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Vaccination with human minor H antigen (HA-1) peptide after allogeneic stem cell transplantation

Submission date	Recruitment status	[X] Prospectively registered
05/11/2008	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
27/11/2008	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
27/11/2008	Injury, Occupational Diseases, Poisoning	[_] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
LUMC2007-02

Study information

Scientific Title

Vaccination with human minor H antigen (HA-1) peptide in patients showing minimal residual disease or mixed chimerism after allogeneic stem cell transplantation and donor lymphocyte infusion

Study objectives
After allogeneic human leukocyte antigen (HLA)-matched stem cell transplantation (SCT), minor histocompatibility antigens (mHags) are the most likely targets for graft-versus-leukaemia (GvL) associated immune reactivity. Among these mHags, human minor H antigen (HA-1) is expressed by both normal haematopoietic cells and their malignant counterparts. HA-1 specific T-cells have been shown to be capable of eliminating HA-1 positive malignant (precursor) cells in HLA-A2 positive HA-1 positive patients after stem cell transplantation and donor lymphocyte infusion (DLI) administration from a HA-1 negative donor. However, after DLI not all patients develop a HA-1 specific T-cell response and a durable GvL effect in this setting.

We hypothesise that vaccination with administration of HA-1 peptide vaccine in HLA-A2 and HA-1 positive patients who had undergone HLA-matched allogeneic stem cell transplantation followed by DLI from a HLA-A2 positive, HA-1 negative, donor showing persistent disease or mixed chimerism eight weeks after DLI can induce an immunological response without severe graft-versus-host disease (GVHD).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Central Committee on Research involving Human Subjects (CCMO) gave approval on the 17th March 2008.

Study design
Single arm open label intervention phase I/II study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mixed chimerism after allogeneic stem cell transplantation

Interventions
Week 0: The study starts when DLI is given in an eligible patient
Week 8: Bone marrow investigation for chimerism and/or disease evaluation. GVHD evaluation and measurement of HA-1 specific T cells. If no HA-1 specific response:
Week 10: First subcutaneous vaccination with HA-1 peptide vaccine and as a control subcutaneous vaccination with Keyhole Limpet Hemocyanin (KLH)
Week 13: Second subcutaneous vaccination with HA-1 peptide vaccine
Week 16: Third subcutaneous vaccination with HA-1 peptide vaccine

Immunological and clinical effects will be evaluated after the first 12 patients treated using the 20mer vaccine. If six or more patients showed an immunological response, the vaccination

program using the 20mer vaccine will be continued, aiming for a total number of 24 patients. If less than 6 patients showed an immunologic response, 12 additional patients will be entered and treated using the 20mer + 9mer vaccine If less than 6 patients showed an immunological response to the 20mer + 9mer vaccine, the vaccination strategy using current peptides will be considered inadequate.

Information on vaccines:

20mer vaccine (300 µg peptide):
The subcutaneous 20mer HA-1 vaccine consists of a single peptide representing the amino-acid sequence 133-152 (LKECVLHDDLLEARRPRAHE) of the HA-1 protein encoded by the gene KIAA0223. The peptide is produced in the Interdivisional GMP-Facility of the LUMC (IGFL), Department of Clinical Pharmacy and Toxicology. Montanide ISA 51 is used as an adjuvant.

KLH:
Immucothel (Biosyn Arzneimittel GmbH) 1 mg is used to test the capacity for generating an immune response in the patient).

20mer and 9 mer combination vaccine (300 µg 20-mer peptide and 250 µg 9-mer peptide):
This investigational medical product (IMP) consists of a peptide that comprises LKECVLHDDLLEARRPRAHE, representing the amino-acid sequence 133-152 of the HA-1 protein encoded by the gene KIAA0223, in combination with a peptide that comprises VLHDDLLEA, representing the amino-acid sequence 137-145 of the HA-1 protein encoded by the gene KIAA0223. The peptides are produced in the Interdivisional GMP-Facility of the LUMC (IGFL), Department of Clinical Pharmacy and Toxicology. Montanide ISA 51 is used as an adjuvant.

Total follow-up is 26 weeks after week 0 (so 16 weeks after vaccination).

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Human minor H antigen (HA-1) peptide

Primary outcome(s)
1. Toxicity (phase 1), monitored every two weeks until end of study
2. Appearance of HA-1 specific CD8+ lymphocytes, monitored at weeks 6 and 8 and from 10 - 26 weeks after DLI

Key secondary outcome(s))
1. Bone marrow chimerism, monitored at weeks 8, 12, 15, 19 and 26
2. Disease activity, monitored at weeks 8, 12, 15, 19 and 26

Completion date
01/12/2012

Eligibility

Key inclusion criteria
1. Patients with acute myeloid leukaemia (AML), myelodysplasia (MDS), acute lymphoblastic leukaemia (ALL), chronic myeloid leukaemia (CML) in accelerated phase or blastic transformation before transplantation, chronic lymphocytic leukaemia (CLL), multiple myeloma (MM) or aggressive lymphoma, who underwent allo-SCT (both myeloablative and non-myeloablative) followed by DLI for persistent mixed chimerism or smoldering disease
2. Patient and donor HLA-A2 positive, patient HA-1 positive, donor HA-1 negative
3. World Health Organization (WHO) performance status of 0, 1 or 2
4. Female patients of childbearing potential must be neither pregnant nor breastfeeding and must agree to use effective contraception (birth control pills, condoms, approved implant, or intra-uterine device [IUD]) during the course of this trial and for at least three months after the last injection
5. Mixed chimerism or persisting disease 8 weeks after DLI
6. Male and female, aged 18 years and older

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Life expectation of less than 3 months
2. Psychological disturbances
3. Severely limited life expectation due to diseases other than the malignancy
4. Human immunodeficiency virus (HIV) positivity
5. Persistent treatment with high-dose corticosteroids (greater than 20 mg prednisone a day), chemotherapy or other immunosuppressive drugs
6. Rapidly progressive disease
7. GVHD grade 3 or 4
8. HA-1 specific immune response (defined by greater than 0.2% of total CD8+ cells in first six patients and defined by greater than 1.0% of total CD8+ cells in patients 4 - 24 if no toxicity greater than grade II in first three patients). No important increase in percentage HA-1 specific CD8+ cells between 6 and 8 weeks after DLI (defined as a doubling of this percentage resulting in a percentage of greater than 0.2%).

Date of first enrolment
01/12/2008

Date of final enrolment
01/12/2012

Locations

Countries of recruitment
Netherlands

Study participating centre
Department of Haematology
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Sponsor information

Organisation
Leiden University Medical Centre (LUMC) (Netherlands)

ROR
https://ror.org/027bh9e22

Funder(s)

Funder type
Research organisation

Funder Name
Dutch Cancer Society (KWF Kankerbestrijding) (The Netherlands)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration