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WT1 TCR gene therapy for leukaemia: a phase I /II safety and toxicity study (WT1 TCR-001)

Submission date 31/03/2010	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 31/03/2010	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 21/04/2020	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-a-type-of-gene-therapy-for-acute-myeloid-leukaemia-and-chronic-myeloid-leukaemia

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2006-004950-25

Protocol serial number
5099

Study information

Scientific Title

A phase I/II safety and toxicity study on the use of WT1 TCR gene therapy for adult patients with acute and chronic myeloid leukaemia

Acronym
WT1 TCR-001

Study objectives
One of the main functions of the immune system is to protect the body from infection. It is now clear that the immune system also plays a role in preventing the development or controlling the growth of some cancers. The most important cells of the immune system for this particular task are a group of white blood cells called the T lymphocytes (T cells). It is known from bone marrow transplantation and T cell infusions that leukaemia can be controlled or cured by a strong T cell immune response. Despite this, many other patients develop leukaemia even with a normal immune system. This study wants to test a new way of strengthening the patient's own immune response to their leukaemia by increasing the number of patient T cells which can recognise and kill the leukaemia cells.

The T cells have a receptor (the T cell receptor [TCR]), which enables them to recognise particular abnormalities on the surface of the target cells (virally infected cells or cancer /leukaemia cells). Each TCR recognises a particular fragment of a protein (peptide epitope). Normally, patients have a wide range of different T cells, which recognise many different epitopes on the surface of 'target cells'. It is possible that they have only a very few, or no T cells, which are able to recognise the abnormal leukaemia cells.

The Wilms' tumour antigen 1 (WT1) is a protein, peptides of which are present at abnormally high levels on the surface of leukaemia cells. In the research laboratory we have identified T cells, which specifically kill leukaemia cells by recognising the WT1 on their cell surface. The TCR determines the specificity of the T cell. Not all patients have T cells with the WT1-specific TCR.

We can generate T cells, which recognise WT1 (and can therefore kill leukaemia cells) by transferring the genes for the WT1-specific TCR into T cells, which normally recognise something else.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Gene Therapy Advisory Committee, 20/12/2007, ref: GTAC 128

Study design
Non-randomised interventional multicentre treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied

Topic: National Cancer Research Network; Subtopic: Haematological Oncology; Disease: Leukaemia (chronic), Leukaemia (acute myeloid)

Interventions
Leucapheresis, After recruitment to the study, patients will undergo leucapheresis to harvest peripheral blood lymphocytes. The peripheral blood T-lymphocytes will be cultured for up to 9 days in vitro for transduction with replication defective retroviral vectors containing the WT1-specific TCR. Bulk transduced T-lymphocytes will be intravenously administered using escalating doses of = 2 x 10^7/kg and = 10^8/kg bulk TCR-td T cells (doses based on numbers of allogeneic T cells safely infused post Allo SCT and t).

Follow Up Length: 12 month(s)

Intervention Type
Genetic

Primary outcome(s)
1. Transduction efficiency - at QP release of genetically modified (transduced) T cells
2. Toxicity and Side effects - every trial visit
3. Integration site analysis of transduced T cells - batched and to be performed at end of study

Key secondary outcome(s))
1. Persistence of TCR-Td T cells - blood sample taken at every trial visit after infusion of T cells (analysis to be performed in batches)
2. WT1-specific Immune Responses - blood sample taken at every trial visit after infusion of T cells (analysis to be performed in batches)
3. Disease responses - BM aspirate and trephine at +8 weeks; qPCR at 7 days, 28 days then monthly until 12 months post T cell infusion

Completion date
17/01/2012

Eligibility

Key inclusion criteria
General inclusion criteria:
All patients will undergo detailed laboratory based assessment prior to the procedure:
1. Aged greater than or equal to 18 years and less than or equal to 75 years
2. Life expectancy greater than 1626 weeks (46 months)
3. World Health Organisation (WHO) performance status of 0 - 2
4. HLA A*0201 positive
5. Completed previous course of chemotherapy greater than or equal to 4 weeks prior to commencing the initial phase of the trial (leucapheresis for collection of patient peripheral blood mononuclear cells [PBMC])
7. Peripheral blood total lymphocyte count greater than 0.5 x 10^9/L
8. Informed consent in writing and ability to co-operate with treatment and follow up
9. Willing, able and available for collection of PBMC/T-cells by leucapheresis
10. Hepatitis B and C, HTLV-1, human immunodeficiency virus (HIV) negative
11. Free from serious concurrent illness
12. Female patients of child-bearing age must have a negative pregnancy test and agree to use

reliable contraceptive methods for the duration of the therapy and for 6 months afterwards
13. Male patients must agree to use appropriate medically approved contraception during the trial and for six months afterwards
14. Haematological and Biochemical Indices:
14.1. Haemoglobin (Hb) = 7.0 g/dl; neutrophils = 0.2 x 10^9/L; total lymphocytes >0.5 x 10^9/L; platelets (Plts) = 40 x 10^9/L
14.2. Serum bilirubin, Alanine amino-transferase (ALT) and/or aspartate amino-transferase (AST) less than 3 x upper normal limit
14.3. Calculated creatinine clearance = 30 ml/min (uncorrected value) or isotope clearance measurement = 30 ml/min

Disease-specific inclusion criteria:
AML or CML proven by morphology, histology, immunophenotyping and cytogenetics (where available):

1. Acute myeloid leukaemia (AML):
Patients not eligible for BMT procedure with:
1.1. AML in 2nd CR or greater
1.2. Good and Standard Risk* AML in 1st CR or PR in patients greater than 60 years; and
1.3. Poor Risk* AML in 1st CR CR/PR or later (slow remitters and/or adverse cytogenetics)
1.4. AML at 1st relapse post BMT in CR or PR after re-induction and consolidation.
[NB, *risk category as defined by MRC criteria: Good Risk: t(15;17), t(8;21), inv 16; Poor Risk: -5; -7; del (5q); abn (3q) or complex (=/>4 abn)].

2. Chronic myeloid leukaemia (CML):
2.1. Patients in chronic phase resistant to Glivec/Imatinib and 2nd generation tyrosine kinase inhibitors (e.g., Dasatinib), AND NOT eligible for allogeneic BMT
2.2. Patients in chronic phase resistant to Glivec/Imatinib and with an identified mutation known to be resistant to 2nd generation tyrosine kinase inhibitors, AND NOT eligible for allogeneic BMT
2.3. Patients = 50 years (and ineligible for myeloablative allo-BMT), with a suboptimal response to Glivec/Imatinib and an identified mutation known to be resistant to 2nd generation tyrosine kinase inhibitors. These patients are at high risk of disease progression. Patients in this group would stop Glivec/Imatinib prior to leucapheresis and receiving TCR-transduced T cells. They will have monthly quantitative RT-PCR for Bcr-Abl and restart Glivec/Imatinib in the event of a log increase in transcript numbers.
2.4. Patients in chronic phase, resistant to Glive/Imatininb and NOT eligible for allo BMT without access to 2nd generation tyrosine kinase inhibitors may be considered after discussion with the Chief Investigator and Sponsor

Resistance to Glivec is defined as (European Leukemianet Criteria, 2006):
No Haematological Response (HR) at 3 months
Incomplete HR or No Cytogenetic Response (CgR) at 6 months
Less than partial CgR (Ph+ >35%) at 12 months
Less than complete CgR at 18 months
Loss of HR or CgR
Development of highly resistant mutations

Suboptimal response to Glivec is defined as (European Leukemianet Criteria, 2006):
Less than complete Haematological response at 3 months
Less than partial CgR (Ph+ >35%) at 6 months
Less than complete CgR at 12 months
Less than major MoR at 18 months

Loss of major MoR
Development of a mutation

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
7

Key exclusion criteria
1. Aged less than 18 years or greater than 75 years
2. Patients should not receive concurrent systemic corticosteroids whilst on the study
3. Major thoracic and/or abdominal surgery in the preceding three to four weeks from which the patient has not yet recovered
4. Patients who are high medical risks because of non-malignant systemic disease, as well as those with active uncontrolled infection
5. Patients with any other condition, which in the Investigator's opinion would not make the patient a good candidate for the clinical trial
6. Patients known to be serologically positive for Hepatitis B, C, HTLV-1 or HIV
7. Concurrent congestive heart failure or prior history of New York Heart Association (NYHA) class III/IV cardiac disease
8. Positive pregnancy test or reluctance to use contraception
9. Pregnant and lactating women are excluded
10. History of severe allergy

Date of first enrolment
18/01/2010

Date of final enrolment
17/01/2012

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Free Hospital
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Sponsor information

Organisation
University College London (UCL) (UK)

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
Department of Health (UK) (ref: 66807)

Funder Name
Leukaemia Research Fund (UK) (ref: 08001)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			21/04/2020	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes