ISRCTN13400668 https://doi.org/10.1186/ISRCTN13400668

Targeted radiotherapy for AL-Amyloidosis – TRALA

Submission date	Recruitment status
08/02/2016	No longer recruiting
Registration date	**Overall study status**
15/11/2016	Completed
Last Edited	**Condition category**
18/01/2023	Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Amyloidosis is the name for a group of rare, serious condition in which an abnormal protein called amyloid is produced by the bone marrow (spongy tissue inside some bones where new blood cells are produced). Overtime, this protein builds up in tissues, affecting the way that organs work. There are several types of amyloid proteins, the most common being AL (A is for amyloid, L is for Light Chain). Chemotherapy (an anti-cancer drug treatment) and a stem cell transplant (a procedure where halthy cells, called stem cells are infused into the body to replace damaged or diseased bone marrow) can both be used to treat AL amyloidosis. In a stem cell transplant, special cells which have the ability to turn into different types of cell (stem cells), which are usually taken from that patient, are infused into the body to replace damaged or diseased cells. With a stem cell transplant, patients have very high doses of chemotherapy, (sometimes with whole body radiotherapy) to damage or destroy the abnormal cells in the bone marrow. The stem cells then replace these cells so the body can start making healthy blood cells again. In this study, doctors want to look at using targeted radiotherapy in place of high dose chemotherapy. Targeted radiotherapy means that the radiation is given directly to their bone marrow. This destroys the abnormal cells in the same way as high dose chemotherapy does. They have the radiation from a radiolabelled antibody (anti CD66 radiolabelled with Yttrium 90) which is as a single treatment into their vein. This treatment has been used alongside chemotherapy for people with different types of blood cancer. But this is the first time it is being used for people with amyloidosis. The aim of this study is to see how safe it is to use targeted radiotherapy as part of their stem cell transplant, learn more about the side effects and see how well it works.

Who can participate?
Adults with amyloidosis

What does the study involve?
Participants have stem cells collected using normal procedures before the study starts. As part of the study patients have a visit to the hospital to work out how much radiation they should have. They have a different radiolabelled drug (anti CD66 radiolabelled with Indium-111) to have this test. This is the dosimetry and imaging visit. This must be favourable before any treatment is given. About 1 week later they have their radiation treatment with radiolabelled drug anti CD66

radiolabelled with Yttrium-90. This is the study treatment. They have both the radiolabelled drugs as an injection into a vein. They might be also asked to have a bone marrow biopsy (sample taken) between 1 to 14 days after having the Yttrium-90. After the dose finding test, participants have scans 1, 3 and 4 days afterwards. 7 days before their transplant they go to their transplant centre. Their neutrophils (white blood cells that fight infection) are at their lowest so they are be antibiotics to help prevent an infection. They then have their stem cell transplant as they would normally. Participants see the study doctors 30 days after transplant to have a physical examination, blood tests and a bone marrow test. 100 days after their transplant they see the doctors at the National Amyloidosis Centre and have the same tests repeated.

What are the possible benefits and risks of participating?
There are no direct benefits involved with participating in this study. Most of the treatments and assessments the patients will receive/undergo will be standard of care (i.e. they will receive this anyway and so there are no risks other than those related to the standard procedures used.

Where is the study run from?
1. Southampton General Hospital (UK)
2. University College Hospital (UK)
3. The Queen Elizabeth Hospital (UK)
4. Freeman Hospital (UK)

When is the study starting and how long is it expected to run for?
December 2013 to July 2020

Who is funding the study?
Leukaemia and Lymphoma Research (UK)

Who is the main contact?
Mrs Yvanne Enever
yvanne.enever@pharmexcel.co.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-targeted-radiotherapy-as-part-of-a-stem-cell-transplant-for-amyloidosis-trala

Contact information

Type(s)
Public

Contact name
Mrs Yvanne Enever

Contact details
Albany Chambers
26 Bridge Road East
Welwyn Garden City
United Kingdom
AL7 1HL
+44 (0) 203 642 6654
yvanne.enever@pharmexcel.co.uk

Additional identifiers

EudraCT/CTIS number
2015-002231-18

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
19732

Study information

Scientific Title
A Phase I/IIa Study of Targeted Radiotherapy alone for Stem Cell Transplant Conditioning in Systemic AL Amyloidosis

Acronym
TRALA

Study objectives
The aim of this study is to assess if targeted radiotherapy used as a sole conditioning treatment prior to autologous stem cell transplantation in patients with Systemic AL Amyloidosis is at least as safe and effective, if not better, than existing treatments for Systemic AL Amyloidosis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central - Hampshire B Research Ethics Committee, 13/11/2015, ref: 15/SC/0565

Study design
Open labelled multi centre phase I/IIa study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Systemic AL-Amyloidosis

Interventions
Three treatment levels with step-wise increase of the infused [90Y]-labelled anti-CD66 radiation activity. There will be 3 patients in each cohort (which can be expanded if required due to toxicities seen). A minimum of 12 patients maximum of 18 will be recruited.

All patients will undergo dosimetry using [111In]- CHX A"-DTPA anti-CD66 antibody (drug product).This is a one off dose and administered intravenously. All patients must have favourable dosimetry before they are treated with - CHX A"-DTPA anti-CD66 antibody (drug product)[90Y]. The conditioning treatment [90Y] again is a one off treatment administered intravenously.

There are three treatment levels, representing increasing infused radiation activity levels:
1. 30.0 MBq/kg lean body weight [90Y]-radio-labelled murine anti-CD66.
2. 40.0 MBq/kg lean body weight [90Y]-radio-labelled murine anti-CD66.
3. 45.0 MBq/kg lean body weight [90Y]-radio-labelled murine anti-CD66

After their conditioning treatment patients will undergo a stem cell transplant. They are then seen at day 30 and day 100 post stem cell transplant, after which they have completed the study.

The study would recruit patients with AL-amyloidosis due to undergo autologous stem cell transplantation.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
1. [111In]-radio labelled anti-CD66 (dosimetry) 2. [90Y]-radio-labelled anti-CD66 (conditioning treatment)

Primary outcome measure
1. Specific organ toxicity as measured, following patient review, using the CTCAE version 4.0
2. Adverse event rate is measured following patient review and interviews and is measured using the definitions of an adverse event under the clinical trials directive 2001/20/EC

Secondary outcome measures
1. Disease response as determined by changes in the free light chain assay (FLCa) pre and post [90Y]-labelled anti-CD66 and post transplantation
2. Clonal plasma cell population as determined by FLOW cytometry pre and post transplantation (D100)
3. NT-proBNP levels are measured by taking blood samples pre and post transplant (D100)
4. Time to progression (TTP) is measured using the NCI definition of TTP which is the length of time from start of treatment with [90Y]-labelled anti-CD66 until Amyloidosis starts to get worse or spread to other parts of the body
5. Overall Survival (OS) is measured using the NCI definition of OS which is the percentage of people in the study who are alive five years after their start of treatment

6. To establish a dosimetry model to be used in AL-Amyloidosis patients by comparing organ dosimetry from previous trials using the same antibody vector
7. Platelet and neutrophil engraftment is assessed by measuring an increase in platelet and neutrophil counts by taking blood samples as per routine practice after transplantation
8. Detection of Human Anti-Mouse Antibodies (HAMA) is measured by taking blood samples at defined intervals post transplantation

Overall study start date
02/12/2013

Completion date
07/07/2020

Eligibility

Key inclusion criteria
1. Aged ≥18 years
2. Diagnosis of systemic AL-amyloidosis, either as a new diagnosis or recurrent disease
3. Measurable clonal plasma cell dyscrasia
4. Amyloid related organ dysfunction or organ syndrome
5. Estimated life expectancy of at least 6 months (as defined at trial entry)
6. Sufficient stem cells for two transplant procedures
7. Bone Marrow (BM) cellularity >20%
8. Eligible for ASCT in AL amyloidosis defined as fulfilling all of the following criteria:
8.1. ECOG Performance Status of 0 or 1
8.2. Cardiac troponin-T <0.07 µg/L
8.3. NYHA heart failure class of <3
8.4. No more than 3 organs involved by amyloidosis by consensus guidelines
8.5. Creatinine clearance or isotope GFR ≥30ml/min
8.6. Bilirubin ≤1.5 times and alkaline phosphatase ≤3 x upper limit of normal
8.7. AST or ALT <2.5 x upper limit of normal range
8.8. Mean left ventricular wall thicknesses of <16mm by echocardiography
8.9. Absence of clinically important amyloid related autonomic neuropathy
8.10. Absence of clinically important amyloid related gastro intestinal haemorrhage
9. Capable of providing written, informed consent
10. Women of child bearing potential should use adequate forms of contraception
10.1. Intrauterine Device (IUD)
10.2. Hormonal based contraception (pill, contraceptive injection etc.)
10.3. Double Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
10.4. True abstinence (this is defined as refraining from heterosexual intercourse after receiving [111In] at the Dosimetry and Imaging visit through to final study visit

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
12 (maximum 18)

Total final enrolment
10

Key exclusion criteria
1. Overt symptomatic multiple myeloma
2. Amyloidosis of unknown or non AL type
3. Localised AL-amyloidosis (in which amyloid deposits are limited to a typical single organ, for example the bladder or larynx, in association with a clonal proliferative disorder within that organ)
4. Trivial or incidental AL amyloid deposits in the absence of a significant amyloid related organ syndrome (e.g., isolated carpal tunnel syndrome)
5. NYHA Class III or IV heart failure
6. Liver involvement by amyloid causing bilirubin >1.5 times upper limit of normal
7. Concurrent active malignancies, except surgically removed basal cell carcinoma of the skin or other in situ carcinomas
8. Pregnant, lactating or unwilling to use adequate contraception
9. Intolerance / sensitivity to any of the study drugs
10. Known positive Human anti-murine antibodies (HAMA)
11. Unable to provide written informed consent

Date of first enrolment
08/07/2016

Date of final enrolment
30/09/2017

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
University College Hospital
235 Euston Road
Fitzrovia
London
United Kingdom
NW1 2BU

Study participating centre
The Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
Freeman Hospital
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

Sponsor details
Tremona Road
Southampton
England
United Kingdom
SO16 6YD
+44 23 8120 6083
Ailsa.duckworth@uhs.nhs.uk

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Charity

Funder Name
Leukaemia and Lymphoma Research

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Data will be tabulated and analysed as described in the statistical plan. A final study report will be prepared by the Chief Investigator (Dr Kim Orchard) for submission to the Ethics Committee and Competent Authority. The time period from the completion of follow-up of the last trial patient and submission of the report will follow regulatory guidelines. All publications relating to the study will follow the Consort Guidelines.
The results will be published on the EUdraCT database and in peer review journals.

Intention to publish date
31/12/2021

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V2.1	08/03/2015	15/11/2016	No	Yes
Other unpublished results		25/06/2021	22/08/2022	No	No
HRA research summary			28/06/2023	No	No