CAR-T Cell Therapy and Hematopoietic Stem Cell Transplantation
Current Status and Future Directions

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What are CAR-T-Cells and How Do You Make Them

1. Apheresis
2. Stimulation and Transduction
3. Expansion
4. Lympho-depletion
5. Infusion

- Retains the functionality of a T-cell with the antigen recognition properties of antibody
- Recognize cell surface antigens independent of MHC, have co-stimulatory signals integrated

*Image, Courtesy of NIH Medical Arts*
CD19 CAR Clinical Updates (NCI-POB)

T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial

Daniel W Lee, James N Kochenderfer, Maryalice Stetler-Stevenson, Yongzhi K Cui, Cindy Delbrook, Steven A Feldman, Terry J Fry, Rimas Orentas, Marianna Sabatino, Niral Shah, Seth M Steinberg, Dave Stroncek, Nick Tschernia, Constance Yuan, Hua Zhang, Ling Zhang, Steven A Rosenberg, Alan S Wayne, Crystal L Mackall

Lee et al. Lancet 2015
67% CR rate (intention to treat)
All responders with CRS
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia


81% Complete remission rate (not intention to treat)
CD22 CAR Results (NCI POB)

Salvage CAR for CD19 negative relapse
Limitations to Durable CAR-T cell Induced Remissions
Cytokine Release Syndrome

**General**
- Fevers
- Chills
- Feeling tired
- Feeling achy
- Pain

**Lungs**
- Breathing fast
- Decreased levels of oxygen in the blood
- Difficulty breathing

**Heart**
- Fast heartbeat
- Decreased blood pressure
- Decreased heart function
- Leaky blood vessels

**Liver**
- Elevated liver tests

**Gastrointestinal**
- Poor appetite
- Nausea
- Vomiting
- Diarrhea

**Kidneys**
- Decreased urine output
- Decreased electrolytes (salts in the blood)

**Blood system**
- Decreased hemoglobin
- Decreased platelets
- Decreased ability to fight infection
- Increased risk of bleeding

**Muscles**
- Muscle aches
- Weakness

**Neurologic**
- Headaches
- Drowsiness
- Confusion
- Difficulty finding words
- Seeing and hearing things
- Seizures
- Dizziness

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**GRADING ASSESSMENT**

**Grade 1 CRS**
- Fever, constitutional symptoms

**Grade 2 CRS**
- Hypotension: responds to fluids or one low dose pressor
- Hypoxia: responds to <40% O2
- Organ toxicity: grade 2

**Grade 3 CRS**
- Hypotension: requires multiple pressors or high dose pressors
- Hypoxia: requires ≥ 40% O2
- Organ toxicity: grade 3, grade 4 transaminitis

**Grade 4 CRS**
- Mechanical ventilation
- Organ toxicity: grade 4, excluding transaminitis

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**TREATMENT**

**Extensive co-morbidities or older age?**

- Yes
  - Vigilant supportive care
  - Tocilizumab + corticosteroids

- No
  - Vigilant supportive care
  - Assess for infection (Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed)
FDA Approvals

• Kymriah (Tisagenlecleucel, Novartis: For children up to age 25 with ALL (August 2017)
  • 81% complete remission rate

• Yescarta™ (axicabtagene ciloleucel, KITE): For adults with Diffuse Large B Cell Lymphoma (October 2017)

• Tocilizumab (anti-IL6 receptor blockade)
  • To treat CRS
Targeting IL6 has demonstrated clinical efficacy in the treatment/prevention of severe CRS

- Tocilizumab, FDA approved
  - IL6 receptor antibody

Lee et al. Blood 2014
Orlowski RJ, et al. BJH. 2016
Stem cell transplantation

Autologous

- Autologous stem cell collection
- Conditioning regimen
- Freeze Stem Cells
- Thaw + transplant

First-line therapy: Multiple Myeloma
- Prolongs PFS and survival (Attal et al-NEJM-1996)

Second-line therapy: Relapsed Hodgkin's and NHL
- Prolongs survival in NHL (Parma Trial-1995)
- Prolongs DFS in HDz (but not survival)
Stem cell transplantation

**Autologous**

- Patient
- Autologous stem cell collection
- Conditioning regimen
- Freeze Stem Cells
- Thaw + transplant

**Allogeneic**

- Tissue or HLA matched
- Stem cell donor
- Allogeneic stem cell collection
- Conditioning regimen
- transplant
Stem Cells Source

Peripheral Blood
- G-CSF subcutaneous injection for 5 days. Mononuclear cells collected by apheresis

Bone Marrow
- Direct aspiration under general

Umbilical Cord Blood
- Placental blood directly drained into bag
How Does Myeloablative Allogeneic BMT Cure?

- Pre-transplant intensive Therapy (kill the cancer)
  1) Conditioning Regimen
- Transplant
  - Rescue the bone marrow
  - Immunotherapy

  - GVL

  - Remission
Allogeneic Hematopoietic Stem Cell Transplantation: Can Cure Patients With Chemotherapy Refractory Hematological Malignancies
T-cell Mediated Graft-Vs-Leukemia Effects Can Cure Chemotherapy Resistant Malignancies

May 2006
1 month
After transplant

NHLBI Hematology Branch Transplant Protocol 02-H-0250
Types of Allogeneic Transplants

• *Conventional High Dose or Myeloablative Transplant*
  – Conditioning fully eradicates the host’s bone marrow

• *Reduced Intensity Conditioning (RIC)*
  – Low dose or non-myeloablative transplant
  – Immunologically eradicates host bone marrow
Use of Reduced Intensity Conditioning on the Rise

Allogeneic Transplants Registered with the CIBMTR

- Myeloablative
- Non-myeloablative

Number of Transplants

Year:
- 2002: 58%
- 2003: 42%
- 2004:
- 2005:
- 2006:
- 2007:
- 2008:
- 2009:
- 2010:
- 2011:
- 2012:
Reduced Intensity Conditioning (RIC): Decreases Risk Of TRM But May Increase Risk of Relapse For Some Malignancies

Possibility of increased risk of relapse (i.e. AML, MDS) with reduced intensity transplants

TRM= Transplant Related Mortality
Trial: Myeloablative vs. Reduced Intensity Allogeneic Transplantation for AML/ MDS

Scott et al JCO 2017

Hourigan et al JCO 2019
Major Improvements in Transplant Safety Over the Past 2 Decades

McDonald G.B. et al Annal Int Med 2020: epub ahead of print

Day 200 NRM

Death After Transplant

2003-2007- n=1148
2013-2017- n=1131

McDonald G.B. et al Annal Int Med 2020: epub ahead of print
In the era of precision medicine, why do we still perform these dangerous allogeneic transplants?

- Remains only curative modality for certain diseases associated with short survival with conventional therapy
  - Relapsed AML
  - Relapsed ALL
  - High Risk MDS

- Is the only curative modality for many non-malignant debilitating diseases
  - Sickle cell Anemia
  - Aplastic Anemia- Relapsed refractory to IST
Allogeneic Transplant For Hematological Malignancies

Survival after HLA-Matched Sibling Donor HCT for AML, 2005-2015

Survival after Unrelated Donor HCT for Myelodysplastic Syndrome (MDS), 2005-2015
Impact of Drug Advances On Transplant Numbers

Impact of Drug Advances On Transplant Numbers

Passweg et al. BMT 2017:Feb;52(2):191-196
REQUIREMENTS FOR ALLOGENEIC TRANSPLANTATION

• An HLA compatible donor to donate stem cells
  – 25% each sibling will be HLA identical
  – In the U.S., there is approximately a 25% that a patients will have an HLA identical sibling

There is a 1:4 Chance of Siblings Being HLA Matched

Parents

Children

HLA Type
Morn  Dad
A
B
DR
Availability of a Stem Cell Sources for Allogeneic Transplantation

Chances of Finding a Stem Cell Donor

<table>
<thead>
<tr>
<th>HLA Matched Sibling</th>
<th>HLA Matched Unrelated Donor</th>
<th>No HLA Matched Donor</th>
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<tr>
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<td>10%</td>
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<td>90%</td>
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Potential Candidates For a Cord Blood Transplant or A Haploidentical Transplant
Graft Donor Sources - who to choose?

1) HLA Identical Sibling (SIB) - still best
2) 8/8 Allele Matched Unrelated Donor (MUD) - maybe still 2^{nd} best
3) alternative donors:
   - HLA-Haploidentical related donor (Haplo)
   - Cord Blood transplant
   - 7/8 Allele Matched Unrelated Donor (MMUD)
Unrelated Donor Transplants: Diversity of Adult Donors on the Be The Match Registry® 2014

Probability of finding a perfect match

- **White**: 56%
- **Minority**: 26%
- **Unknown, Other or Declined**: 18%

Minority includes donors who identified their race or ethnicity as:
- American Indian or Alaska Native
- Asian
- Black or African American
- Hispanic or Latino
- Native Hawaiian or Other Pacific Islander

Bone Marrow Donors Worldwide
- 52 countries
- 72 Registries

Source: National Marrow Donor Program/Be The Match FY 2014
Unrelated Cord Blood Transplantation (UCBT)

Unrelated Cord Blood (UCB) transplants are a transplant option for patients lacking an HLA identical donor:
- Cord blood is a rich source of Hematopoietic progenitor cells - more than human BM

60-80% of patients will have a cord unit in the public registry that could be used for a transplant

Advantages of Cord Blood

- Lower Graft vs. Host Disease (GVHD)
- HLA-mismatched Transplants Possible
- Off the shelf product quickly available
- Cord Grafts available to Patients with Rare HLA Types And Ethnic Minorities
Cord Transplants Compares Favorably with Matched Unrelated Donor Transplants

![Graph](image)

A Survival

- Cord Blood
  - Adjusted
  - Unadjusted
- HLA-Matched
  - Adjusted
  - Unadjusted
- HLA-Mismatched
  - Adjusted
  - Unadjusted

Survival

- Probability of Survival
- Years after Transplantation
- No. at Risk
  - Cord blood: 140, 73, 36, 13, 4
  - HLA-matched: 344, 170, 95, 39, 11
  - HLA-mismatched: 98, 39, 28, 16, 6

B Relapse

- Probability of Relapse
- Years after Transplantation
- No. at Risk
  - Cord blood: 140, 74, 39, 13, 4
  - HLA-matched: 344, 161, 87, 35, 11
  - HLA-mismatched: 98, 40, 29, 15, 6

Milano et al NEJM 20
Haploidentical BM Transplants

- Transplants that utilize stem cells collected from a relative who only matches for half of the HLA tissue antigens

  • **Advantages:**
    - Virtually every patient will have a haplo-identical relative to serve as a stem cell donor

  • **Disadvantages:**
    - Higher incidence of graft versus host disease
    - Obligates use of T-cell depletion
Post Transplant Cyclophosphamide Following T-cell Replete Haploidentical Transplantation of BM or PBSC

Chemotherapy to kill cells
That cause graft-vs-host disease

Fuchs E. et al JHU
Haploidentical Transplant With Post-Transplant Cyclophosphamide has similar outcome to matched unrelated transplants

Survival

Figure 3. Overall survival. (A) The probability of OS by donor type after myeloablative conditioning regimen, adjusted for age and disease risk index. (B) The probability of OS by donor type after reduced intensity conditioning regimen, adjusted for disease risk index and secondary AML.
Allogeneic HCT Recipients in the US, by Donor Type

- URD-BM / PB
- HLA-iden Sib
- Other Relative
- URD / UCB

MUDs
Sibs
Haplo
cords

CIBMTR Data 2019
Questions To Be Answered

• Does the potential benefit of a transplant justify the risk?  
  (i.e. do I have a disease that chemotherapy can cure or make me live a long time or a disease where chemotherapy is unlikely to cure in contrast to a transplant that has a higher probability of cure)

• Is my disease controlled sufficiently to where a transplant would help? Timing is everything!!  
  i.e. Acute leukemias should be in remission before transplant

• Do I Have a stem cell donor?  
  • HLA tissue matched sibling  
  • Matched Unrelated donor  
  • Cord blood or haplo-identical donor

• What are the chances I could be harmed by a transplant?  
  • Am I Healthy enough to go through the procedure?  
  • Am I young enough?  
  • Have prior treatments put me at increased risk for complications