Managing MF and SS with Allogeneic HSCT

Youn H Kim, MD

Department of Dermatology
Director, Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer Institute & School of Medicine
Disclosure statement

Youn Kim, MD

- Steering Committee
  - Eisai, Kyowa, Millennium

- Consultant or Advisory Board
  - Actelion, Celgene, Galderma, Soligenix, Neumedicines, Seattle Genetics, Miragen

- Investigator
  - Kyowa, Merck, Millennium, Seattle Genetics, Actelion, Eisai, Genentech, Tetralogic
Allogeneic HSCT in MF/SS
Why?
# Efficacy of Systemic Agents in CTCL

## Efficacy data for FDA approval

<table>
<thead>
<tr>
<th>Agent (Class)</th>
<th>Indication</th>
<th>Year</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romidepsin (HDAC inhibitor)</td>
<td>CTCL with prior systemic therapy</td>
<td>2009</td>
<td>Pivotal</td>
<td>96</td>
<td>34%</td>
<td>15 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Supportive</td>
<td>71</td>
<td>35%</td>
<td>11 mo</td>
</tr>
<tr>
<td>Denileukin diftitox (Fusion protein)</td>
<td>Tumors that express CD25</td>
<td>1999, 2008</td>
<td>Pivotal</td>
<td>71</td>
<td>30%</td>
<td>4 mo</td>
</tr>
<tr>
<td>Bexarotene (RXR activator)</td>
<td>Cutaneous manifestations</td>
<td>1999</td>
<td>Pivotal</td>
<td>96</td>
<td>32%</td>
<td>5+ mo</td>
</tr>
<tr>
<td>Vorinostat (HDAC inhibitor)</td>
<td>Cutaneous manifestations</td>
<td>2006</td>
<td>Pivotal</td>
<td>74</td>
<td>30%</td>
<td>6+ mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Supportive</td>
<td>33</td>
<td>24%</td>
<td>4 mo</td>
</tr>
</tbody>
</table>

**Need better therapies, more options:**

- Pralatrexate & belinostat approved for PTCL
- **Brentuximab vedotin (anti-CD30 ADC)**
- **Mogamulizumab (anti-CCR4 mab)**

**Both in phase 3 trials in CTCL**
New targeted therapies in clinical development in CTCL

**Tumor cell surface molecules:**
- CCR4
- CD158k/KIR3DL2
- CD164

**Microenvironment, immune mechanisms:**
- Lenalidomide
- PD-1, PD-L1, IDO
- CD47/SIRP

**Tumor proliferation, metabolism, survival, progression mechanisms:**
- new proteasome inhibitors
- PI3K inhibitors
- mTOR inhibitors
- JAK inhibitors
- Oligonucleotide inhibitor of miR-155-5p (MRG-106)
- Inhibitors of Bcl-2 (ABT-263/199), MCL-1
- New epigenetic modulators
- PARP inhibitors
Great clinical response to brentuximab vedotin in MF/SS

Sézary syndrome, IVA₁

Responses are not long-lasting
Road to a CURE
How do we make the nice responses last?
*Partnering with immunotherapy*

![Graph showing tumor-directed killing and immune modulatory therapy over time.](image)
Immunotherapy strategies in CTCL

- **Tumor-specific monoclonal antibodies**
- **Immune-modulating agents or antibodies**
- **Vaccine-based approaches**
- **Cytokine therapy**
- **Adoptive T-cell transfer**
- **Allogeneic HSCT**

**Molecules and Targets**

- CD25, CD30, CCR4, KIR3DL2
- TLR-A
- IMiDs
- T_{reg}
- CTLA4
- PD-1/PD-L1
- CD47/SIRP
- ECP
- DC-based Idiotype
- In situ strategy

**Cytokines**

- IFNs, IL2, IL12
Immunotherapy strategies in CTCL

- Tumor-specific monoclonal antibodies
- Cytokine therapy
- Immune-modulating agents or antibodies
- Adoptive T-cell transfer
- Allogeneic HSCT
- Vaccine-based approaches

TILs

lymphoma

M
Can we cure our patients with MF or SS?

Autologous  →  High-dose therapy followed by stem cell rescue
Benefit of no GVHD
No durable response in MF/SS, not recommended
Unable to eliminate all tumor cells

Allogeneic  →  Graft vs. lymphoma effect
Risk of GVHD
Increasing evidence of durable clinical, cytogenetic, molecular remissions in MF/SS
Able to eliminate residual tumor cells

How to maximize GVL effect while minimizing GVHD risk

Harnessing the graft-versus-lymphoma effect in allo HSCT as the ultimate cellular immune therapy
Allogeneic HSCT in MF/SS
Who, When, and How
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Clinical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Limited patch/plaque</td>
<td>Topical steroid, retinoid (bex), NM phototherapy, local RT, imiquimod</td>
</tr>
<tr>
<td>IB/IIA</td>
<td>Generalized patch/plaque</td>
<td>Phototherapy + bexarotene or IFN</td>
</tr>
<tr>
<td>IIB</td>
<td>Tumors</td>
<td>ECP ± IFN, bexarotene</td>
</tr>
<tr>
<td>III</td>
<td>Erythroderma</td>
<td>Allo-HSCT</td>
</tr>
<tr>
<td>IV</td>
<td>Extracutan disease</td>
<td>Combination chemo</td>
</tr>
</tbody>
</table>

**Overall life-expectancy < 5 yrs**

**Clinical Trials**

**Alternatives**
- Brentuximab, pralatrexate, liposomal doxorubicin, gemcitabine, other
Elements to consider for allogeneic HSCT

- Age, comorbidities/PS profile
- MF vs SS
- Clinical stage/TNMB (dz burden)
- Additional prognostic factors
  - Folliculotropism, LCT (skin vs EC sites), other
- Prior therapies and responses/DOR
- Available donor (type, source)
- Adequate disease control
- Preparatory/conditioning regimens
- GVHD prophylaxis & management
- Management of disease progression post-transplant

Overall life-expectancy < 5 yrs
Cumulating evidence of durable GVL in MF/SS
Total Skin Electron Beam and Non-Myeloablative Allogeneic Hematopoietic Stem-Cell Transplantation in Advanced Mycosis Fungoides and Sézary Syndrome

Madeleine Duvi, Michele Donato, Bouthaina Dabaja, Heather Richmond, Lotika Singh, Wei Wei, Sandra Acholonu, Issa Khouri, Richard Champlin, and Chitra Hosing

**N = 19 MF or SS, 2001-2008**
Median f/u 19 mo (1.3-8.3 yrs)
OS 79% at 2 yrs
PFS 53% at 2 yrs

**GVHD:**
- Acute, 12 of 18 (67%), 5 Gr II-IV (28%)
- Chronic, 12 (67%)

**Failure post-transplant:**
- 7 of 18 evaluable with relapse or progression, median time to event 50 d (28-718)
- **TRM at 2 yrs 12%**
6 deaths, 2 due to dz
Allogeneic Hematopoietic Cell Transplantation for Patients With Mycosis Fungoides and Sézary Syndrome: A Retrospective Analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation

Rafael F. Duarte, Carmen Canals, Francesco Onida, Ian H. Gabriel, Reyes Arranz, William Arcese, Augustin Ferrant, Guido Kobbe, Franco Narni, Giorgio Lambertenghi De Filieri, Eduardo Olavarria, Norbert Schmitz, and Anna Sureda

2010;28:2365
2014;32:3347

EBMT N= 60; 36 MF, 24 SS; 1997-2007
Median age, 46.5 (22-66); 73% stage IV
45 MRD; 73% RIC/NMA; 67% “advance dz phase”

Long-term outcome data:
Median f/u = 7 yrs
OS 46% at 5 yrs, 44% at 7 yrs (2-yr 54%)
PFS 32% at 5 yrs, 30% at 7 yrs (2-yr 34%)

GVHD: aGVHD 40%; Gr II-IV 28%; cGVHD 27%

Failure post-transplant:
- Disease progression/relapse, 27 (45%), median 3.8 mo after HCT (only 2 events after 2 yrs)
- 7-yr TRM 22%, latest event at 14 mo (22% 2-yr)

Factors a/w adverse outcome:
- Advanced phase dz at HCT (RFS/PFS, OS)
- URD (NRM, PFS, OS)
- Myeloablative (NRM, OS)
33 deaths, 19 due to dz
26 or 27 alive remain in CR
Original Article
Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome

MJ Lechowicz, HM Lazarus, J Carreras, GG Laport, CS Cutler, PH Wiernik, GA Hale, D Maharaj, RP Gale, PA Rowlings, CO Freytes, AM Miller, JM Vose, RT Maziarz, S Montoto, DG Maloney and PN Har

Total N= 129; 2001-2009
Age, median 52 (27-72)
Median f/u 36 mo (3-97)
OS 54%, 38% at 1, 3 yrs
PFS 31%, 19% at 1, 3 yrs

Subset N=52 w/ higher level data:
- 39% stage IV, 20% stage I at dx
- From dx → tx, median 38 mo
- Dz status at transplant;
  • Never CR n=33 (63%)

NMA/RIC 83, MAC 46
No sig diff in PFS/OS/NRM
Acute GVHD 74%, II-IV, 41%
Chronic GVHD at 2 yr, 43%

Failure post-transplant:
- TRM 19%, 22% at 1, 3 yrs
- RDP 50%, 58% at 1, 3 yrs
69 deaths, 35 due to dz
Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French Society of Bone Marrow Transplantation and French Study Group on Cutaneous Lymphomas


N = 37, 2002-2013
31 (84%) MF/SS, 18 stage IV
Median f/u 29 mo (3-120)
OS 57% at 2 yrs
PFS 31% at 2 yrs
MRD 46%; 2 cord blood
GVHD:
- Acute: 26 (70%) median time to GVHD 24 d; 18 Gr II-IV (49%)
- Chronic: 15 (44% at 2-yr)
Failure post-transplant:
- TRM 18% at 1, 2 yrs
- 51% with PD
14 deaths, 8 due to dz, 6 TRM
A New Approach in Donor Cell Transplant Non-Myeloablative Regimen with TLI/ATG “Protective conditioning”

Enable donor cell engraftment aGVHD reduced to <10% (vs. 20-65%)

Total Lymphoid Irradiation (TLI)

Anti-Thymocyte Globulin (ATG, Rabbit anti-T cell antibodies)

TSEBT +

Inverted Y field

Lymph Nodes
  - Cervical
  - Supra-clavicular
  - Mediastinal
  - Axillary
  - Periaortic
  - Iliac
  - Inguinal
  - Femoral

NEJM 353:1321, 2005
Stanford study on going
Protective Conditioning for Acute Graft-versus-Host Disease

Robert Lowsky, M.D., Tsuyoshi Takahashi, M.D., Ph.D., Yin Ping Liu, M.D., Sussan Dejbakhsh-Jones, M.S., F. Carl Grumet, M.D., Judith A. Shizuru, M.D., Ph.D., Ginna G. Laport, M.D., Keith E. Stockerl-Goldstein, M.D., Laura J. Johnston, M.D., Richard T. Hoppe, M.D., Daniel A. Bloch, Ph.D., Karl G. Blume, M.D., Robert S. Negrin, M.D., and Samuel Strober, M.D.

TLI/ATG conditioning suppresses GVHD by:
- Altering host immune profile to favor regulatory NKT cells
- Polarization of donor T cells toward secretion of non-inflammatory Th2 cytokines (IL4)
- Promotes expansion of donor CD4+CD25+FoxP3+ Treg cells

Does not affect donor CD8+ T-cell cytolytic function and graft antitumor activity

JI 2007;178:6242, Blood 2009;113:4458
Phase II study of non-myeloablative allogeneic transplantation using TLI-ATG in MF/SS

Study Design

TLI, total lymphoid irradiation, 8 Gy (80 cGy x 10)
ATG, rabbit anti-thymocyte globulin (1.5 mg/kg x 5)

Transplant
~5 x 10^6 CD34/kg PBSC

Donor Chimerism
MRD

Skin Biopsy
Staging Study (BM, PET/CT)

Derm evaluation
Clinical data, n=32 Stanford NMA allo regimen

*TSEBT with TLI + ATG*

- **32 patients transplanted (over 5.5 years)**
  - 12 MF (all LCT+), 20 SS
  - Stage IV 81% (26/32)
    - 6 IIB, 23 IVA, 3 IVB
  - Median age, 62 yrs (range 20-74)
  - Median prior systemic tx, 5 (range 2-14)

- **Active disease at time of TSEBT, 100% (32/32)**
  - Skin 100%, Blood 44%, LN 63%, Visceral 16%

- **Donor**
  - Sibling 32%
  - Unrelated 68% (15 full-match, 5 one-mismatch)
Clinical outcome update (median f/u 36 mo)

- **Transplant course**
  - Outpatient allograft infusion, 100%
  - Re-admission within 100 days, 69%
    - Median hospital stay, 4 days

- **Graft-versus-host disease**
  - Acute GVHD (22%)
    - Grade I, n=2
    - Grade II, n=4
    - Grade IV, n=1
    - Cumulative incidence of grade II-IV, 17%
  - Chronic GVHD
    - Extensive, n=7
    - Cumulative incidence of extensive, 24%
Clinical outcome update (median f/u 36 mo)

- **Best clinical response at 3-month**
  
<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>19</td>
</tr>
<tr>
<td>PR</td>
<td>7 (near CR)</td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
</tr>
<tr>
<td>ORR</td>
<td>90%</td>
</tr>
</tbody>
</table>

- **Transplant-related mortality (TRM)**
  
<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD</td>
<td>1</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>1</td>
</tr>
<tr>
<td>2(^\text{nd}) malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1</td>
</tr>
</tbody>
</table>
  
  | NRM                     |       |
  | 1-yr NRM                | 3.4%  |
  | 2-yr NRM                | 9.4%  |

- Graft loss in 6 pts (3 received 2\(^\text{nd}\) allo HSCT)
Clinical outcome update, median f/u 36 mo

Median
- OS: Not reached
- PFS: 42.9 months

SS with better PFS outcome, \( p = 0.027 \);
OS similar

OS 75% at 2-years
PFS 51% at 2-years
Mycosis fungoides, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT 5.0+ yr (NED, no GVHD)
Mycosis fungoides, stage IVA w/ LCT in skin, LN+: CR

Pre-TSEBT

3.5+ yr (NED*)

*Late onset aGVHD with pregnancy and non-compliance with GVHD prophylaxis
Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT
CD4+/CD26-: 99%, abs 19,780

4.0+ yr (NED, no GVHD)
CD4+/CD26-: normalized
Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

Pre-transplant

4.0+ yr (NED, no GVHD)
CANCER

Minimal Residual Disease Monitoring with High-Throughput Sequencing of T Cell Receptors in Cutaneous T Cell Lymphoma

Wen-Kai Weng,¹* Randall Armstrong,¹ Sally Arai,¹ Cindy Desmarais,² Richard Hoppe,³ Youn H. Kim⁴

¹Division of Blood and Marrow Transplantation, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA. ²Adaptive Biotechnologies, Seattle, WA 98102, USA. ³Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA 94305, USA. ⁴Department of Dermatology, Stanford University School of Medicine, Stanford, CA 94305, USA.
Monitoring minimal residual disease by High-throughput sequencing of T-cell receptor

Peripheral blood mononuclear cells and skin biopsy

\[\text{Extraction of genomic DNA}\]

High-throughput sequencing of rearranged TCR\(\beta\) CDR3 using solid phase PCR (Illumina GA2 system)

\textit{Up to 1,000,000 reads in blood; 200,000 reads in skin}

Robins et al, Blood 2009;114:4099
WK Weng, Y Kim. Sci Transl Med 2013 5:214ra171
Detection of tumor specific malignant clonal sequence

**TABLE 1. CHARACTERISTICS OF MALIGNANT TCR CLONAL SEQUENCE**

<table>
<thead>
<tr>
<th>Patient</th>
<th>% of Malignant Clone</th>
<th>TCRβ CDR3 Sequence (5'-3')</th>
<th>V Gene</th>
<th>J Gene</th>
<th>CDR3 Length</th>
<th>Tissue Source</th>
<th>Vβ Usage by Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>69.03 %</td>
<td>TGTGCCAGCAGCTTA TCC GGGAC GCCCCC CAATGAGCA</td>
<td>TRBV 7-3</td>
<td>TRBJ 2-1</td>
<td>36</td>
<td>PBMC</td>
<td>n/a</td>
</tr>
<tr>
<td>#2</td>
<td>31.89 %</td>
<td>TGTGCCAGCAGCAGTTACTC GGGACTAGGG AGG AATGAGCA</td>
<td>6</td>
<td>TRBJ 2-1</td>
<td>36</td>
<td>PBMC</td>
<td>Vβ 13.1 (TRBV6-5, 6-6, 6-9) n/a</td>
</tr>
<tr>
<td>#3</td>
<td>51.67 %</td>
<td>TGTGCCAGCAGTGA GGTCA GGCAGC TAG TCACCCCT</td>
<td>TRBV 6-1</td>
<td>TRBJ 1-6</td>
<td>36</td>
<td>Skin</td>
<td>n/a</td>
</tr>
<tr>
<td>#4</td>
<td>81.52 %</td>
<td>TGTGCCAGCTCACCCGAC G GGGACAGGGG CAGATACGCA</td>
<td>TRBV 18</td>
<td>TRBJ 2-3</td>
<td>36</td>
<td>PBMC</td>
<td>Vβ 18 (TRBV18)</td>
</tr>
<tr>
<td>#5</td>
<td>78.09 %</td>
<td>TGCAGCCAGCAGCTTGG CC GGGGC TCGG GATACGCA</td>
<td>TRBV 5-1</td>
<td>TRBJ 2-3</td>
<td>33</td>
<td>PBMC</td>
<td>n/a</td>
</tr>
<tr>
<td>#6</td>
<td>78.70 %</td>
<td>TGTGCCAGTAGTATAAG GTT CTAGCGGG AC TAGCA CAGATA CGCA</td>
<td>TRBV 19</td>
<td>TRBJ 2-3</td>
<td>42</td>
<td>PBMC</td>
<td>Vβ 17 (TRBV19)</td>
</tr>
<tr>
<td>#7</td>
<td>91.72 %</td>
<td>TGCAGCAGCAGTGAAG GGGACAGGGG A AATCCACCCCT</td>
<td>TRBV 5-1</td>
<td>TRBJ 2-2</td>
<td>36</td>
<td>Skin</td>
<td>n/a</td>
</tr>
<tr>
<td>#8</td>
<td>76.09 %</td>
<td>TGTGCCAGCAGCAGTGAAG GGGACAGGGG A AATCCACCCCT</td>
<td>TRBV 2</td>
<td>TRBJ 1-6</td>
<td>39</td>
<td>PBMC</td>
<td>Vβ 22 (TRBV2)</td>
</tr>
<tr>
<td>#9</td>
<td>59.66 %</td>
<td>TGTGCCAGCAGCAGTTAG TT GGGAG GGGTTC GAC CTGAAGC</td>
<td>TRBV 9</td>
<td>TRBJ 1-1</td>
<td>39</td>
<td>PBMC</td>
<td>Vβ 1 (TRBV9)</td>
</tr>
<tr>
<td>#10</td>
<td>18.33 %</td>
<td>TGCAGTGTAG CC GGCACAGGGG GCACAGATA CGCA</td>
<td>TRBV 20.1</td>
<td>TRBJ 2-3</td>
<td>42</td>
<td>PBMC</td>
<td>Vβ 2 (TRBV 20.1)</td>
</tr>
</tbody>
</table>

Sci Transl Med 2013, 5:214ra171
## Minimal Residual Disease (MRD) in Blood Post Transplant

<table>
<thead>
<tr>
<th>Malignant Sequence</th>
<th>Total Read</th>
<th>% of Malignant Clone</th>
<th>% of Donor T Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-TSEBT</td>
<td>848,393</td>
<td>1,229,026</td>
<td>69.029</td>
</tr>
<tr>
<td>Pre-TLI/ATG</td>
<td>1,057,097</td>
<td>1,356,526</td>
<td>77.926</td>
</tr>
<tr>
<td>Day+30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day+60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day+90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day+180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day+270</td>
<td>0</td>
<td>877,242</td>
<td>0.000</td>
</tr>
<tr>
<td>Day+360</td>
<td>0</td>
<td>764,859</td>
<td>0.000</td>
</tr>
<tr>
<td>Day+540</td>
<td>0</td>
<td>2,263,923</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Monitoring MRD by HTS may predict true molecular and clinical cure and may predict disease relapse.
Fewer relapse with molecular remission

42% of patients achieved molecular remission

\( P = 0.038 \)
Allogeneic HSCT

**MRD monitoring with TCR HTS**

Clinical benefit demonstrated in advanced stage MF/SS

- Can cure with allo HSCT, more safely, and provide lasting anti-tumor effect
  - SS better outcome than MF regardless of +/- LCT

- Regardless of center preference of transplant regimens, similar PFS, OS

- Longer follow-up needed to better assess post transplant complication issues and management

**TCR HTS is a valuable means to monitor MRD after allo HSCT**

- Molecular remission may predict better long-term outcome
Allogeneic HSCT as ultimate immunotherapy in CTCL

- Combined newer targeted therapies, chemotherapies, radiation therapy, followed by allogeneic HSCT
- Immune-modulating agents or antibodies
- Adoptive cell transfer
- Allogeneic HSCT

CTCL

Vaccine-based approaches

long-lasting, curative outcome
Stanford Multidisciplinary Cutaneous Lymphoma Group