Long-term safety and survival outcomes after TK-expressing donor lymphocyte infusion (TK-DLI) in allogeneic hematopoietic stem cell transplantation (HSCT)

Fabio Ciceri

Hematology and BMT Unit
San Raffaele Scientific Institute
Milano, Italy
Adoptive T-cell gene therapy

Viral-mediated gene transfer

- Redirecting specificity (TCR/CAR)
- Controlling toxicity (suicide genes)
- Increasing performances
Suicide gene therapy in allogeneic HSCT: TK cells

Donor haemat. stem cells

HSC transplant (day 0)

Graft versus Infection (GvI)

TK cells

Graft versus Leukaemia (GvL)

Graft versus Host Disease (GvHD)

Abrogation by administration of ganciclovir

TK-cell infusion (day +21)

Donor T cells

GMP facility

donor T cells transduction, selection and expansion

HSCT donor (from bone marrow or peripheral blood)

Haemat. stem cells

Donor T cells

HSV-TK

The TK suicide gene therapy allows a dynamic modulation of alloreactivity

Only proliferating TK cells are sensitive to ganciclovir

Ganciclovir administration during GvHD should result in the selective control of GvHD with preservation of anti-tumor and anti-infection activity
Safety and efficacy in clinical trials of cell therapy with TK cells

<table>
<thead>
<tr>
<th>Clinical application</th>
<th>N° of treated patients</th>
<th>Clinical response (n° of patients)</th>
<th>Incidence of GvHD n° pts</th>
<th>Complete response of GvHD to GCV</th>
<th>Immunity against HSV-TK</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Relapse</td>
<td>23 23 3 9 5</td>
<td>11a 6a 1a 2a 4a</td>
<td>4 0 1 1 2</td>
<td>3/3b Ne 0 1/1 2/2</td>
<td>9/23 Ne Ne Ne Ne</td>
<td>Bonini et al., 1997, Ciceri et al., 2007 Champlin et al., 1999 Munshi et al., 1997 Burt et al., 2003 Onodera, 2008</td>
</tr>
<tr>
<td>Day 0 in HLA-identical TCD-SCT</td>
<td>12 3</td>
<td>4a 1a</td>
<td>5 1</td>
<td>5/5c 1/1</td>
<td>4/12 Ne</td>
<td>Tiberghien et al., 2001 Fehse et al., 2004</td>
</tr>
<tr>
<td>Day 60 in HLA-identical TCD allo-SCT</td>
<td>9</td>
<td>7a</td>
<td>1</td>
<td>1/1</td>
<td>1/9</td>
<td>Weissinger et al., 2011</td>
</tr>
<tr>
<td>Add-back after TCD haplo-SCT</td>
<td>41</td>
<td>29a</td>
<td>13</td>
<td>11/11</td>
<td>0/41</td>
<td>Bonini et al., 2007 Ciceri, Bonini et al., 2009 Ongoing</td>
</tr>
<tr>
<td>TOTAL</td>
<td>128</td>
<td>65 (51%)</td>
<td>28 (22%)</td>
<td>24/24 (100%)</td>
<td>14/128</td>
<td></td>
</tr>
</tbody>
</table>
Safety and efficacy in clinical trials of cell therapy with TK cells

<table>
<thead>
<tr>
<th>Clinical application</th>
<th>N° of treated patients</th>
<th>Clinical response (n° of patients)</th>
<th>Incidence of GvHD n° pts</th>
<th>Complete response of GvHD to GCV</th>
<th>Immunity against HSV-TK</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Relapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4</td>
<td>3/3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9/23</td>
<td>Bonini et al., 1997, Ciceri et al., 2007</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>Ne</td>
<td>Ne</td>
<td>Champlin et al., 1999</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>Ne</td>
<td>Ne</td>
<td>Munshi et al., 1997</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>1/1</td>
<td>Ne</td>
<td>Burt et al., 2003</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>2/2</td>
<td>Ne</td>
<td>Onodera, 2008</td>
</tr>
<tr>
<td>Day 01 HLA identical SCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 60 HLA identical allo-SCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add-back after TCD haplo-SCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>128</td>
<td>65 (51%)</td>
<td>28 (22%)</td>
<td>24/24 (100%)</td>
<td>14/128</td>
<td></td>
</tr>
</tbody>
</table>

- Cumulative follow-up >223 person/year
- 25 patients > 5 years follow-up
- Longest follow-up 14 years (TK cells still present)
Infectious mortality in CD34+ T-cell depleted haplo-HSCT

Late mortality

ALL (n=61)  51 ± 6%
AML (n=85)  49 ± 4%

Ciceri et al., Blood 2008
TK007 phase II: TK cells add-back in haplo

54 enrolled (median age: 50y)

4 drop-out (no HSCT)

22 did not receive TK cells infusion

28 treated with TK cells

22 immune-reconstituted (>100 CD3+ cells/μL)

6 no immune-reconstitution

28 treated with TK cells
TK007: clinical impact on infections

54 enrolled
(median age: 50y)

22 did not receive TK cells infusion

4 drop-out (no HSCT)

28 treated with TK cells

Immune-reconstituted
Patients

Non immune-reconstituted patients

N. Infections/pt/month

N. Infections/pt/month

MOLMED
GvHD is sensitive to ganciclovir

- Acute GvHD considered related to the HSV-TK cells occurred in 10 patients out of 30 treated in TK007 trial.
- One patient developed a chronic GvHD.
- The clinical treatment patients experiencing GvHD was as follow:
  - 1 patient grade 1 (skin), no treatment;
  - 7 patients grade 2 (skin), 3 treated with GCV and 4 with valGCV;
  - 1 patient grade 3 (skin), treated with valGCV;
  - 1 patient grade 4 (gut and liver), treated with GCV;
  - 1 patient chronic GvHD (skin, mouth and eyes), treated with valGCV, mycophenolate mofetil and dexamethasone.
TK cells dynamics by GCV in case of GvHD

Does GvHD control impair protection against infections?

In case of GvHD (10 pts), GCV infusion promptly and selectively eliminate Tkpos alloreactive cells.

Activation of the suicide machinery does not compromise immune protection against pathogens.
TK cells persist > 1 year after HSCT
Gene modified Tk-cells persist for >14 years in vivo

Donor’s TK cells

SFCMM-2 retroviral vector

At relapse (+14 years)
G418 selection

Gene modified Tk-cells persist for >14 years in vivo
Persisting TK cells maintain GCV sensitivity

FACS Sorting and Polyclonal expansion

In vivo dynamics of memory T cells:
GCV sensitivity
TK008: a randomized phase III multicentric clinical trial

Key inclusion criteria:
- AML-ALL at high-risk in first CR
- AML-ALL in ≥ second CR
- secondary AML in CR
- absence of HLA-matched family or unrelated donor

Stratification
- complete response (1st v > 1st), very-high-risk vs high-risk
- country

Primary endpoint:
- Leukemia-free survival

Secondary aims:
- NRM, overall survival, immune-reconstitution, engraftment, aGvHD, cGvHD, relapse, disease-free survival, infectious, safety, quality of life, pharmaco economics

- 1-year NRM standard haplo: 60%
- 1-year NRM ph II study TK: 37%
- Relapse rate standard haplo 25%
- Relapse rate ph II study TK 18%
- Power = 80%; HR = 0.55
- LFS 30% in standard haplo
- LFS 52% expected in TK008 exp arm
- 91 events (death + leukemia relapse)
- N=170 patients
Implementing haplo-HCT in treatment algorithm

*Unrelated donor transplant search success RATE is stable*
Haplo SCT is a growing option in adults with acute leukemias
Haplo-HCT outcome is NOT inferior to standard matched donor-HCT
249 HCT – CR at transplant
TK-cells in HCT

conclusions

- TK donor T cells infusions are safe in hematopoietic cell transplantation from matched and mismatched donors
- Immune reconstitution provides effective anti-infectious and anti-tumor control
- Haplo-HCT with TK cells offer clinical outcomes comparable to standard matched HCT, in prospective single-center intention-to-treat analysis

- A phase III trial of TK cells in haplo-HCT is running in US and EU (TK008 trial, NCT00914628)
ACKNOWLEDGEMENTS

HSR BMT UNIT
M.T. LUPO-STANGHELLINI
Jacopo PECCATORI
Massimo BERNARDI
Consuelo CORTI
and all MDs and Nurses

HSR TIGET
Pietro GENOVESE
Angelo LOMBARDO
Oscar MUNIZ PELLO
Mario AMENDOLA
Lucia SERGI SERGI
Luigi NALDINI

FHCRC, Seattle
P.D. GREENBERG
J. KUBALL

SANGAMO BIOSCIENCES
M. HOLMES
P. GREGORY

HSR. Exp. Hematol.
Elena PROVASI
Zulma MAGNANI

Attilio BONDANZA
Luca VAGO
Monica CASUCCI
Shin KANEKO
Sara MASTAGLIO
Veronica VALTOLINA
Serena Kimi PERNA
Maddalena NOVIELLO
Alessandra FORCINA
Barbara CAMISA
Nicoletta CIERI
Giacomo OLIVEIRA
Laura FALCONE

Chiara BONINI
HSR Dept. Pathology
Maurilio PONZONI
Francesca SAVNITO
Claudio DOGLIONI

HSR Mol. and Functional Immunogenetics Unit
Katharina FLEISCHHAUER

MolMed SpA
Claudio BORDIGNON
And all the staff!!!

HADASSAH H, Jerusalem
Shimon SLAVIN
Shoshana MORECKI
Aliza ACKERSTAIN

ISTITUTO CLINICO HUMANITAS, Milano
Luca CASTAGNA
Armando SANTORO

HAMMERSMITH, London
Jane APPERLEY
Eduardo OLAVARRIA

HANNOVER MEDICAL SCHOOL, Hannover
Evy WEISSINGER
Arnold GANSER
Michael STADLER

G.PAPANICOLAOU HOSPITAL , Thessaloniki
Evangelia YANNAKI
Athanasios FASSAS,
Achilles ANAGNOSTOPOULOS