Graft-versus-Host Disease: Advances in Prevention and Treatment

Celebrating a Second Chance at Life Survivorship Symposium

April 29 – May 5, 2023

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Colorado Blood Cancer Institute,
part of the Sarah Cannon Cancer Institute at
Presbyterian/St. Luke’s Medical Center

Topics We’ll Discuss

• Introduction to graft versus host disease
• Discuss new strategies to avoid graft versus host disease
• Discuss new treatments for graft versus host disease
  • Available new drugs
  • Drugs under investigation
Transplant from donor

Blood forming cells: STEM CELLS
• Replace Host’s stem cells

Immune Cells:
• They can attack the recipient “Graft versus host disease”
• They can destroy cancer cells “Graft Versus Leukemia”

Graft-vs-Host Disease (GVHD)

• Biological consequence of the transfer of a donor immune cells into the recipient
• Immunosuppressive medications are necessary to prevent GVHD
• GVHD can be eliminated by removing immune cells (T-cells) from the donor collection
Graft-vs-host disease (GVHD)

- GVHD is associated with anti cancer graft-versus-leukemia (GVL) effect
- If you completely remove the donor immune cells increases risk of disease relapse.

GVHD: Acute and Chronic

- Acute GVHD: Skin, GI, Liver
- Chronic GVHD: Skin, Mouth, Eyes GI, Liver, MSK, Fascia, Lungs, etc
- Alloreactivity
- Immunodeficiency
- Classic Acute
- Late Acute
- Chronic Overlap
- Classic chronic

Day 0 50 100 180 1 yr 2 yrs 3 yrs 5 yrs
- Activity
- Inflammation
- Injury
- Repair
- Damage
- Fibrosis
Acute GVHD

- Leading cause of mortality
- Grade II-IV occurs in ~70% pts
- Grade III-IV occurs in 10-15%
- ~2-6 weeks after transplant
- 30-40% refractory to 1st line of treatment

Chronic GVHD

- Most serious and common long-term complication transplant
- Occurs in 30% - 55% of patients
- ~4-6 months after transplant
- 50% of patients have 3 or more involved organs
- On average therapy is required for 2-3 years
Transplant from donor: How to define success

- Cure the blood cancer
- NO Graft vs Host Disease

Transplant from Donor: General Schema

**CONDITIONING**
- Chemo +/- Radiation
- More or less intense
- Prevent Rejection
- Destroy cancer cells

**POST TRANSPLANT IMMUNOSUPPRESSION**
- Drugs given in vein or pills
- Prevent GVHD
Transplant from Donor: General Schema

Infusion of Cells from Donor

Day -6                  0          +15           +30         +100       +180

Cyclosporine + Methotrexate
Tacrolimus + Methotrexate
Tacrolimus + MMF
Tacrolimus + Rapamycin + MMF

CONDITIONING
• Chemo +/- Radiation
• More or less intense
• Prevent Rejection
• Destroy cancer cells

We collect from donor a mix of many kind of cells:
Stem Cells and LOTS and LOTS of immune cells.

• Some immune cells can induce GVHD (Naïve T-cell)
  • ALLOREACTIVE – BAD guys

• Some immune cells can prevent or reduce GVHD (Regulatory Tcells)
  • TOLERANCE – GOOD guys
Strategies to Avoid GVHD

- Post-transplant Cytoxan (PTCy)
- Graft manipulation

How post-transplant Cytoxan (PTCy) works

Alloreactive T-cell cause GVHD (the BAD ones)

Alloreactive T-cell expand and are destroyed by Cytoxan

All other T-cells thrive
Post transplant Cytoxan (PTCy): Study and Clinical Data

- PTCy (+TAC/MMF) is already used world-wide for transplant from children or parents (Haplo)

- BMT CTN 1203 clinical trial showed promising results in transplant from siblings and unrelated donors.

- **Phase III BMT CTN 1703** study evaluated outcomes post reduced-intensity conditioning transplant in patients randomized to receive PTCy + TAC + MMF vs standard TAC+ MTX

PTCy=post-transplant cyclophosphamide  TAC=tacrolimus  MMM=mycophenolate mofetil

BMT CTN 1703: Study Design

431 Patients received reduced-intensity transplant from well matched donors

PTCy  
TAC+MMF  (n = 214)

TAC+MTX  (n = 217)
BMT CTN 1703: Study Design

Infusion of Donor Cells

Day

-6

0

+15

+30

+100

+180

Reduced intensity CONDITIONING

PTCy

TAC + MMF

(n = 214)

OR

TAC + MTX

(n = 217)

MTX = methotrexate

BMT CTN 1703: Patients Transplanted

PTCy + TAC + MMF

(n = 214)

TAC + MTX

(n = 217)

Men 63%

58%

Women 37% 42%

Age: average 66 years 66 years

Age: range 21-79 years 26-78 years

Disease

- Leukemia 60% 58%

- MDS 29% 30%

- Lymphoma 11% 8%

Donor type

- Related 28% 31%

- Unrelated 72% 69%

Holtan et al ASH 2022

2023 SURVIVORSHIP SYMPOSIUM
## BMT CTN 1703: Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients living without disease and without GVHD 1 year post transplant</th>
<th>Patients with acute GVHD 100 days post transplant</th>
<th>Patients with chronic GVHD 1 year post transplant</th>
<th>Patients with Cancer Relapse 1 year post transplant</th>
<th>Transplant mortality 1 year post transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCy + TAC + MMF (n = 214)</td>
<td>53%</td>
<td>6%</td>
<td>12%</td>
<td>21%</td>
<td>12%</td>
</tr>
<tr>
<td>TAC + MTX (n = 217)</td>
<td>35%</td>
<td>15%</td>
<td>25%</td>
<td>20%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Holtan et al. ASH 2022
BMT CTN 1703: Conclusions

PTCy + TAC + MMF:
2023 new standard of care
for GVHD prophylaxis in well-matched donor transplant for adults receiving reduced-intensity conditioning

Other Ways to Reduce GVHD: Look at the Donation

We collect from donor a mix of many kind of cells: Stem Cells and LOTS and LOTS of immune cells.

- Some immune cells can induce GVHD (Naïve T-cell)
  - ALLOREACTIVE – BAD guys
- Some immune cells can prevent or reduce GVHD (Regulatory Tcells)
  - TOLERANCE – GOOD guys
Other Ways to Reduce GVHD

Donor collection:
- Let’s remove the bad guys
- Let’s help the good guys

“Let’s remove the BAD guys” approach

- “Naïve” Tcells are removed [CD45RA+]
- Stem Cells + “Memory” Tcells infused to the recipient

138 patients with leukemia, Donors were fully matched

Bleakley et al. JCO 2022
138 patients with leukemia,
Donors were fully matched
“Let’s remove the BAD guys” approach

“Naïve” T-cell depleted (n = 138)

<table>
<thead>
<tr>
<th>Patients with acute GVHD g≥3</th>
<th>4%</th>
<th>None severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 days post transplant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with chronic GVHD</th>
<th>7%</th>
<th>None severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year post transplant</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Patients living without disease and without GVHD</th>
<th>68%</th>
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<tbody>
<tr>
<td>3 year post transplant</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>77%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 year post transplant</td>
<td></td>
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</tbody>
</table>

“Let’s help the GOOD guys” approach

ORCA-T

Donor cells

Stem Cells

Regulatory Tcell [CD4+CD127lo]

The GOOD guys

Conventional T-cell
“Let’s help the GOOD guys” approach: ORCA-T

The “good guys” have time to expand

Infusion #1
- Stem Cells
- Regulatory Tcell

Infusion #2
- Conventional T-cell

Chemo Conditioning

Day
-6 0 +2 +3 +100 +180

Tacrolimus

ORCA-T: clinical trials

- **127 patients**, with high-risk blood cancers
- Donors were fully matched-related (n=66) or unrelated (n=61).
- Transplant was with high-dose chemo or radiation
- Post-transplant single-agent tacrolimus
- Outcomes were compared with 375 matched patients from the CIBMTR registry

NCT04013685
NCT01660607
## ORCA-T: Results

<table>
<thead>
<tr>
<th>Measure</th>
<th>ORCA-T (n = 127)</th>
<th>CIBMTR Control (n = 375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with <strong>acute GVHD</strong> <em>g&gt;3</em> 180 days post transplant</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>Patients with <strong>chronic GVHD</strong> 1 year post transplant</td>
<td>6%</td>
<td>38%</td>
</tr>
<tr>
<td>Relapse free survival 1 year post transplant</td>
<td>81%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Non Relapse mortality</strong> 1 year post transplant</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Overall Survival</strong> 1 year post transplant</td>
<td>91%</td>
<td>68%</td>
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</tbody>
</table>

A multi-center randomized controlled phase 3 trial comparing Orca-T to standard of care is currently enrolling across the US (NCT05316701).
GVHD treatment: Principles

- Steroids: mainstay of Systemic Treatment
- Acute: 40-60% response < 5 days
- Chronic: needs long course, combo not better
- When steroids don’t work: always poor outcome

GVHD: CHALLENGES

- No treatment fits all patients
- Largely ineffective treatments
- Treatment is toxic, immunosuppressive, might be needed lifelong
- Impact on quality of life, return to family life, relationships, work
GVHD: Ideal treatment

- Effective
- Not toxic
  - Does not reduce immune defenses
  - Does not damage organs in the long-run

New drugs approved for GVHD treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of GVHD</th>
<th>FDA approved</th>
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<tbody>
<tr>
<td>Ibrutinib (Imbruvica)</td>
<td>Chronic</td>
<td>2/8/2017</td>
</tr>
<tr>
<td>Ruxolitinib (Jakafi)</td>
<td>Acute</td>
<td>5/24/2019</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>9/22/2021</td>
</tr>
<tr>
<td>Belomosudil (Rezurock)</td>
<td>Chronic</td>
<td>7/16/2021</td>
</tr>
</tbody>
</table>
Ibrutinib
(Imbruvica)

- **Pill:** once a day with water
- Already used for treatment of lymphomas and leukemia

**How does it work?**
- Blocks B and T cells responsible for GVHD
- Stops production of antibodies involved in GVHD
- Stops production of inflammatory substances (cytokines) involved in GVHD

In original study including 42 patients with bad GVHD resistant to steroids:
- In 31% of patients, GVHD went away completely
- 38% of patients had partial resolution of GVHD
- In 55% of patients, the response lasted at least 11 months
- 64% of patients could reduce the usage of steroids like prednisone

**It works on sclerotic GVHD:**
- 61% of patients with sclerosis showed improvement and in 39% tightening of the skin went away

Waller EK, BBMT 2019
PCYC-1129-CA
Ibrutinib (Imbruvica)

Adverse effects:

>20%

- Fatigue;
- Bruising
- Low platelets
- Muscle spasm
- Nausea
- Pneumonia
- Mount sore

~5%

- Irregular heartbeat

Ruxolitinib (Jakafi)

- **Pill:** twice a day
- Already used for other blood diseases (myelofibrosis and P.Vera)

- **How does it work?**
  - *Modulates immune system* to switch off GVHD: regulates the development, proliferation, and activation of several immune cell types.
Ruxolitinib

**REACH2 Trial: acute GVHD**
Randomly assigned 309 patients with severe steroid-refractory acute GVHD to receive ruxolitinib 10 mg twice daily (n = 154) or best available therapy (n = 155)

- The improvement was seen in **62%** of patients compared to 39%.
- GVHD went completely away in **34%** of patients on ruxolitinib vs 19% in the control group
- The good response was maintained after 2 months of treatment in more patients in the ruxolitinib group than in the control group (40% vs. 22%)

Zeiser R, NEJM 2020

**REACH3 Trial: chronic GVHD**
- Randomly assigned 329 patients with moderate or severe steroid-refractory or dependent chronic GVHD to receive ruxolitinib 10 mg twice daily (n = 165) or best available therapy (BAT; n = 164)

- The improvement was seen in **50%** of patients compared to 26%.
- The responses lasted up to 1 year and 7 months
- Patients reported improved quality of life and symptoms

Zeiser R, NEJM 2021
Ruxolitinib (Jakafi)

Adverse effects:
>35%
- Anemia
- Low platelets

>20%
- Infection, fungal, viral
- Liver test go up

Belumosudil (Rezurock)

- Pill: once or twice a day with food
- Totally new drug designed to fight fibrosis (ROCK inhibitor)

- How does it work?
  - Modulates immune system to switch off GVHD, does not depress the immune system
  - Anti-fibrosis
Belumosudil

- 77% of patients treated improved; noted responses in all affected organs
- In 50% of patients the response lasted at least 14 months
- Very well tolerated
- Signals of response in patients who experienced treatment failure with ruxolitinib and ibrutinib.

Cutler et al, Blood 2021
Study: ROCKstar

Belumosudil (Rezurock)

Adverse effects:
>20%
- Fatigue
- Edema, muscular pain
- Liver test go up
- Headache
- GI upset
Axalitimab:
Anti CSF-1R antibody that blocks cells involved in GVHD (macrophage)

- 40 patients with very bad GVHD, received, on average 4 previous therapies: 65% had already ibrutinib, 52% ruxolitinib, 20% belumosudil

- Infusion IV every 2 weeks

- 67% of patients improved, worked in all affected organs
- Responses noted by the first month of treatment
- Drug was well tolerated, minimal drug-drug interactions

Ongoing clinical trial AGAVE-201 (NCT04710576)

On the Horizon: DRUG on CLINICAL TRIAL

Thank you !!!

My Patients!
My Nurses
My colleagues

BMTInfonet

Pharmacists
Transplant coordinators
Case managers
Social workers
Administrative staff
QUESTIONS?

Marcello Rotta, MD
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