Wilms tumor gene (WT1) mRNA¨Ctransfected autologous dendritic cell vaccination for patients with acute myeloid leukemia. A pilot dose escalation study.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27609

Source
NTR

Brief title
WT1-1

Health condition

acute myeloid leukemia

Sponsors and support

Primary sponsor: Antwerp University Hospital, Antwerp, Belgium
Source(s) of monetary or material Support: Stichting tegen Kanker België;
European Hematology Association (EHA);
UZA cell therapy fund

Intervention

Outcome measures

Primary outcome

Safety of multiple DC injections. Assessment of acute toxicity and/or auto-immunity.

Secondary outcome

Detection of WT1-specific T cell immunity by:

1. IFN-gamma ELISPOT;

2. WT1 Tetramer analysis (if patient is HLA*A0201 positive);

3. DTH skin test;

Clinical response as evidenced by decreased WT1 RNA levels in peripheral blood measured by quantitative RT-PCR.

Study description

Background summary

Rationale:

Vaccines made from a person's white blood cells (dendritic cells) and a specific leukemia antigen (Wilms tumor antigen-1) may induce an effective immune response to kill residual leukemic cells and/or prevent leukemia relapse.

Purpose:

This pilot trial is studying the feasibility and safety of intradermal mRNA-transfected dendritic cell vaccination therapy in patients with acute myeloid leukemia.

This is an open-label phase I dose-escalation study of autologous mRNA-transfected dendritic cell vaccination. The study will be conducted at the Hematology Department of the Antwerp University Hospital in Belgium. In total, 9 patients with AML in remission or with smouldering

course will be enrolled after verification of the eligibility criteria. The size of cohorts of patients will be of 3 patients per dose level.

Patients undergo 1 leukapheresis in order to obtain sufficient PBMC. CD14+ monocytes will be isolated using magnetic bead-labeled CD14 antibodies using the CliniMACS device (Miltenyi Biotech, Germany). Unlabeled CD14-negative cells will be cryopreserved and used for immunological assays (pre-vaccination T cells). Purified CD14+ monocytes are cultured for 6 days with GM-CSF and IL-4 in CellGRO medium + 1% human AB serum. At day 6, DC are pulsed with keyhole limpet hemocyanin (KLH) as an heterologous helper antigen and allowed to mature using TNF-alpha and prostaglandin E2 for 48 hrs. Mature KLH-loaded DCs will be harvested, washed, and electroporated with in vitro transcribed mRNA encoding the full-length WT1 protein as described previously (Van Tendeloo et al., Blood 2001). One batch is used directly for the 1st vaccination while the other batches are frozen for future vaccinations. Patients receive DC vaccine intradermally every 2 weeks for a total of 4 times in the absence of disease progression or unacceptable toxicity.
Cohorts of 3 patients will receive escalating doses of dendritic cells:

Group A (lowest dose): 5 x 10e+6 DCs

Group B (middle dose): 10 x 10e+6 DCs

Group C (highest dose): 20 x 10e+6 DCs

Study objective

Therapeutic vaccination with patient-specific dendritic cells loaded with the Wilms tumor antigen WT1 can prevent leukemia relapse in AML patients in remission.

Study design

D-8 aferesis

D0 vaccine #1

D+7 vaccine #2

D+14 vaccine #3

D+21 vaccine #4

D+35 DTH test + immune analysis.

Intervention

4 intradermal vaccinations with autologous dendritic cells loaded with mRNA coding for the WT1 protein.

Contacts

Public
Antwerp University Hospital, Department of Hematology
Wilrijkstraat 10,
Zwi Berneman
Edegem B-2650
Belgium
Phone: +32 3 821 37 80
Scientific
Antwerp University Hospital, Department of Hematology
Wilrijkstraat 10,
Zwi Berneman
Edegem B-2650
Belgium
Phone: +32 3 821 37 80

Eligibility criteria

Inclusion criteria

1. Tumor type: Acute Myeloid Leukemia (AML) according to the WHO criteria (ea at least 20% blasts in the marrow). This % should be assessed on a BM aspiration or, in case of dry tap, on a BM biopsy. All FAB subtypes except M3.

Patients with Myelodysplastic Syndrome, category of Refractory Anemia with Excess Blasts (RAEB): RAEB I (WHO: medullary blast count ¡Ü 10% and a peripheral blast count ¡Ü 5%) and RAEB II (WHO: medullary blast count > 10% and/or > 5% peripheral blasts) can be included in the study in absence of other non-experimental treatment modalities.

2. Extent of disease: remission (partial or complete) or smouldering course. Complete remission (CR) is defined as no blasts in the peripheral blood and no more than 5% blasts in the bone marrow. This definition is related to the hematological remission if it is not specified.

Partial remission (PR) is defined as a decrease of at least 50% in the percentage of blasts to 5 to 25% in the bone marrow aspirate.

Smouldering course is defined as a relatively low marrow blast count and slowly progressive disease.

WBC count at registration < 30 x 109/L.

3. Overexpression of WT1 RNA (>1 copy of WT1 per 1000 copies ABL) in peripheral blood as assessed by quantitative RT-PCR at the time of diagnosis.

4. Prior treatments: Patients must have received at least one prior antileukemic chemotherapeutic regimen and must be more than 1 month past the last treatment and/or 6 months past allogeneic/autologous stem cell transplantation.

5. Age: ¡Ý 18 years.

6. Performance status: WHO PS grade 0-1 (Appendix B);

7. Objectively assessable parameters of life expectancy: more than 3 months;

8. Prior and concomitant associated diseases allowed with the exception of underlying autoimmune disease and positive serology for HIV/HBV/HCV;

9. No concomitant use of immunosuppressive drugs;

10. Adequate renal and liver function, i.e. creatinin and bilirubin = 1.2 times the upper limit of normal;

11. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial;

12. Women of child-bearing potential should use adequate contraception prior to study entry and for the duration of study participation.

Exclusion criteria

1. Subjects with concurrent additional malignancy (with exception of non-melanoma skin cancers and carcinoma in situ of the cervix);

2. Subjects who are pregnant;

3. Subjects who have sensitivity to drugs that provide local anesthesia.

Study design

Design

Study type: Interventional

Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-03-2005
Enrollment:	10
Type:	Actual

Ethics review

Positive opinion

Date:	30-12-2008
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL1537
NTR-old	NTR1608
Other	EC Antwerp University Hospital : 5/6/29
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results

Summary results

1. Lion E, Smits EL, Berneman ZN, Van Tendeloo VF. Acute myeloid leukemic cell lines loaded with synthetic dsRNA trigger IFN-gamma secretion by human NK cells. Leukemia Research 2008; Oct 7. [Epub ahead of print]
IF 2.561

2. Van de Velde ALR, Berneman ZN, Van Tendeloo VFI. Latest inputs in immunotherapy of hematological malignancies using dendritic cells. Bulletin du Cancer 2008; 95: 320-326 (review)
IF 0.906

3. Smits E, Ponsaerts P, Berneman Z, Van Tendeloo VFI. The Use of TLR7 and TLR8 Ligands for the Enhancement of Cancer Immunotherapy. The Oncologist 2008 (in press).
IF 4.876

4. Cools N, Van Tendeloo VFI, Smits ELJM, Lenjou M, Nijs G, Van Bockstaele DR, Berneman ZN, Ponsaerts P. Immunosuppression induced by immature dendritic cells is mediated by TGF-beta/IL-10 double-positive CD4+ regulatory T cells. Journal of Cellular and Molecular Medicine 2008; 12(2): 690-700.
IF 6.555

5. Van Gulck ER, Vanham G, Heyndrickx L, Coppens S, Vereecken K, Atkinson D, Florence E, Kint I, Berneman ZN, Van Tendeloo V. Efficient in vitro expansion of HIV-specific T cell responses by gag mRNA-electroporated dendritic cells from treated and untreated HIV-1-infected individuals. J Virol 2008 ;82(7):3561-73. Epub 2008 Jan 30.
IF 5.341

6. Van Tendeloo VFI, Ponsaerts P, Berneman ZN. Messenger RNA-based gene therapy as a tool for gene and cell therapy. Current Opinion in Molecular Therapeutics 2007;9(5):423-431 (review)
IF 2.411

7. Smits ELJM, Ponsaerts P, Van de Velde ALR, Van Driessche A, Cools N, Lenjou M, Nijs G, Van Bockstaele DR, Berneman ZN, Van Tendeloo VFI. Proinflammatory response of human leukemic cells to dsRNA transfection linked to activation of dendritic cells. Leukemia 2007; 21(8):1691-1699.
IF 6.146

8. Bontkes HJ, Kramer D, Ruizendaal JJ, Kueter EWM, Van Tendeloo VFI, Meijer CJLM, Hooijberg E. Dendritic cells transfected with Interleukin-12 and tumor associated antigen mRNA induce high avidity cytotoxic T-cells. Gene Therapy 2007;14(4):366-75
IF 4.836

9. Van Gulck ERA, Ponsaerts P, Heyndrickx L, Vereecken K, Moerman F, De Roo A, Colebunders R, Van den Bosch G, Van Bockstaele DR, Van Tendeloo VFI, Allard S, Verrier B, Marañ¨®n C, Hoeffel G, Hosmalin A, Berneman ZN, Vanham G. Efficient stimulation of HIV-1-specific T-cells using dendritic cells electroporated with mRNA encoding autologous HIV-1 Gag and Env protein. Blood 2006; 107(5): 1818-27.
IF 10.131

10. Van Driessche A, Gao L, Stauss HJ, Ponsaerts P, Van Bockstaele DR, Berneman ZN, Van Tendeloo VFI. Antigen-specific cellular immunotherapy of leukemia. Leukemia 2005; 19, 1863¨C1871 (review)
IF 6.612

11. Van Driessche A, Ponsaerts P, Van Bockstaele DR, Van Tendeloo VFI, Berneman ZN.Messenger RNA electroporation: An efficient tool in immunotherapy and stem cell research. Folia Histochemica et Cytobiologica 2005, 43(4): 213-216.
IF 0.789

12. Ponsaerts P, Van Tendeloo VFI, Berneman ZN. Cancer immunotherapy using RNA-loaded dendritic cells. (review) Clinical and Experimental Immunology 2003; 134: 378-384
IF 2.347

13. Ponsaerts P, Van Tendeloo VFI, Cools N, Van Driessche A, Lardon F, Nijs G, Lenjou M, Van Broeckhoven C, Van Bockstaele DR, Berneman ZN. mRNA-electroporated mature dendritic cells retain transgene expression, phenotypical properties and stimulatory capacity after cryopreservation. Leukemia 2002; 16: 1324-1330
IF 4.693

14. Ponsaerts P, Van den Bosch G, Cools N, Van Driessche A, Nijs G, Lenjou M, Lardon F, Van Broeckhoven C, Van Bockstaele DR, Berneman ZN, Van Tendeloo VFI. Messenger RNA electroporation of human monocytes, followed by rapid in vitro differentiation, leads to highly stimulatory antigen-loaded mature dendritic cells. Journal of Immunology 2002;169:1669-1675.
IF 7.014

15. Van Meirvenne S, Straetman L, Heirman C, Dullaers M, De Greef C, Van Tendeloo VFI, Thielemans K. Efficient genetic modification of murine dendritic cells by electroporation with mRNA. Cancer Gene Ther 2002;9:787-97
IF 2.929

16. Van Tendeloo VFI, Ponsaerts P, Lardon F, Lenjou M, Nijs G, Van Broeckhoven C, Van Bockstaele D, Berneman ZN. Highly efficient gene delivery by mRNA electroporation of human hematopoietic cells: superiority to lipofection and passive pulsing of mRNA and to electroporation of plasmid cDNA for tumor antigen loading of dendritic cells. Blood 2001; 98: 49-56