Secondary Outcomes	• Safety including early toxicity until day +100 after HSCT, serious adverse reactions (SARs) until the end of the longer-term follow-up phase [Time Frame: until 12 mths after HSCT] • Hepatic sinusoidal obstruction syndrome (HSOS), lung toxicity (CTCAE term pulmonary fibrosis), hepatic toxicity and infections of any CTCAE grade (non-serious and serious) [Time Frame: until day +100 after HSCT] • Donor-type chimerism [Time Frame: on day +28, day +100 and 12 mths after HSCT] • Non relapse mortality (NRM), transplant related mortality (TRM), graft failure rate, incidence of relapse/progression, relapse-free/progression-free survival (RFS/PFS) and overall survival (OS) [Time Frame: after 12 mths after HSCT and until the end of the longer-term follow-up phase] • Incidence and severity of acute (until day +100) and chronic (until 12 mths after HSCT) graft versus host disease (aGvHD/cGvHD) [Time Frame: until 12 mths after HSCT] • Use of rescue therapies including donor-lymphocyte infusions (DLIs) and further conditioning regimens [Time Frame: until 12 mths after HSCT]

	• PK parameters of Treosulfan and its epoxides [Time Frame: day -6 prior to HSCT]
Key Results	No correlation was found between treosulfan exposure and the early clinical outcome parameters: engraftment, acute graft-versus-host disease and donor chimerism. This study provides the first evidence in a large cohort of paediatric patients of high variability in treosulfan pharmacokinetics and an association between treosulfan exposure and early toxicity.
Adverse effects (AEs)	High treosulfan exposure (>1650 mg*h/l) was associated with an increased risk of mucosal [Odds ratio (OR) 4·40; 95% confidence interval (CI) 1·19–16·28, P = 0·026] and skin toxicity (OR 4·51; 95% CI 1·07–18·93, P = 0·040).

Trial	NCT02349906, MC-FludT.16/NM; treosulfan; phase II
Sponsor	Medac GmbH
Status	Ongoing
Source of Information	Trial Registry[5]
Location	5 EU countries, not UK
Design	Randomised, active-controlled
Participants	n=100 (planned); aged 0-17 yrs; non-malignant disease; indicated for HSCT; prior to HSCT
Schedule	Treosulfan 10, 12 or 14g/m^2/day (based on body surface area) IV on days -6, -5, and -4 given over 2 hours **or** Busilvex 3.2 to 4.8mg/kg/day (based on body weight) IV on days -7, -6, -5 and -4, given in 1, 2 or 4 portions per day
Follow-up	Active follow-up 100 days
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	None stated
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study primary completion date reported as December 2018

ESTIMATED COST and IMPACT

COST

Treosulfan is already marketed in the UK for the treatment of palliative treatment of epithelial ovarian cancer; 5 vials of 1g powder for solution for injection has an NHS indicative price of £269, and 5 vials of 5g powder for solution for injection has an NHS indicative price of £1,040.[26]

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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