Adoptive Cell Transfer (ACT)

John Haanen
Aim of this presentation

• Basic aspects of ACT
• How does it work and how well does it work?
• Is there still a place for ACT in the era of checkpoint inhibitors?
What is ACT?

• Infusion of an immune cell product with the aim to induce or augment an anti-tumor immune response
Which cells are transferred?

- Mostly CD3+ T cells
  - Tumor-infiltrating lymphocytes
  - Antigen-receptor gene modified T cells (blood derived)
    - TCR gene modified T cells
    - Chimeric antigen receptor (CAR) gene modified T cells
  - T cell clones/lines (oligoclonal population) from blood

- Other cell types: NK cells, DC
How does ACT work?

How effective is ACT?
ACT with CD3+ T lymphocytes
How effective is ACT?

• Infusion of peripheral blood derived T cells
• Infusion of TCR gene modified T cells
• Infusion of TIL
Isolation of melanoma-specific CD8 T cells from peripheral blood

Labarriere et al. Clin Dev Immunol 2013
Infusion of MART-1 specific T cells

Table 1. Patient Demographics and Treatment Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>KPS (%)</th>
<th>Prior Therapy</th>
<th>Disease Sites</th>
<th>Melan-A Expression*</th>
<th>No. of T-Cell Infusions</th>
<th>Adverse Effects</th>
<th>Eosinophilia (%)†</th>
<th>Clinical Course</th>
<th>Duration of Clinical Course (months)</th>
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</table>

Abbreviations: KPS, Karnofsky performance status; F, female; Chemo, chemotherapy; Immuno, immunotherapy; Sk, skin; Lu, lung; Fever I°, WHO grade I, < 38°C; PD, progressive disease; M, male; Li, liver; B, bone; LN, lymph node; Fever II°, WHO grade II, 38-40°C; PR, partial regression; SD, stable disease; MR, mixed response; IFN, interferon; CR, complete regression.

*Staining of tumor specimens was performed with an anti-Melan-A (A103; Novocastra, Newcastle, United Kingdom) monoclonal antibody; 2+, 50-75% of cells reactive; 3+ > 75% of cells reactive.

†Maximum peak eosinophil levels after T-cell transfer; eosinophils % of total leukocytes.

Infusion of MART-1 and gp100-specific T cell clones

Yee et al. PNAS 2002

Table 1. Patient demographics and clinical summary

<table>
<thead>
<tr>
<th>ID no.</th>
<th>Age</th>
<th>Sex</th>
<th>Previous Tx*</th>
<th>Disease sites†</th>
<th>Target antigen</th>
<th>No. of infusions</th>
<th>Toxicity‡</th>
<th>Response</th>
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<td>M</td>
<td>IFN</td>
<td>Lu</td>
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<td>Progressive disease</td>
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49.9

Yee et al. PNAS 2002
Successful treatment of metastatic melanoma by adoptive transfer of blood-derived polyclonal tumor-specific CD4+ and CD8+ T cells in combination with low-dose interferon-alpha

Els M. E. Verdegaal · Marten Visser · Tamara H. Ramwadhdoebé · Caroline E. van der Minne · Jeanne A. Q. M. J. van Steijn · Ellen Kapiteijn · John B. A. G. Haanen · Sjoerd H. van der Burg · Johan W. R. Nortier · Susanne Osanto

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Metastatic Melanoma with Autologous CD4+ T Cells against NY-ESO-1

Naomi N. Hunder, M.D., Herschel Wallen, M.D., Jianhong Cao, Ph.D., Deborah W. Hendricks, B.Sc., John Z. Reilly, B.Sc., Rebecca Rodmyre, B.Sc., Achim Jungbluth, M.D., Sacha Gnjatic, Ph.D., John A. Thompson, M.D., and Cassian Yee, M.D.
Conclusion

- Infusion of peripheral blood derived melanoma-specific T cells is feasible
- Time consuming (4-16 weeks)
- Few but sometimes lasting responses are seen
- How to improve?
  - Are we targeting the right antigens?
  - Are we infusing the right T cells?
  - Combination therapy?
Infusion of gene-modified T cells

Kershaw et al. Nat Rev Cancer 2013
Genetically modified peripheral blood lymphocytes

**Schedule of treatment**

**Patient: I**

- Informed consent + screening
- Leukapheresis
- Preparation of gene modified T cells
- Start chemotherapy: Cyclophosphamide + fludarabin for total of 7 days
- Infusion of transduced T cells
- High dose IL-2
- Monitoring response and survival

**Periods**

-7

0

mnd 1, 2, 3, 6
Clinical experience with TCR gene therapy

- **2006: MART-1 TCR gene therapy**
  - RR 13% (n=15)
  (Morgan et al., Science 2006)

- **2009: MART-1 and gp100 TCR gene therapy**
  - RR 30% (MART-1 TCR; n=20)
  - RR 19% (murine gp100 TCR; n=16)
  (Johnson et al., Blood 2009)
DMF5 and gp100 specific TCR were highly expressed by transduced CD4 and CD8 T cells

Johnson et al., Blood 2009
Clinical activity of MART-1 and gp100-specific TCR gene therapy
Clinical experience with TCR gene therapy

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• **2014:** MART-1 TCR gene therapy + DC vaccination
  – Response in 11/14 (not according RECIST)
  – SD at 90 days in 50%
  (Chodon et al. Clin Cancer Res 2014)
Schedule and persistence of gene modified T cells after infusion

Chodon et al., Clin Cancer Res 2014
Clinical responses upon adoptive T-cell transfer

Chodon et al., Clin Cancer Res 2014
TCR gene therapy for melanoma

• **2006: MART-1 TCR gene therapy**
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  – Response in 11/14 (not according RECIST)
  – SD at 90 days in 50%
    (Chodon et al. Clin Cancer Res 2014)

• **2012: MART-1 TCR gene therapy** (Haanen et al. unpublished)
Clinical experience with TCR gene therapy

- 2006-2014: MART-1 and gp100 TCR gene therapy

- 2011: NY-eso-1 TCR gene therapy in melanoma and synovial sarcoma
  - RR 45% (n=11) and 67% (n=6)
  
  (Robbins et al., J Clin Oncol 2011)
## Patient characteristics and outcome

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Sites of Disease</th>
<th>Prior Treatment</th>
<th>No. of Cells ($\times 10^5$)</th>
<th>No. of IL-2 Doses</th>
<th>% of CD3 Positive</th>
<th>% of CD8 Positive</th>
<th>% of CD4 Positive</th>
<th>NY-ESO-1 Tetrramer Positive</th>
<th>$\beta 13.1$ Positive</th>
<th>Tumor Cell Targets (pg/mL IFN-γ)*</th>
<th>NY-ESO-1 Positive</th>
<th>NY-ESO-1 Negative</th>
<th>Response†</th>
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<td>PR (8)</td>
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A: Pretreatment | 12 months

Robbins et al., J Clin Oncol 2011
Conclusion

• Infusion of TCR gene modified T cells is feasible and can result in objective responses
• Infused T cell can persist for months
• Can be very toxic!
• Finding the right target is key
• Is one target enough?
• How to improve?
  – Combination with other IT?
Infusion of tumor Infiltrating Lymphocytes

TIL are grown from melanoma tumors

Rapid Expansion

Infusion of TIL + IL-2

Patient pretreated with lymphodepleting chemotherapy

- High response rate in phase II trials in multiple centers (US, Israel, NL, UK, DK)
- Clinical effect at least partially mediated by CD8 T cells
Clinical data N10TIL003: ongoing CR at 24 months

Prior to TIL

3 wks post TIL

8 wks post TIL

12 wks post TIL

Biopsy at wk 7 showed no viable tumor cells
TIL therapy

- > 300 metastatic melanoma patients have been treated world wide in at least 8 centers
- Objective responses observed in 38-72% of treated patients
- In ITT analysis (n=80): ORR 29%
- Median survival of treated patients: ± 16 m
- Long-term CRs
Which cytotoxic T cells mediate cancer regression?
Could we specifically boost their numbers?

TIL are grown from melanoma tumors

Rapid Expansion

Infusion of TIL + IL-2

Patient pretreated with lymphodepleting chemotherapy

The big unknown
What could tumor-specific cytotoxic T cells detect on human cancer?

1. Self antigens (to which tolerance is incomplete)
   *Shared between patients*

2. ‘Neo-antigens’, epitopes that arise as a consequence of tumor-specific mutations
   *In large part patient-specific, hence generally ignored*
TILs against shared tumor antigens

• In the majority of TILs T cells specific for shared antigens can be found
  – Melanocyte differentiation Ags (Mart-1, gp100, etc)
  – Cancer/Testis gene products (NY-eso-1, MAGE, SSX-2, etc)
  – Overexpressed Ags (Meloe etc.)

• Low frequency (mostly below 1%)
• No correlation with response

Kvistborg et al., Oncoimmunology 2012
TIL therapy broadens the tumor-reactive CD8⁺ T cell compartment in melanoma patients

Pia Kvistborg,¹,† Chengyi Jenny Shu,¹,† Bianca Heemskerk,¹ Manuel Fankhauser,¹ Charlotte Albæk Thrue,² Mireille Toebes,¹ Nienke van Rooij,¹ Carsten Linnemann,¹ Marit M. van Buuren,¹ Jos H.M. Urbanus,¹ Joost B. Beltman,³ Per thor Straten,² Yong F. Li,⁴ Paul F. Robbins,⁴ Michal J. Besser,⁵,⁶ Jacob Schachter,⁵ Gemma G. Kenter,⁷ Mark E. Dudley,⁴ Steven A. Rosenberg,⁴ John B.A.G. Haanen,¹ Sine Reker Hadrup² and Ton N.M. Schumacher¹,*
What could tumor-specific cytotoxic T cells detect on human cancer?

1. Self antigens (to which tolerance is incomplete)
   *Shared between patients*

2. ‘Neo-antigens’, epitopes that arise as a consequence of tumor-specific mutations
   *In large part patient-specific, hence generally ignored*
Analyzing the neo-antigen-specific T cell repertoire in human cancer?

Generate map of tumor-specific mutations (ExomeSeq)

Determine which mutated genes are expressed (RNASeq)

Predict epitopes for each mutation/ each HLA-allele *in silico*

Screen for T cell recognition of mutated epitopes
Pt 008: CR upon TIL therapy

Resected tumor material

Isolate tumor cells

Isolate tumor-infiltrating T cells

Screen with MHC multimer technology

Identify tumor-specific mutations

Predict potential epitopes
Pt 008: CR upon TIL therapy

Infusion TIL product

Profound neo-antigen reactivity in TIL product
Pt 008: CR upon TIL therapy

Major increase in neo-antigen specific T cell reactivity upon TIL therapy
Pt 004:

- Resected tumor material
  - Isolate tumor cells
  - Isolate tumor-infiltrating T cells
    - Screen with MHC multimer technology
  - Identify tumor-specific mutations
  - Predict potential epitopes
Pt 004:

DNAH17\textsubscript{H\rightarrow Y} (0.003%)  
\text{VLFEDAVAH} \rightarrow \text{VLFEDAVAY}

CDK4\textsubscript{R\rightarrow L} (1.604%)  
\text{ARDPHSGHFV} \rightarrow \text{ALDPHSGHFV}

GCN1L1\textsubscript{L\rightarrow P} (0.407%)  
\text{ALLETLSSL} \rightarrow \text{ALLETPSSL}

Mutations can result in neo-antigens derived from oncogenes and (presumed) passenger genes.

Pt 004:

DNAH17$_{H\rightarrow Y}$ (0.003%)
VLFEDAVA$_H$ > VLFEDAVAY

CDK4$_{R\rightarrow L}$ (1.604%)
ARDPHSGHFV > ALDPHSGHFV

GCN1L1$_{L\rightarrow P}$ (0.407%)
ALLETL$LLL$ > ALLET$P$LLL
Are neo-antigens superior cancer rejection antigens?
Are neo-antigens superior cancer rejection antigens?

- Develop peptide exchange MHC streptamers to create defined TIL products
Are neo-antigens superior cancer rejection antigens?

CDK4_{R>L}  
Pre-enrichment: 2.2%  
Post-joint enrichment: 72.2%

GCN1L1_{L>P}  
Pre-enrichment: 0.59%  
Post-joint enrichment: 20.2%

Combined:  2.8%  92.4%
1) Inject human melanoma (NSG-mice)
1) Inject human melanoma (NSG-mice)

2a) Inject autologous bulk T-cell product

2b) Inject autologous neo-Ag enriched T-cell product
1) Inject human melanoma (NSG-mice)

2a) Inject autologous bulk T-cell product

2b) Inject autologous neo-Ag enriched T-cell product

3) Monitor tumor growth
Neo-antigen enriched TIL can mediate superior tumor control
Conclusion

• TIL infusion is feasible and can result in objective responses including durable CRs
• Neo-antigen-specific T cells are present in the majority of melanoma TIL
• Neo-antigen specific TIL play a (superior) role in tumor rejection
Is there a place for ACT in the immune checkpoint blockade era?

• Unresolved Q:
  – We need a RCT comparing TIL with standard of care
  – Can TIL be combined with checkpoint inhibitors? (anti-PD1)
  – Can TIL be improved by selection of tumor-reactive T cells (CD137 or PD1 enrichment)
  – Can TIL be improved by knock-down of PD1 or Ppp2r2d?
  – Can we boost the neo-antigen specific cells by vaccines?
European TIL trial consortium

- **NL:**
  - **John Haanen:** NKI-AVL, Amsterdam, The Netherlands
  - Joost van den Berg: TIL production by AmBTU and Sanquin

- **DK:**
  - **Inge Marie Svane:** Herlev Hospital, Copenhagen,
  - Marco Donia: TIL production

- **UK:**
  - **Robert Hawkins:** University of Manchester and the Christie NHS Foundation Trust, UK
  - Ryan Guest: TIL production by CTL
Taking the next step for TIL based ACT

Randomized phase III study comparing TIL based ACT to standard ipilimumab treatment in metastatic melanoma

To obtain EMA approval of ‘classical’ TIL therapy as an ATMP
TIL preparation harmonization procedure

- Three different production sites at blood supply units
- Establishment of uniform production methods and common SOP
- Validation procedure finalized

Procedure and protocol approved by VHP European Committee
Study design

Patients: 168 patients with metastatic (stage IV) melanoma and a resectable metastasis will be randomized 1:1 between arm A, standard treatment (ipilimumab) and arm B, TIL treatment.

Arm A: standard ipilimumab (3 mg/kg x 1 day i.v., q3w, 4 treatments).

Arm B: non-myeloablative chemotherapy (cyclophosphamide 60 mg/kg/day x 2 days i.v., fludarabine 25 mg/m²/day x 5 days i.v.) followed by intravenous adoptive transfer of at least 5 x 10⁹ TIL followed by high dose interleukin-2 (600,000 IU/kg/dose every 8 hours for up to 15 doses).

Stratification: Patients will be stratified for BRAF V600 mutation, 1st or 2nd line treatment, and treatment center.
Primary endpoint: PFS at 6 months by RECIST 1.1

Secondary endpoints:
- PFS according to RECIST 1.1 and irRC.
- ORR according RECIST 1.1 and irRC
- CR rate
- Overall survival
- Safety
- Constructive technology assessment (CTA) will be performed to evaluate the impact on patient, organizational and economic consequences
Cancer exome-guided immunomonitoring

Nienke van Rooij
Marit van Buuren
Daisy Philips
Mireille Toebes
Laura van Dijk
Pia Kvistborg

Ton Schumacher

MHC-based technologies
Chemical Biology
Boris Rodenko
Huib Ovaa

CCIT, Copenhagen
Sine Hadrup

STAGE Therapeutics
Lothar Germeroth

PDX models
Kristel Kemper
Daniel Peeper

Sanger Institute
Sam Behjati
Mike Stratton

Utrecht University
Can Kesmir

Clinical translation
Bianca Heemskerk
Sander Kelderman
Raquel Gomez
Joost van den Berg
Samira Michels
Bastiaan Nuijen
Christian Blank