CAR T-cells in Non-Hodgkin Lymphoma, A Hopeful Option

Presented by Blood & Marrow Transplant Information Network
BMTInfoNet.org

Thursday, January 13, 2022

Many thanks to Kite, a Gilead Company, for its support of this webinar.
Meet The Speaker

Gary Simmons, DO

Dr. Gary Simmons is a hematologist-oncologist specializing in stem cell transplantation and cellular immunotherapies for the treatment of blood cancers, including various forms of leukemia, myeloma and lymphoma.

He serves as Medical Director of the Ambulatory Clinics and leads the Disease Working Group in Cellular Immunotherapies and Transplantation at Virginia Commonwealth University in Richmond, VA.
CAR T-cells in Non-Hodgkin Lymphoma, A Hopeful Option

Gary L. Simmons, DO
Assistant Professor
Medical Director, Ambulatory Clinics Cellular Immunotherapy and Transplantation
Leader of Disease Working group in Cellular Immunotherapy and Transplantation
Virginia Commonwealth University, Richmond Virginia
Disclosures

- Speaker’s bureau Kite/Gilead
- ASH Advisory Board Kite
- Consultant for Jazz Pharmaceuticals
<table>
<thead>
<tr>
<th>Learning Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review</strong></td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
</tr>
<tr>
<td><strong>Explain</strong></td>
</tr>
<tr>
<td>The History of Immuno-oncology and the need for CAR T</td>
</tr>
<tr>
<td><strong>Review</strong></td>
</tr>
<tr>
<td>FDA indications in Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td><strong>Describe</strong></td>
</tr>
<tr>
<td>Differences between stem cell transplant and CAR T cells</td>
</tr>
<tr>
<td><strong>Review</strong></td>
</tr>
<tr>
<td>Review the treatment of CAR T: Both the success and toxicities here at VCU</td>
</tr>
<tr>
<td><strong>Look</strong></td>
</tr>
<tr>
<td>Look at the future in immunotherapy</td>
</tr>
</tbody>
</table>
Epidemiology

• NHL is most common hematologic malignancy in US\(^1\)
  • 77,240 case per year
  • 19,940 deaths in 2020

• Diffuse large B Cell lymphoma is most common subset of NHL\(^2\)

Front Line Treatments in NHL

**Diffuse Large B Cell**
- Chemo First Line

**Follicular**
- Watch and Wait
- Chemo-Immunotherapy
- Radiation

**Mantle Cell**
- Chemotherapy
- Autologous Stem Cell Transplant
- Maintenance
The immune system is unable to eradicate or control cancer cells when:

- **T cells are unable to recognize tumor cells as foreign**
- **Tumor-specific T cells are deficient in number**
- **T cells are unable to function properly**

Outcomes for Patients with Relapsed/Refractory NHL

- Retrospective, 636 patients
- Relapsed/Refractory DLBCL
- Complete Response 7%
- Median Survival 6.3 months

Relapsed/Refractory B Cell Malignancies

• Mantle Cell Lymphoma
  • Disease progression after (Ibrutinib) have poor prognosis
  • Overall response rate 25-42%
  • Overall Survival 5.8 months

• Follicular Lymphoma
  • After ≥ 2 lines of therapy, The Complete Response rates were ≤ 14%,
  • Median Duration of Remissions were ≤ 13 months

1 Peter Martin, Blood March 2016.
Immune Therapy
Paradigm Shift in Oncology Treatment

Chemotherapy
- Cell cycle
- Not specific
- Autologous Stem Cell Transplant

Targeting Therapies
- CD 20 monoclonal antibodies (Lymphoma)
- HER 2 monoclonal antibodies (Breast Cancer)

Immunotherapies
- Allogeneic Stem Cell Transplant
- IL 2
- Checkpoint Inhibitors
- CAR T
Metastatic renal cell cancer cured with high-dose bolus IL-2 in January 1994

Nobel Prize in Physiology or Medicine 2018

Checkpoint inhibitors for Metastatic Melanoma

Stephen Rosenberg, MD PhD

James P. Allison

Tasuku Honjo

Carl June, MD
A long journey...to CAR T
## Immune System - B cells and T cells

<table>
<thead>
<tr>
<th>B Cells</th>
<th>T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have receptors that are specific for a protein and excellent binding to it</td>
<td>Have receptors that require specific receptors (Matched)</td>
</tr>
<tr>
<td>Present the protein to T cells</td>
<td>T cells need a lot of signals to get them excited</td>
</tr>
<tr>
<td>Not great at killing infected cells</td>
<td>Excellent at killing tumor cells when activated</td>
</tr>
</tbody>
</table>

*Abbreviations: B-Cells = B lymphocytes; T-Cells = T lymphocytes*
Patient Flow and Therapy Timeline

- **Collect patient’s white blood cells over 1-2 hours**
- **Ship to manufacturer**
- **Manufacture CAR T cells. Process takes 2-4 weeks**
- **Ship product to site**
- **Inpatient 3 days of Chemotherapy**
- **Infuse patients CAR T cells over 30 min and observe 7 days**

**Isolate and activate T cells**
**Engineer T cells with CAR gene**
**Grow and expand number of T cells**
**Conditioning Chemotherapy**
**Infusion And Follow-up**
Chimeric Antigen Receptor (CAR) T cell Therapy

Novel immunotherapy approach that involves engineering patient’s own immune cells

- Reprograms patients’ own T cells to recognize tumor cells as foreign
- Expands patients’ own T cells
- Reactivates patients’ own T cells to kill target cells

https://www.cancer.gov/about-cancer/treatment/research/car-t-cells
FDA Indications for CAR T-cells in Relapsed/Refractory NHL

Diffuse Large B Cell Lymphoma
Follicular Lymphoma and Marginal Zone
Mantle Cell Lymphoma
Primary Mediastinal B Cell Lymphoma
<table>
<thead>
<tr>
<th>Indications</th>
<th>Axicabtagene Ciloleucel(^1)</th>
<th>Axicabtagene Ciloleucel(^2)</th>
<th>Tisagenlecleucel(^3)</th>
<th>Brexucabtagene Autoleucel(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL, Primary Mediastinal B Cell Lymphoma, Transformed FL to DLBCL (ZUMA 1)</td>
<td>Relapsed Refractory Follicular Lymphoma (ZUMA 5)</td>
<td>DLBCL, TFL,</td>
<td>Relapsed Mantle Cell Lymphoma (ZUMA 2)</td>
<td></td>
</tr>
<tr>
<td># prior Rx</td>
<td>Majority &gt;3</td>
<td>2</td>
<td>2-7</td>
<td>Median 3</td>
</tr>
<tr>
<td>Median Age</td>
<td>58 (range 25-76)</td>
<td>62 (range 34-79)</td>
<td>56 (22-76)</td>
<td>65 (range 38-79)</td>
</tr>
<tr>
<td>Prior allo allowed</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>74%</td>
<td>91%</td>
<td>54%</td>
<td>85%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>55%</td>
<td>60%</td>
<td>40%</td>
<td>59%</td>
</tr>
</tbody>
</table>

For Comparison in Scholar -1 with chemotherapy ONLY 7% Respond

---

1. Neelapu SS et al. 2 year Follow Up and High Risk Subset Analysis of ZUMA1 in patients with Refractory Large B Cell Lymphoma. 2018 American Society of Hematology Dec 1-4 San Diego

CAR T-Cells...!
CAR T-Cells: From Referral to Treatment
Questions to ask your physician

- Should we get a biopsy to prove it has come back?
- Should I be referred to transplant / CAR t-cell center?
- Do we need to start treatment now or can I wait until I meet with transplant/car t-cell team?
- Patients can go online and search for authorized treatment centers for CAR T at [www.bmtinfonet.org/car-t-medical-centers](http://www.bmtinfonet.org/car-t-medical-centers)
## Differences between Stem Cell Transplant and CAR T cells

<table>
<thead>
<tr>
<th>Autologous Transplant</th>
<th>Allogeneic Transplant</th>
<th>Car T –cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Principle: Uses high dose chemotherapy to kill cancer</td>
<td>• Principle: use new donor immune cells – B, T, NK T cells</td>
<td>• Principle: use engineered T Cells to kill cancer</td>
</tr>
<tr>
<td>• Best results if in remission</td>
<td>• Best if in remission</td>
<td>• Patients are not in remission</td>
</tr>
<tr>
<td>• Toxicity from chemo</td>
<td>• Toxicity from GVHD, infection</td>
<td>• Collect T cells 2-4 hours</td>
</tr>
<tr>
<td>• Collect stem cells over 1 week</td>
<td>• Donor gives cells</td>
<td>• In hospital 2 weeks</td>
</tr>
<tr>
<td>• In hospital 3 weeks</td>
<td>• In hospital 4-6 weeks</td>
<td>• Toxicity of T cells expanding</td>
</tr>
<tr>
<td>• Short recovery (1 month)</td>
<td>• Long recovery outpatient (months)</td>
<td>• Short recovery ~ 30 days</td>
</tr>
<tr>
<td>• Risk of death from procedure &lt; 1%</td>
<td>• Risk of death from procedure 10-15%</td>
<td>• Risk of death from procedure &lt;2%</td>
</tr>
</tbody>
</table>
## Disease Determines the Treatment

<table>
<thead>
<tr>
<th>Autologous</th>
<th>Allogeneic</th>
<th>CAR T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>Leukemia – AML, ALL, CML</td>
<td>NHL</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>MDS</td>
<td>Myeloma</td>
</tr>
<tr>
<td>Relapsed NHL</td>
<td>Myelofibrosis</td>
<td></td>
</tr>
<tr>
<td>Relapsed Hodgkin Lymphoma</td>
<td>Aplastic Anemia</td>
<td></td>
</tr>
</tbody>
</table>
VCU Algorithm

Relapsed Diffuse Large B Cell Lymphoma

- Relapsed < 12 months or never in remission
  - CAR T cells
  - Second Line Chemo and ASCT

- Relapsed > 12 months after being in remission
  - 2nd line Chemotherapy & ASCT

Relapse

- Allogeneic Transplant
  - CAR T cells

ASCT: Autologous Stem Cell Transplant (transplant using your own stem cells)
Allogeneic Stem Cell Transplant (Donor stem cells)
General Processes

Referred from your doctor to transplant/car t cell center

The team reviews options for the disease based on current literature and clinical trials

Organ testing is performed to determine candidacy

Consents are signed and collection begins

1-day for CAR

~1-week for Stem Cells
Toxicities of CAR T

Cytokine Release Syndrome (CRS)

Immune Cell Associated Neurotoxicity Syndrome (ICANS)
Cytokine release syndrome (CRS)

- Mediated by high levels of inflammatory cytokines, such as IL-6

Cytokine Release Syndrome (CRS)

Symptoms
- Fevers
- High heart rates
- Low blood pressure
- Kidney and liver Injury
- Clotting
- Heart damage
- Trouble breathing
Management of CRS is based on clinical parameters

CRS can be fairly well managed with high level of clinical surveillance, fluids, and vasopressors

The IL-6 receptor antibody tocilizumab is the consensus first line treatment for CRS grade 2+

Second line treatment for CRS varies by protocol and/or institutional guidelines
Immune Effector Cell Neurotoxicity Syndrome (ICANs)

Impaired handwriting

Day 4
9 am

Day 5
01:30 PM
Toci 8 mg/kg

Day 5
03:30 PM

Day 6
9 am

I love Shawnee, KS.

MMSE score 29/30

27/30

I miss my kids.

29/30

Immune Effector Cell Associated Neurotoxicity (ICANs)

- Confusion
- Tremor
- Seizure
- Aphasia (trouble speaking)
- Headache
- Hallucinations
Neurotoxicity Management at VCU

- ICU Level Care
- Continuous electroencephalogram (EEG)
- Examination of the cerebrospinal fluid (CSF)
- Keppra
- Steroids – Dexamethasone required
Post Hospitalization
What we watch for after CAR T cell therapy

**FDA mandates the patients remain <2hr from center received CART-cells for 30 days**
- At VCU we require < 30 minutes to the center

**Monitor Low Blood Counts**
- May need transfusions for several months

**Low IgG – this is expected post CAR**
- May need IVIG if having recurrent infections

**Fevers and Infections**
- Higher risk of infections
- Use ppx acyclovir, levofloxacin and fluconazole

**Delayed Neurotoxicity , Rare but has occurred**
- FDA – patients cannot drive or operate heavy machinery for 8 weeks after CAR T cells due to risk of neurotoxicity
Limitations to CAR – CD 19

1. Proteins need to be expressed on outside of cell
2. Must be able to live without the cell being attacked
The Future of Immunotherapies in Cancer
VCU – Cellular Immunotherapy Program

- FDA Approved CAR T cells in RELAPSED SETTING
  - Myeloma
  - Mantle Cell Lymphoma
  - Diffuse Large B Cell Lymphoma
  - Follicular Lymphoma
  - B Cell Acute Lymphoblastic Leukemia
- Clinical trials using T-Cell Receptor therapies for metastatic sarcoma
- Coming is Gene Therapy to treat sickle cell disease and thalassemia
- Coming are Tumor Infiltrating Lymphocytes (TIL) therapies for lung cancer and solid tumors
Summary

• The paradigm shift of immunotherapy has reached lymphoma and myeloma with CAR T Cells

• CAR T cell therapy is a novel therapy that has shown to show great responses in patients highly treated hematologic B cell malignancies with Curative Intent

• Immune therapy is a powerful therapy with toxicities requiring complex monitoring and care of patients

• Ongoing trials will challenge stem cell transplant vs CAR T cells
Acknowledgements to the CIT Working Group

CIT
Gary L. Simmons, DO
John McCarty MD
Amir Toor, MD
William Clark, MD
Harold Chung, MD
May Aziz Pharm D
Melissa Hunt – ANP, Lead
CIT – Advanced Practioners

Nursing
Jessican Gray RN
Kristen Oliver RN

Billing/Coding/Payor
Penny Trentham
Tessa Proto
Denna Chabner
Suzanne Britt
Kyra McDaniel
Debra Hunt
Carrie Cybulski

Apheresis
Susan Roseff, MD
Elizabeth Godbey, MD

Cellular Therapeutics Laboratory
Christina McLaughlin
Margaret Schwerdtferger

QAPI
Ashley Brizendine

CIBMTR
Marilyn Burns

BMT Research
Kathryn Candler
Charles Hall

Pharmacy Administration
Rodney Stillman
Craig Kirkwood
Denise Lowe

Informatics/IT Office
Victoria Brock
Reuben Southall

MR ICU
Kristin Miller MD
Audrey Roberson RN
In Closing

We at VCU are grateful to all patients and families for their trust and support!

I am happy to answer any questions – Thank You!
Questions?

Gary Simmons, DO

*Many thanks to Kite, a Gilead Company for its support of this webinar.*
Let Us Know How BMT InfoNet Can Help YOU!

Visit our website:  bmtinfonet.org

Email us: help@bmtinfonet.org

Give us call:  888-597-7674

We're here to help every step of the way!