Hematopoietic Stem Cell Transplantation

Imad A. Tabbara, M.D., FACP
Professor of Medicine
George Washington University
STEM CELLS

Have the capacity to:

- Self renew (make more stem cells by cell division)

&

- Differentiate into mature, specialized cell
Types of Stem Cells

- **Embryonic SC** found in:
  - Embryos

- **Adult SC** found in:
  - Bone marrow & peripheral blood
  - Muscle, brain, skin & liver
  - Placental cord
  - Baby teeth
Hematopoietic Stem Cells

- Harvested from bone marrow, blood & umbilical cord
- They are CD 34 (+)
- A minimum of 2.5-3.0 million CD34 (+) cells/kg of recipient’s body weight are needed to induce engraftment and bone marrow recovery
Indications for Hematopoietic Stem Cell Transplants in the US, 2013

- **Allogeneic** (Total N=8,197)
- **Autologous** (Total N=11,258)

Number of Transplants

- Myeloma / PCD
- AML
- ALL
- CML
- NHL
- HD
- MDS / MPD
- CLL
- Aplastic Anemia
- Other Non-Malignant Dis
- Other Cancer

Allogeneic Transplant Recipients in the US, by Donor Type

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

*2014 Data incomplete
Conditioning Regimens
<table>
<thead>
<tr>
<th>Myeloablative Regimens</th>
<th>Most Common Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide/TBI “Cy/TBI” (fractionated, 1200 cGy)</td>
<td>Leukemia, lymphoma, MDS/MPD</td>
</tr>
<tr>
<td>Busulfan/Cyclophosphamide “Bu/Cy”</td>
<td>Leukemia, MDS/MPD</td>
</tr>
<tr>
<td>BCNU/Etoposide/Ara-C/Melphalan “BEAM”</td>
<td>Lymphoma (mainly Auto)</td>
</tr>
<tr>
<td>Cyclophosphamide/TBI/Etoposide</td>
<td>Lymphoma (Auto)</td>
</tr>
<tr>
<td>Cyclophosphamide/ATG</td>
<td>Aplastic Anemia</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Myeloma (Auto)</td>
</tr>
<tr>
<td>Fludarabine/Busulfan “Flu/Bu”</td>
<td>MDS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reduced Intensity Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine/TBI (200-400 cGy)</td>
</tr>
<tr>
<td>Intermediate dose melphalan, others</td>
</tr>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>High Dose Cyclophosphamide</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>High Dose Busulfan</td>
</tr>
<tr>
<td>High Dose Melphalan</td>
</tr>
<tr>
<td>Fludarabine</td>
</tr>
</tbody>
</table>
Autologous Transplantation

- More than 30,000 annually
- 2/3 for MM and NHL
- High Dose Myeloablative Therapy
- “Stem cell rescue”
Autologous Transplantation

- Treat underlying disease with ablative therapy
- Risk for tumor contamination
- CD34 selection did not change relapse rates and increased infection risks especially for CMV
- 100 day Non-relapse mortality: less than 5%
- Does not have GVHD issue
- Risk for secondary MDS/AML
PBSC have replaced BM as source of hematopoietic stem cells

- Superior in speed of engraftment post-transplant
- Decreased TRM to less than 5% and decreased morbidity
- No anesthesia and hospitalization for BM harvest
- Better able to collect stem cells from patients who previously received pelvic irradiation
- Decreased tumor contamination
Autologous HSCT For Multiple Myeloma

Intergroupe Francais du Myelome

Medical Research Council

Tandem Autologous Transplants: IFM 94:
Overall Survival

P < 0.01

Mel 140 -> Mel 140 + TBI

42%
(20)

Mel 140 + TBI

21%
(10)

Attal, NEJM, 2003
Autologous Bone Marrow Transplantation vs. Salvage Chemotherapy In Relapses Of Chemotherapy-sensitive Aggressive NHL

Event-free Survival

Overall Survival

Probability of Survival after Autologous Transplants for Diffuse Large B-Cell Lymphoma, 2000-2009
- By Disease Status -

P < 0.0001
Survival after Autologous Transplants for Hodgkin Lymphoma, 2002-2012

Survival after Transplants for Mantle Cell Lymphoma, 2003-2013

Survival after Transplants for Multiple Myeloma, 2003-2013

- Autologous (n=37,385)
- Allogeneic (n=1,012)

p < 0.001

Survival after Autologous Transplants for Multiple Myeloma, 2000-2013

2000-2003 (n=8,432)
2004-2007 (n=10,760)
2008-2011 (n=15,617)
2012-2013 (n=9,706)
Causes of Death after Autologous Transplants done in 2011-2012

- Primary Disease: 69%
- Infection: 20%
- Organ Failure: 3%
- Second Malignancy: 7%
- Other: 1%

ALLOGENEIC STEM CELL TRANSPLANTATION
Allogeneic Donor Selection

- 25% likelihood of HLA matching with a sibling
- 1% chance of HLA matching with another relative.

First option by conventional practice:
- HLA matched family member
- Then HLA matched Unrelated donor:
  - 60-70% chance of finding an 8 of 8 allele level, HLA-A, B, C, or DRB1 matched unrelated donor for Caucasian patients
  - 10% to 30% for U.S. ethnic minorities

Likelihood of a Sibling Match

Match likelihood  \[ 1 - \text{no match} \]

“n” siblings \[ 1 - (0.75)^n \]

1 sibling \[ 1 - (0.75)^1 = 0.25 \]

2 siblings \[ 1 - (0.75)^2 = 0.44 \]

4 siblings \[ 1 - (0.75)^4 = 0.68 \]

7 siblings \[ 1 - (0.75)^7 = 0.87 \]
DONOR ASSESSMENT
Initial Evaluations

Donors

Evaluation:

- H and P, (hx of medical issues including malignancy plus hx of recreational drug use, transfusions, pregnancy, abortion, travel, vaccinations); determine caregiver support and reliability.

- Routine labs plus urine analysis, CMV PCR/Ab, hep A, hep BcAb, hep BsAg/Ab, HTLV I/II, HIV I/II, EBV, VZV, toxo, RPR, β-HCG (females < age 55) West Nile (allo), Chagas Disease (allo). Chest X-ray (hx of pulmonary disease and SAT< 90%), and EKG (DM, Cardiovascular disease, Pulmonary disease, smoke >20 pack years, age: > 40 yr male and > 50 yr female)

- Ethical issues: 1 physician serves 2 persons whose medical care is interdependent

Patients

Evaluation:

- H and P (same)

- Routine Labs plus (same)

- Restaging studies

- BM

- Dental Evaluation

- RT consult if TBI or other RT

- ? Fertility preservation

- ECG/Cardiac ejection fraction

- PFTs (DLCO > 50)

- PPD as clinically indicated

- CXR

- Sinus CT if clinically indicated

- Other tests/regulatory standards as indicated

Other Considerations for Allogeneic Donor Selection

- CMV status of recipient and donor
- Age of donor (relevant if multiple donors are available)
- History of intermarriage in families rarely produce HLA ID cousins or combination of rare haplotype and common HLA haplotype.
- Mismatch HLA A, B and C increases risk of Graft rejection. Mismatch of HLA DR increase risk for GVHD (can occur the alternate way for Class I and II).
  - Single Ag mismatched related transplants
    - In the graft versus host direction have higher GVHD but same survival
    - In the host versus graft direction have higher graft failure and lower survival
    - Unknown whether to prefer single Ag mismatched related donor versus MUD
Other Considerations for Allogeneic Donor Selection

- For haploidentical related donors
  - **Mother** may be best choice (Tolerance of fetal Ags during pregnancy)
  - Sibling donors – no difference in gender of donor related to outcome.
- ABO match – usually not an issue; but prefer match
Success in HLA-Matched Unrelated Matching Varies With Population

- Asian: 50%
- Japanese: 99%
- African American: 50%
- North American Caucasian: 93%
ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Old Paradigm
The allograft is a rescue product to replace the defective stem cells following ablation with cytotoxic therapy.

New Paradigm
A major therapeutic component of an allogeneic stem cell transplant is the "graft vs. leukemia" effect mediated by T-cells in the allograft.
Graft-versus-Leukemia Effect

Bar graph showing the effect of different conditions on Leukemic Relapse:
- Identical Twin
- T-Depletion Allogeneic
- No GVHD
- GVHD

Bone Marrow Transplant

Leukemic Relapse (%)
Most patients after allogeneic transplant are cured by immunotherapy not by chemotherapy?

- Higher relapse after T-cell depleted or syngeneic transplants
- Higher relapse in patients without GVHD
- Remission of underlying malignancy may occur after stopping immunosuppression
- Remission can be induced by donor lymphocyte infusion (DLI)
Non-Myeloablative Allogeneic HSCT

- Requires the suppression of the patient’s immune system to prevent graft rejection
- Depends on the donor immune system to induce graft-vs-tumor effect
- Effective only in patients with complete or near complete remission of their malignant disease, at the time of transplant
NON-ABLATIVE HEMATOPOIETIC CELL TRANSPLANT

Preparative Regimen

HSCT

CSA/MTX

IS Withdrawal

Recipient

Donor

Mixed Chimera

Complete Chimera

A B

A B

A A

A L

A L
Donor Lymphocyte Infusion (DLI)

- Effective in inducing remission in patients with persistent or recurrent disease, after transplant, without additional cytotoxic therapy
- Increases risk for GVHD (40-60%)
- Direct correlation of GVHD & response
Nonablative BMT for AML

Cumulative Proportion Surviving

Months After Transplant

had GVHD

no GVHD

P = 0.0002
Complications Following Allogeneic Transplantation

-10 0 20 40 60 80 100
Days From Transplant (Day 0)

- Chemo/TBI
- Mucositis, VOD/SOS
- Chemo/TBI
- Acute GVHD
- Chronic GVHD
- Bacterial, Fungal
- CMV and Other Infections
- VZV, Bacterial

Allo Stem Cells

Cyto-penias
Sinusoidal Obstructive Syndrome (Veno-occlusive Disease)

• Incidence: 10-60% of patients
• Occurs 7-10 days after conditioning regimen
• Tender hepatomegaly, jaundice, fluid retention
• Reversal of flow in portal system by doppler
• Risk Factors: Prior liver disease, previous chemotherapy (gemtuzumab), Busulfan or TBI in the conditioning regimen, C282Y allele of the HFE gene
• Mortality increases with severity of hyperbilirubinemia
• Treatment: supportive care, thrombolytic rx (tPA), defibrotide
Graft-versus-Host Disease

GVHD Syndrome After AlloHCT

Acute GVHD: rash, GI, liver

Chronic GVHD: skin, eyes, mouth, GI, liver, musculoskeletal, lungs, GU

Alloreactivity

Immunodeficiency
- Classic acute
- Late acute
- Chronic overlap

Autoimmunity
- Classic chronic

Day 0 50 100 180 1y 2y 3y 5y

Activity (inflammation) injury repair Damage (fibrosis)
Acute Graft-vs-Host Disease

• Occurs within 100 days post transplant
• Multi-organ involvement: Skin, GI tract, liver
• **Risk Factors:** Older age (patient/donor), HLA mismatch, unrelated donor, parous female donor

• **Prophylaxis:**
  – **T cell depletion:** effective but increased graft rejection and relapse of malignancy
  – **Immunosuppressive agents:** Cyclosporin, tacrolimus (FK506), Mycophenolate Mofetil, Sirolimus, methotrexate, steroids

• **Treatment:** Steroids
Ursodiol

- A large multi-center trial of prophylaxis after myeloablative allogeneic
  
  - beneficial effect on the incidence of clinical jaundice, severe acute GVHD and survival.

- Decrease in the number of patients with jaundice and elevated serum alanine aminotransferase (ALT).

- Lower incidence of grade 3-4 acute GVHD

- Lower incidence of stage 2-4 liver GVHD

Chronic GVHD

• Chronic multi-system disorder
• Occurs >100 days after allogeneic transplant
• Incidence: 30-80%
• Characterized by:
  – Chronic immunosuppression
  – Immune aberration
  – Organ dysfunction
  – Decreased survival
Diagnosis of Chronic GVHD

• NIH consensus Working Group standardized criteria:
  – No time limit
  – Requires the presence of at least one diagnostic clinical sign of chronic GVHD (scleroderma or esophageal thickening) or the presence of at least one distinctive manifestation (keratoconjunctivitis sicca) confirmed by pertinent biopsy or other relevant tests (e.g. Schirmer’s)
  – Exclusion of other possible diagnoses to explain clinical findings e.g. infection.

• Global assessment of chronic GVHD severity has been developed to replace the historical “extensive/limited” classification.
Chronic GVHD

- **Risk Factors:**
  - Prior acute GVHD
  - Unrelated donors
  - Older patient/donor pairs
  - Blood stem cells
  - Donor lymphocyte infusion

- **Treatment:** Steroids
Chronic GVHD

Carpenter P.
Blood; 2011
vol. 118 no.
10 2679-2687
Autoantibodies
M-skeletal
Infections
Endocrine
Metabolism
Nutrition
Pain
Quality of life
Disability

Spectrum of manifestations
In cGVHD
- 50% Incidence
- 15% Life Threatening
Infectious Complications

• Bacterial, Fungal
  – In the peri-transplant period
  – Increased risk for fungal infections in patients with prolonged neutropenia and/or chronic high dose steroid treatment

• Viral
  – HSV: rare due to prophylactic Acyclovir
  – CMV:
    • High mortality
    • Prevention: CMV negative blood products, leukocyte-depleted blood products, antigenemia monitoring
Infectious Complications

- **Viral**
  - Varicella: delayed >3 months post transplant

- **Pneumocystis**
  - Very rare with prophylactic therapy (TMP-SMX, Pentamidine)
LONG-TERM COMPLICATIONS
(ADULTS)
CIBMTR Summary Slides. Available at: http://www.cibmtr.org

Causes of Death after HLA Match Sibling Transplants done in 2011-2012

- Primary Disease: 48%
- GVHD: 18%
- Infection: 13%
- Organ Failure: 16%
- Second Malignancy: 4%
- Other: 1%

Causes of Death after Unrelated Donor Transplants done in 2011-2012

- Primary Disease: 37%
- GVHD: 20%
- Infection: 17%
- Organ Failure: 6%
- Second Malignancy: 19%
- Other: 1%
Reduced Mortality after Allogeneic BMT

Decreased risk of severe GVHD; viral, bacterial, and fungal infections; and damage to the liver, kidneys, and lungs.

Reasons for Improvement in Allogeneic BMT Over Time

• Better HLA matching
• Better supportive care including anti-fungal and anti-viral therapy
• Less aggressive conditioning regimens i.e. targeted busulfan
Long Term Complications After BMT

- **Relapse**
- **Sequela of GVHD**
  - Immunity and infections issues
  - Ocular, skin and oral ie. Cataracts, Oral cGVHD (mucosal changes, poor dentition, xerostomia)
  - Esophageal (webs, rings, submucosal fibrosis & strictures, aperistalsis, Pill esophagitis etc.)
  - Muscle, connective tissue and skeletal ie. Osteoporosis
  - Respiratory
  - Liver
- **Chronic renal insuf.**
- **CHF**
- **Iron overload**
- **Endocrine** (hypothyroidism, adrenal insufficiency /gonadal dysfunction)
- **Psychiatric** /integration into normal life, sexual dysfunction.
- **CNS**
- **Secondary cancers**
Bone Loss in Long-term Survivors

- Occurs predominantly within the first 6–12 months after autologous and allogeneic HCT.
- Recovery first occurs in the lumbar spine and is followed by a slower recovery in the femoral neck.
- Recovery slowed by steroids.
- DXA scan to determine use of anti-resorptive agents.
Late Mortality From Therapy Related Secondary Cancers After Autologous and Allogeneic Transplant

• After autotransplant:
  – 12 X more likely to die of new malignancy than general population
    • Hematological cancers (68%)
    • Solid tumors (32%)

• After allotransplant:
  – 3.6 X more likely to die of new malignancy than general population
    • Solid tumors (82%)

n=3372/35% auto TX

©2003 by American Society of Clinical Oncology
Survival and mortality rates for patients younger than age 18 years (solid line), 18 to 45 years (short-dashed line), and older than age 45 years (long-dashed line) at the time of transplantation.

Martin P J et al. JCO 2010;28:1011-1016
Long Term Outcome of Patients Who Survived Initially At Least Five Years After Transplant

- Mortality rates remained four- to nine-fold higher than the expected population rate for at least 30 years after transplantation.
- Yield an estimated 30% lower life expectancy compared with that in the general population, regardless of current age.
- In rank order, the leading causes of excess deaths were second malignancies and recurrent disease, followed by infections, chronic graft-versus-host disease, respiratory diseases, and cardiovascular diseases.
Survival after HLA Match Sibling Donor Transplants for AML, 2003-2013

- Early (n=7,988)
- Intermediate (n=2,146)
- Advanced (n=2,882)

p < 0.001

Years

By Disease Status

Probability, %
Survival after Unrelated Donor Transplants for AML, 2003-2013

Early (n=8,804)
Intermediate (n=4,443)
Advanced (n=4,692)

p<0.001

Pasquini MC, Zhu X.
CIBMTR Summary Slides, 2015. Available at: http://www.cibmtr.org
Survival after Allogeneic Transplants for Follicular Lymphoma, 2003-2013

- HLA Match Sibling, Sensitive (n=920)
- HLA Match Sibling, Resistant (n=159)
- Unrelated Donor, Sensitive (n=733)
- Unrelated Donor, Resistant (n=168)

AUTOLOGOUS T-CELL THERAPY
CD19 CAR-T Cells Induce Durable Responses in Relapsed/Refractory CD19-Positive Lymphomas
CTL019 in B-Cell Lymphomas: Background

• CTL019: engineered T-cells target CD19; provide activating and costimulatory signals (CD3ζ, 4-1BB)

• CD19-targeted CAR-modified T-cell therapy has shown efficacy in relapsed/refractory ALL, CLL[1-3]

• Current study evaluated feasibility, efficacy, safety of CTL019 CAR T-cell therapy in pts with advanced CD19-positive B-cell NHLs[4]

CD-19 targeted chimeric antigen receptor (CAR) therapy

- Pt’s T cells are harvested
- CAR directed against CD19 is introduced into these T cells
- These T cells are expanded ex vivo (for 2 wks), and then infused
1) T Cell Collection
2) T Cell Transfection
   1. Binding
   2. Fusion
3) T Cell Adoptive Transfer
   +/- Lymphodepleting conditioning
4) Transcription and protein expression
5) CAR cell membrane insertion
4) T Cell Adoptive Transfer
   1. Binding
   2. Fusion
3) T Cell Adoptive Transfer
   +/- Lymphodepleting conditioning
4) Transcription and protein expression
5) CAR cell membrane insertion
4) T Cell Adoptive Transfer
   1. Binding
   2. Fusion
3) T Cell Adoptive Transfer
   +/- Lymphodepleting conditioning
4) Transcription and protein expression
5) CAR cell membrane insertion

4) Patient Monitoring
   a) Disease response
      - CT scans
      - Bone marrow biopsies
      - Peripheral blood flow cytometry
   b) CAR-T Cell persistence
      - Immunohistochemistry of bone marrow biopsy
      - RT-PCR and flow cytometry of blood and bone marrow aspirate
CD19 CAR Therapy

- CD19 is almost exclusively expressed in malignant and normal B-cells, hence is a good target for CAR therapy in B-cell malignancies.

- CAR-modified T cells proliferate/persist in vivo (3+ years).

- In 14 R/R-CLL pts, ORR 57% (4 CRs)

- AEs: delayed cytokine release (CRS) syndrome, B-cell aplasia, hypogammaglobulinemia, neurologic complications

- CRS treatment: tocilizumab (IL-6 inhibitor), steroids

T-Cell Therapy: Cytokine Release Syndrome

Fever
Hypotension
CNS changes: mental status, seizures, obtundation.
Fractionated Dosing Optimizes CAR T-Cell Therapy in Adult R/R ALL
CTL019 in Adults With R/R ALL

- Prognosis poor for adults with relapsed/refractory ALL
- Anti-CD19 CAR T-cell therapy has demonstrated high response rates in children and adults with ALL\(^{[1-4]}\)
- CRS occurs frequently with CAR T-cell therapy, may result in death\(^{[1-5]}\)
  - Correlates with anti-CD19 CAR T-cell activation and expansion, marked cytokine elevations, disease burden
  - Clinical syndrome: high fever, myalgias, fatigue, anorexia, capillary leak, hypoxia, hypotension
  - Management includes supportive care, anti–IL-6 tx (tocilizumab)
- Updated data on safety and efficacy of 2 dosing approaches with CTL019, anti-CD19 CAR T-cell therapy, in 30 adults with R/R CD19+ ALL\(^{[6]}\)

CTL019 in Adult R/R ALL

- CTL019 administered to 30 adults on 2 clinical trials\(^{[1-3]}\)

Pts with CD19+ R/R ALL;
18 yrs of age or older;
ECOG PS 0 or 1;
> 5% BM blasts;
previous allogeneic SCT,
blinatumomab permitted
(N = 30)

Baseline assessment (BM) Day -1

Lymphodepletion

Response assessment Day 28

CTL019: 1 of 4 regimens
Modified in response to AEs and efficacy
- High dose (5 x 10\(^8\)), split* dosing
- High dose (5 x 10\(^8\)), single† dosing
- Low dose (5 x 10\(^7\)), split* dosing
- Low dose (5 x 10\(^7\)), single† dosing

*Split dosing: Day 1, 10%; Day 2, 30%; Day 3, 60% (doses held for early signs of CRS).
†Single dosing: Day 1, 100%.

2. ClinicalTrials.gov: NCT02030847.
### CTL019 in Adult ALL: Pt Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pts (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>44 (21-72)</td>
</tr>
<tr>
<td>Previous allogeneic SCT, n (%)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Previous blinatumomab therapy, n (%)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Philadelphia chromosome positive, n (%)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Baseline ALL burden, n (%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 5% blasts</td>
<td>27 (90)</td>
</tr>
<tr>
<td>0.01% to 5% blasts</td>
<td>3 (10)</td>
</tr>
<tr>
<td>&lt; 0.01% blasts</td>
<td>0</td>
</tr>
</tbody>
</table>

**CTL019 in Adult ALL: CRS Correlated With Efficacy (Response)**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>Schedule</th>
<th>N</th>
<th>CRS ≥ Gr 3, %</th>
<th>Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High dose (5 x 10^8)</td>
<td>Split</td>
<td>15</td>
<td>66</td>
<td>86 (0 TRM)</td>
</tr>
<tr>
<td>2</td>
<td>High dose (5 x 10^8)</td>
<td>Single</td>
<td>6</td>
<td>100</td>
<td>100 (3 TRM)</td>
</tr>
<tr>
<td>3</td>
<td>Low dose (5 x 10^7)</td>
<td>Split</td>
<td>6</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Low dose (5 x 10^7)</td>
<td>Single</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>---</td>
<td>---</td>
<td>30</td>
<td>75</td>
<td>72 (3 TRM)</td>
</tr>
</tbody>
</table>

- 3 CRS-related deaths, all in single high-dose (5 x 10^8) cohort; concurrent infection/sepsis* noted, other factors similar to entire cohort
- Dose and neurotoxicity relationship unclear: 12 events reported (encephalopathy/delirium and seizures)
  - All self-limited and returned to baseline by Day 28

*Included influenza B, pseudomonas, and stenotrophomonas (n = 1 each).
CTL019 in Adult ALL: Conclusions

• CTL019 dose and schedule correlate with response but also toxicity
• Fractionated (split) dosing allows for treatment modification to address CRS-related toxicity and maintain response
• CRS with concurrent sepsis portends poor prognosis
• Future studies needed to evaluate other dosing regimens and best timing for prophylactic and anticytokine therapy to minimize toxicity and optimize response

19-28z CAR T Cells in R/R B-Cell ALL: Study Design

- Phase I single-arm study with ongoing enrollment

Leukapheresis and 19-28z CAR T-cell production

R/R CD19+ B-cell ALL pts ≥ 18 yrs of age or older no active CNS involvement, significant heart disease, or GvHD requiring immunosuppressants; prior HSCT allowed (N = 46)

Lymphodepleting chemotherapy

Cyclophosphamide ± Fludarabine

2 days later

19-28z CAR T cells 1* or 3† x 10^6 cells/kg

Disease Assessment Days 28-35

- Median follow-up: 6 mos
- 46 pts evaluable for toxicity, 45 pts evaluable for disease response
- Primary objective: evaluate safety/antitumor activity

* Morphologic disease (≥ 5% blasts).
† Minimal disease (< 5% blasts).

19-28z CAR T Cells in R/R B-Cell ALL: Conclusions

- High CR rate (82%) achieved in R/R B-cell ALL adults, often with MRD negativity
  - Independent of disease risk factors or burden
  - No subsequent allo-SCT required in subset of pts
- Achieving MRD-negative status after 19-28z CAR T infusion associated with superior OS vs MRD+
- Efficacy/safety of modified T-cell infusion similar in pts with/without prior allo-SCT
- Enrollment ongoing in phase II trial of 19-28z CAR T cells in adults with relapsed B-cell ALL

# Umbilical Cord Blood Transplantation

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ease of procurement post-transplant and no donor risk.</td>
<td>Limited cell dose in each unit and defects in bone marrow homing:</td>
</tr>
<tr>
<td>• Availability for immediate use</td>
<td>– Delayed blood count recovery and engraftment</td>
</tr>
<tr>
<td>• Low risk of GVHD despite HLA mismatch.</td>
<td>– Higher rates of graft failure post-transplant (5-15%)</td>
</tr>
<tr>
<td>• Reduced risk of transmissible infections.</td>
<td>– Delayed immune reconstitution and increased infections</td>
</tr>
<tr>
<td>• Lower incidence of graft versus host disease (offset by mismatching).</td>
<td>– Limit for large recipients</td>
</tr>
<tr>
<td>• Extends transplant to minority populations (a unit can be found for many patients (4-6 of 6 HLA matched))</td>
<td>Expense (2 cords, extended hospital stay)</td>
</tr>
</tbody>
</table>
Double Cord Blood Transplants

• In adults more frequent than single cords since 2005.

• Engraftment rate is comparable although higher Grade II acute GVHD in double cords versus single cord; chronic GVHD is equal.

• At day 21 post transplant single unit dominance can be detected in 80% (facilitator versus unit with ‘engrafting potential’ OR graft versus graft effects).

• Patients with mixed chimerism at 1 year more prone to GVHD.
Haploidentical Related Donor Transplants

• Strategies for GVHD prophylaxis paved the way to test this possible approach.
  – Administering cyclophosphamide after transplantation to limit mutual donor/recipient allograft reactivity

• Advantages:
  – Likely available parent, child or sibling as a potential donor
  – Additional progenitor and immune cells available for cellular therapies

• Disadvantages:
  – With T-cell depletion:
    • Delayed immune reconstitution
    • Increase the risk of opportunistic infections and relapse
    • With post-transplant cytoxan – less risk of above

HLA mismatched haploidentical vs unrelated CB grafts comparison of parallel CTN phase 2 studies

**Figure 4**

Brunstein et al Blood 2011
HLA mismatched haploidentical vs unrelated CB grafts comparison of parallel CTN phase II studies

Figure 2
HLA mismatched haploidentical vs unrelated CB grafts comparison of parallel CTN phase II studies

Figure 3