Cellular Therapy Implementation: The MDACC Approach

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Department of Stem Cell Transplantation and Cellular Therapy

Administrative Directors Conference
BMT Tandem Meetings
February 24, 2017
Outline

• Cellular therapy
  – Goals of care
  – Requirements for institution

• Manufacture and administration of cellular therapy products
  – CAR

• Oversight of trials
  – CARTOX

• Management of cost??
What is cellular therapy?

• Cells used to modulate an immune response for therapeutic intent.
• May elicit or mitigate a response.
• Cell types include dendritic, natural killer, mesenchymal stromal, T and B-cells.
• Common products
  – Chimeric antigen receptor modified T cells
  – Vaccines using dendritic cells
  – Viral-specific T cells
Increasing cellular therapy trials in SCT

57 clinical trials in SCT; 21 cell therapy trials to prevent or treat disease, treat infection, or repair tissue.

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Cell source</th>
<th>Therapeutic intent</th>
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<tbody>
<tr>
<td>2011-0493</td>
<td>NK cells, unmanipulated</td>
<td>Combine with CBT, decrease relapse</td>
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<tr>
<td>2012-0501</td>
<td>Modified T-cells with iCasp suicide gene</td>
<td>Early DLI post alloSCT to prevent relapse</td>
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<tr>
<td>2012-0708</td>
<td>NK cells, unmanipulated</td>
<td>Combine with haploSCT, decrease relapse</td>
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<tr>
<td>2012-0819</td>
<td>NK cells, unmanipulated, from allo-donor</td>
<td>Combine with alloSCT, decrease relapse</td>
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<tr>
<td>2013-0032</td>
<td>MSC</td>
<td>IP infusion for refractory ovarian cancer</td>
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<tr>
<td>2013-0620</td>
<td>Auto-CMV CTL</td>
<td>Prevent CMV reactivation in CMV negative donor SCT</td>
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<td>2013-0657</td>
<td>Most closely-HLA matched CMV CTL</td>
<td>Treat resistant CMV infection/viremia</td>
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<tr>
<td>2013-1018</td>
<td>CD19 CAR</td>
<td>Treat active CD19+ disease</td>
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<tr>
<td>2014-0150</td>
<td>Fucosylated T-regulatory cells</td>
<td>Decrease GVHD</td>
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<tr>
<td>2014-0279</td>
<td>Most closely-HLA matched BK-CTL</td>
<td>Treat resistant BK infection/viremia</td>
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<tr>
<td>2014-0519</td>
<td>MSC</td>
<td>Repair in chemo-induced cardiomyopathy</td>
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<tr>
<td>2014-0830</td>
<td>Activated T-cells</td>
<td>Restore immune function in patients with CLL</td>
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<td>2014-0297</td>
<td>Cord blood-derived NK, unmanipulated</td>
<td>Treat active disease</td>
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<tr>
<td>2015-0327</td>
<td>MSC</td>
<td>Lung injury repair in ARDS</td>
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<td>2015-0576</td>
<td>Blinatumomab</td>
<td>Maintenance following alloSCT in ALL</td>
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<td>Cord blood-derived NK, unmanipulated</td>
<td>Combine with autoSCT, decrease relapse in NHL</td>
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<td>2016-0051</td>
<td>MSC</td>
<td>Cord blood expansion</td>
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<td>2016-0236</td>
<td>PNK-007, cord-blood NK</td>
<td>Treat refractory AML</td>
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<td>2016-0641</td>
<td>Cord blood-derived NK, CAR-NK</td>
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<td>2016-0688</td>
<td>BPX-501 T cells</td>
<td>Combine with haploSCT, decrease relapse</td>
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<tr>
<td>2016-1097</td>
<td>MAGE-A3/A6 engineered T cells (KITE-718)</td>
<td>Advanced solid tumors, HLA-DPB1*04:01 positive</td>
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## Cellular therapy trials throughout institution

<table>
<thead>
<tr>
<th>Protocol #</th>
<th>Sponsor</th>
<th>Protocol Title</th>
<th>PI</th>
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<tr>
<td>2015-0528</td>
<td>Adaptimmune</td>
<td>A Pilot Study of Genetically Engineered NY-ESO-1 Specific NY-ESO-1c259T in</td>
<td>Dr. Dejka Araujo</td>
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<td>HLA-A2+ Patients with Synovial Sarcoma</td>
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<td>2012-0501</td>
<td>Bellicum</td>
<td>A Phase 1/2 Trial Evaluating Treatment of Emergent Graft versus Host Disease</td>
<td>Champlin, Richard</td>
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<td></td>
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<td>(GVHD) With AP1903 After Planned Donor Infusions (DUS) of T-cells Genetically</td>
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<td>Modified with the iCasp9 Suicide Gene in patients with Hematologic Malignancies</td>
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<td>2013-1018</td>
<td>Intrexon/ Ziopharm</td>
<td>CD19+ Chimeric Antigen Receptor T-Cells for Patients with Advanced Lymphoid</td>
<td>Dr. Partow Kabiraei</td>
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<td>2015-0668</td>
<td>Janssen R&amp;D LLC</td>
<td>A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-64252781,</td>
<td>Dr. Michael Wang</td>
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<td>a Humanized CD19 x CD3 Dual-Affinity Re-Targeting (DART?) Protein in Subjects</td>
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<td>with Relapsed or Refractory B-cell Malignancies</td>
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<td>2015-0140</td>
<td>Juno</td>
<td>The Rocket Study: A Phase 2, Single-arm, Multicenter Trial to Determine the</td>
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<td>Efficacy and Safety of JCAR015 in Adult Subjects with Relapsed or Refractory B-</td>
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<td>Cell Acute Lymphoblastic Leukemia</td>
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<td>2014-0815</td>
<td>KTE</td>
<td>A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19</td>
<td>Dr. Sattva Neelapu</td>
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<tr>
<td></td>
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<td>in Subjects with Refractory Aggressive Non-Hodgkin’s Lymphoma</td>
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<td>2015-0372</td>
<td>KTE</td>
<td>KTE-C19-102 A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-C19 in</td>
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<td>Subjects with Relapsed/Refractory Mantle Cell Lymphoma</td>
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<td>Adult Subjects with Relapsed/Refractory B-Precuror Acute Lymphoblastic Leukemia</td>
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<td>Novartis</td>
<td>Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety</td>
<td>Dr. Jason Westin</td>
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<td>of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell</td>
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<td>Lymphoma (DLBCL)</td>
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<td>Dr. Amir Jazaeri</td>
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<td>Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Patients</td>
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<td>with Recurrent or Treatment Refractory Ovarian Cancer</td>
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<td>PENDING</td>
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<td>2016-0573</td>
<td>Immmatics</td>
<td>ACTolog</td>
<td>Dr. Lia Tsimeridou</td>
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<td>and Efficacy of MAGE-A10c796T in Subjects with Stage 111b or Stage IV Non-Small</td>
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<td>and Efficacy of MAGE-A10c796T in Subjects with Stage 111b or Stage IV Non-Small</td>
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<td>Phase I/II Study of Planned BPX-501 T Cells Infusion after Partially Mismatched,</td>
<td>Ciurea, Stefan</td>
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<td>Related, TCR Alpha Beta+T Cells Depleted HSCT in Adults with Advanced Hematologic</td>
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<td>Malignancies at High Risk for Relapse</td>
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<td>2016-0341</td>
<td>Intrexon/Ziopharm</td>
<td>A Phase 1 Safety Study of Adoptive Cellular Therapy Using Autologous T Cells</td>
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<td>Transduced with Lentivirus to Express a CD33 Specific Chimeric Antigen Receptor</td>
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<td>in Patients with Relapsed or Refractory CD33-Positive Acute Myeloid Leukemia</td>
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<td>A Phase 1, Multicenter, Open-Label Study of JCAR017, CD19-targeted Chimeric</td>
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<td>Antigen Receptor (CAR) T Cells, for Relapsed and Refractory B-cell Non-Hodgkin</td>
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<td>Lymphoma (NHL)</td>
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Goals of management

• EFFICIENTLY process trials through regulatory bodies.

• EFFECTIVELY manufacture product.

• SAFELY administer product in patient.
Clinical trial review

- Protocols routinely reviewed by CRC/IRB.
- Protocols testing genetically modified products need to be reviewed by the NIH RAC committee.
  - Pre-RAC committee developed to determine if RAC review necessary
- Protocols using gene-modified products need to follow patients for 15 years based on current FDA guidance.
Cellular therapy manufacture: Apheresis

- The CAR is introduced into T cells using viral or non-viral means.
Cellular therapy manufacture: GMP

• GMP facility
  • 11 Class 10,000 suites
  • Unidirectional personnel flow
  • Single pass air
  • Redundancy
• Accreditations:
  – FACT
  – CAP
  – CLIA
Outline

• Cellular therapy
  – Goals of care
  – Requirements for institution
• Manufacture and administration of cellular therapy products
  – CAR
• Oversight of trials
  – CARTOX
• Management of cost?
Chimeric Antigen Receptor (CAR) Modified T cells

Normal T cell

TCR
Peptide
MHC I
β2-microglobulin

Tumor

CAR T cell

CAR
CD19

Tumor

Genetically engineered T cells altered to express an artificial receptor, CAR

Adapted from Hinrichs & Restifo. Nat Biotech 2013
Development of CAR T cell therapy

<table>
<thead>
<tr>
<th>Function</th>
<th>First Generation CAR</th>
<th>Second Generation CAR</th>
<th>Third Generation CAR</th>
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<tbody>
<tr>
<td>Killing ability</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Ability to multiply</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cytokine secretion</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Persistence</td>
<td>+</td>
<td>+</td>
<td>++</td>
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</tbody>
</table>

Adapted from Maus et al. Blood 2014;123:2625-2635
2nd generation CD19 CAR T cells in clinic

MSKCC/Fred Hutch
NCI
U Penn
MDACC

CD19 Ab
CD28/4-1BB
CD3ζ

Gene transfer
Retrovirus
Lentivirus
Sleeping beauty

Juno Therapeutics
JCAR
Kite Pharma
KTE-C19
Novartis
CTL-019
Ziopharm
Profound efficacy

62 yo M with DLBCL
Prior therapies
- R-CHOP
- Radiation
- R-GDP
- Radiation
- R-ICE
- R-Revlimid

Remains in CR at 9 months following infusion of KTE-C19, ZUMA-1 trial.
Unique mechanism of action

CAR T cell expansion and persistence after KTE-C19 infusion

- Peak expansion of CAR T cells observed within 2 weeks
- CAR T cells detectable one year after infusion

Locke, Neelapu et al, Mol Ther (In press)
Unique toxicity: Cytokine release syndrome

- IL6 levels correlate with degree of CRS.
- Tocilizumab, antibody binds to IL6 receptor.

Perez, et al, ASH, 2015
Representative patient: Hospital course

• 34 yo F with Stage II DLBCL
  ✓ R-CHOP x 6 achieved CR followed by relapse 7 months later
  ✓ R-ICE x 2 followed by HDT-ASCT achieved CR
  ✓ Relapsed 4 months after ASCT and received KTE-C19 CAR T cell therapy

• Days 1-6 – Fevers up to 39.5 deg C, tachycardia, hypotension, hypoxia, severe fatigue, and loss of appetite (Lee Grade 2 CRS)

• Day 5 – Noted to have difficulty in handwriting and subsequently had word-finding difficulty and became confused and disoriented.
  ✓ Tocilizumab 8 mg/kg was administered
  ✓ Mental status returned to baseline about 8 hours later

• Day 9 – Patient was discharged home
Fever, hypotension, hypoxia, encephalopathy

C-reactive protein (CRP) level normalized after fevers subsided
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

Shawna is a friend.

I'm surprised.

I miss my kids.

27/30

27/30

29/30
Ongoing complete remission at 12 months

Baseline

Day 30

Remains in CR at 12 months
Outline

• Cellular therapy
  – Goals of care
  – Requirements for institution
• Manufacture and administration of cellular therapy products
  – CAR
• Oversight of trials
  – CARTOX
• Management of cost??
Enhancing Patient Safety: CARTOX Committee

Drs. Ethan Dmitrovsky, George Wilding, Aman Buzdar

Co-Chairs – EJ Shpall, MD and Patrick Hwu, MD

**Principal Investigators**

**Leukemia**
- William Wierda
- Nitin Jain

**Lymphoma and Myeloma**
- Sattva Neelapu
- Jason Westin
- Michael Wang

**Stem Cell Transplantation and Cellular Therapy**
- Elizabeth Shpall
- Partow Kebriaei

**Gynecologic Oncology**
- Amir Jazaeri

**Investigational Cancer Therapeutics**
- David Hong

**Pediatrics**
- Michael Rytting

**Sarcoma Medical Oncology**
- Dejka Araujo

**Thoracic / Head and Neck Medical Oncology**
- John Heymach
- George Blumenschein
- Vincent Lam

**Consultants**

**Critical Care**
- Cristina Gutierrez
- Joseph Nates

**Emergency Medicine**
- Patricia Brock
- Terry Rice

**Neuro-Oncology**
- Sudhakar Tummala
- Monica Loghin
- John de Groot

**Nursing**
- Patty Johnston
- Joaquin Buitrago
- Venice McDougle

**Pharmacy**
- Alison Gulbis
- Sandra Horowitz

**EHR / Information Services**
- Andrew Lee
- Cary Goodman

**Division of Cancer Medicine**
- Suzanne Davis
CARTOX Committee undertakings

- Weekly meetings
- Multi-disciplinary group of care providers
- Develop comprehensive care plans for patients receiving cellular therapies
- Implement comprehensive training of health-care providers managing CAR patients
- Discuss active patients weekly
- Review relevant published data
**CARTOX management plan**

- **Required**: Comprehensive training of all floor nurses, mid-level practitioners, pharmacy staff, and physicians managing CAR patients:
  - Lecturers, slide sets and sign-in sheet provided
  - Reviews CARTOX diagnosis and management algorithms
  - Webinar in development for Education Center (Sept 2016)

- **Required**: Patients to be treated only in designated clinical units, with sufficient telemetry beds:
  - Care to be provided by CARTOX-trained personnel experienced in managing these complicated patients
CARTOX management plan

• PIs to inform CARTOX Teams at patient admission.
  – PI responsible for daily follow-up, coordination of consulting and management information, and final decisions on care.

• All patients will have baseline brain MRI.

• CARTOX Neurology Team will perform daily evaluations and EEGs as indicated, oversee neurotoxicity grading, and assist with management of neurologic changes.

• CARTOX Intensive Care Team will perform daily evaluations; if significant deterioration in status, will assist primary team in seamless transfer to MICU.
CARTOX management plan

- CARTOX Pharmacy Team will ensure availability of critical CRS-supportive care agents (eg, tocilizumab) for at least 6 patients at all times.

- CARTOX Epic Electronic Medical Record and Pharmacy Teams will ensure availability of standard admission and supportive care orders for each patient.

- CARTOX Epic Electronic Medical Record Team will provide CRS and Neurotoxicity grading systems within EHR:
  - RNs and MDs can assign toxicities and automatically calculate CRS or neurotoxicity grade.
CARTOX Guidelines for CRS and Neurotoxicity Assessment and Management

• Overall goal is to maximize the benefit from the CAR T cell therapy while minimizing the risk for life-threatening complications of CRS and neurotoxicity.
MD Anderson CARTOX: CAR Cell Therapy Toxicity Assessment and Management

Neelapu, Tummala, Kebriaei, Wierda, Loghin, Gutierrez, Shpall.

**Step 1:** Determine if the subject has CRS and/or neurotoxicity

- Yes
- No

**Step 2:** Determine the grade of CRS and/or neurotoxicity

- ✓ Determine grade of organ toxicity when present

**Step 3:** Manage CRS and/or neurotoxicity

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1. Adapted from Lee et al, Blood 2014;124:188-195
Step 1 – Determine if the patient has cytokine release syndrome (CRS)

- If the patient has any of the following symptoms or signs within the first 3 weeks of CAR cell therapy infusion, may have CRS.

1. Fever (temperature ≥ 38°C)
2. Hypotension (SBP <90)
3. Hypoxia (O2 saturation <90% on room air)
4. Organ toxicity
   a. Cardiac – tachycardia, arrhythmias, heart block, low or high ejection fraction
   b. Respiratory – tachypnea, pleural effusion, pulmonary edema
   c. Gastrointestinal – Nausea, vomiting, diarrhea
   d. Hepatic – Increased AST, ALT, or bilirubin
   e. Renal – Acute kidney injury (increased creatinine), decreased urine output
   f. Skin – Rash
   g. Coagulopathy – Disseminated intravascular coagulation (DIC)
   h. Neurologic – confusion, disorientation, agitation, dysphasia, aphasia, tremor, seizures, motor weakness, incontinence, increased intracranial pressure, papilledema, cerebral edema

Adapted from Lee et al, Blood 2014;124:188-195
Step 2 – Determine the grade of CRS

- CRS grade should be determined at least twice daily and any time there is a change in patient’s status.

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptom/Sign</th>
<th>CRS Grade 1\textsuperscript{a}</th>
<th>CRS Grade 2\textsuperscript{b}</th>
<th>CRS Grade 3\textsuperscript{b}</th>
<th>CRS Grade 4\textsuperscript{b}</th>
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<tbody>
<tr>
<td>Vital signs</td>
<td>Temp $\geq 38^\circ$C</td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
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<tr>
<td>SBP $&lt; 90$</td>
<td>No</td>
<td>Responds to IV fluids or low-dose vasopressor</td>
<td>Needs high-dose or multiple vasopressors</td>
<td>Life-threatening</td>
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<tr>
<td>Needing oxygen for $O_2$ sat $&gt;90%$</td>
<td>No</td>
<td>$FiO2 \geq 40%$</td>
<td>$FiO2 \geq 40%$</td>
<td>Needing ventilator support</td>
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<tr>
<td>Organ toxicity\textsuperscript{c}</td>
<td>See Step 1</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3 or grade 4 transaminitis</td>
<td>Grade 4 except grade 4 transaminitis</td>
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</tbody>
</table>

\textsuperscript{a} Grade 1 CRS may manifest as fever and/or grade 1 organ toxicity

\textsuperscript{b} For Grades 2, 3, or 4 CRS, any one of the criteria other than temperature is sufficient

\textsuperscript{c} CTCAE, version 4 for grading of organ toxicity.

Adapted from Lee et al, Blood 2014;124:188-195
### Step 3 – Manage CRS and organ toxicity

**High risk for severe CRS: Bulky disease, co-morbidities, early onset CRS (<3 days)**

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Symptom or Sign</th>
<th>Management</th>
</tr>
</thead>
</table>
| Grade 1   | Fever or grade 1 organ toxicity | • Acetaminophen and hypothermia blanket as needed for fever  
• Ibuprofen if fever is not controlled with above; use with caution or avoid if thrombocytopenic  
• Assess for infection with blood and urine cultures, and chest x-ray  
• Consider antibiotics and filgrastim if neutropenic  
• IV fluids as needed  
• Symptomatic management of constitutional symptoms and organ toxicities |
| Grade 2   | Hypotension             | • IV fluid bolus of 500 – 1000 mL normal saline  
• Tocilizumab 8 mg/kg IV q 6h as needed for up to 3 doses / 24h  
• May give a second IV fluid bolus if SBP remains <90 in 1 hour  
• If hypotension persists after two fluid boluses, start vasopressors, transfer patient to ICU, and obtain ECHO  
• In patients at high-risk* or if hypotension persists after 1-2 doses of tocilizumab, may use Dexamethasone 10 mg IV q 6h  
• Manage fever and constitutional symptoms as in Grade 1 CRS |
|           | Hypoxia                 | • Use supplemental oxygen as needed  
• Use tocilizumab +/- corticosteroids as in hypotension  
• Manage fever and constitutional symptoms as in Grade 1 CRS |
| Grade 2   | organ toxicity          | • Manage organ toxicity as per standard guidelines  
• Use tocilizumab +/- corticosteroids as in hypotension  
• Manage fever and constitutional symptoms as in Grade 1 CRS |
### Step 3 – Manage CRS and organ toxicity

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Symptom or Sign</th>
<th>Management</th>
</tr>
</thead>
</table>
| Grade 3   | Hypotension     | • IV fluid boluses as needed as in Grade 2 CRS  
• **Tocilizumab** 8 mg/kg IV q 6h as needed for up to 3 doses / 24h if not administered previously  
• Use **vasopressors** as needed  
• Transfer patient to ICU and obtain ECHO if not done already  
• Start **Dexamethasone** 10 mg IV q 6h*  
• Manage fever and constitutional symptoms as in Grade 1 CRS  
| Hypoxia    |                 | • Use supplemental oxygen as needed  
• Use **tocilizumab + corticosteroids** as above  
• Manage fever and constitutional symptoms as in Grade 1 CRS  
| Grade 3 organ toxicity or grade 4 transaminitis |                | • Manage organ toxicity as per standard guidelines  
• Use **tocilizumab + corticosteroids** as above  
• Manage fever and constitutional symptoms as in Grade 1 CRS  
| Grade 4   | Hypotension     | • Manage as in Grade 3 CRS  
| Hypoxia    |                 | • **Mechanical ventilation**  
| Grade 4 organ toxicity excluding transaminitis |                | • Manage as in Grade 3 CRS  

*Methylprednisolone has also been used at doses ranging from 1 mg/kg IV q12 h or 500 mg IV q12 h for 3 days followed by rapid taper at 250 mg q12 h x 2 days, 125 mg q12h x 2 days, and 60 mg q12 h x 2 days). Steroid taper may be individualized depending on toxicity*
Neurotoxicity with CAR T cells

- **Symptoms and signs**: encephalopathy, somnolence, global aphasia, seizures, confusion, delirium, tremors, paralysis of limbs, incontinence
  - Onset of neurotoxicity symptoms may be **biphasic**
    - 1\textsuperscript{st} phase (Days 0-5) – symptoms may appear with other CRS symptoms
    - 2\textsuperscript{nd} phase (After day 5) – starts after CRS symptoms have subsided
    - Neurotoxicity such as seizures may occur as late as 3\textsuperscript{rd} or 4\textsuperscript{th} week after CAR T cell therapy
  - Neurotoxicity typically lasts 2-4 days but may vary in duration from few hours to few weeks. It is generally reversible.
  - **Corticosteroids** treatment of choice in managing neurotoxicity.
  - **Tocilizumab** might reverse neurological toxicity during the 1\textsuperscript{st} phase which typically occurs with CRS symptoms.
  - **Seizure prophylaxis** is recommended with levetiracetam (Keppra 750 mg oral/IV q 12 hrs) from day 0 to day 30.
Neurotoxicity pathophysiology

• Pathophysiology remains unclear.

• Two potential explanations include:
  ✓ Passive diffusion of cytokines
  ✓ Trafficking of T cells into central nervous system

• CSF is usually positive for CAR T cells.

• MRI of brain is usually negative although reversible leukoencephalopathic changes and cerebral edema have been observed rarely.

• EEG is either non-focal with generalized slowing or might show non-convulsive seizure pattern.
Step 1 – Simplified 10-point neurological examination

- “Orientation to year, month, city, hospital, President: 5 points
- Ability to write a standard sentence (e.g. National bird is the bald eagle): 1 point
- Name 3 objects (point to clock, pen, button): 3 points
- Count 10 backwards from 100: 1 point

MDACC 10-point Neurotoxicity Grading

- Normal – score 10
- Mild neurotoxicity – score 7-9
- Moderate neurotoxicity – score 3-6,
- Severe neurotoxicity – score 1-2, mild papilledema (grade 1 and 2) with CSF opening pressure < 20 mm Hg
- Critical neurotoxicity – Obtunded / stuporous and/or any new motor weakness and/or convulsive status epilepticus, and/or higher grade papilledema (grade 3, 4, and 5), CSF opening pressure ≥ 20 mm Hg, cerebral edema seen on neuro-imaging
## Step 2 – Determine CTCAE and MDACC grade of neurotoxicity

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of consciousness</strong></td>
<td>Mild drowsiness / sleepiness</td>
<td>Moderate somnolence, limiting instrumental ADL</td>
<td>Obtundation or stupor</td>
<td>Life-threatening needing urgent intervention or mechanical ventilation</td>
</tr>
<tr>
<td><strong>Orientation / Confusion</strong></td>
<td>Mild disorientation / confusion</td>
<td>Moderate disorientation, limiting instrumental ADL</td>
<td>Severe disorientation, limiting self-care ADL</td>
<td>-</td>
</tr>
<tr>
<td><strong>ADL / Encephalopathy</strong></td>
<td>Mild limiting of ADL</td>
<td>Limiting instrumental ADL</td>
<td>Limiting self-care ADL</td>
<td>-</td>
</tr>
<tr>
<td><strong>Speech</strong></td>
<td>Dysphasia not impairing ability to communicate</td>
<td>Dysphasia with moderate impairment in ability to communicate spontaneously</td>
<td>Severe receptive or expressive dysphasia, impairing ability to read, write or communicate intelligibly</td>
<td>-</td>
</tr>
<tr>
<td><strong>Seizure</strong></td>
<td>Brief partial seizure; no loss of consciousness</td>
<td>Brief generalized seizure</td>
<td>Multiple seizures despite medical intervention</td>
<td>Life-threatening; prolonged repetitive seizures</td>
</tr>
<tr>
<td><strong>Incontinent or motor weakness</strong></td>
<td></td>
<td></td>
<td>Bowel / bladder incontinence; Weakness limiting self-care ADL, disabling</td>
<td>-</td>
</tr>
<tr>
<td><strong>MDACC 10-point Neurotoxicity grade</strong></td>
<td>Mild (7-9)</td>
<td>Moderate (3-6),</td>
<td>Severe (1-2), grade 1 and 2 papilledema with CSF opening pressure (op) &lt; 20 mm Hg</td>
<td>Critical (Obtunded; convulsive status epilepticus; motor weakness, grade 3, 4 &amp; 5 papilledema, CSF op ≥ 20 mm Hg, cerebral edema)</td>
</tr>
</tbody>
</table>
## Step 3 – Manage neurotoxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| **Grade 1** | • Vigilant supportive care; Aspiration precautions  
• Daily simplified neurologic examination  
• Fundus exam to document +/- papilledema  
• MRI brain and diagnostic lumbar puncture with opening pressure (op); MRI spine if focal signs  
• Daily 30 min EEG; if no seizures on EEG, continue levetiracetam 750 mg q 12 h  
• If EEG shows non-convulsive status epilepticus, treat as per algorithm  
• Consider Tocilizumab 8 mg/kg IV if associated with Grade 2 or greater CRS |
| **Grade 2** | • Manage as per Grade 1  
• Consider ICU transfer if associated with Grade 2 or greater CRS  
• Tocilizumab 8 mg/kg IV if associated with Grade 2 or greater CRS |
| **Grade 3** | • Manage as per Grade 1  
• Tocilizumab 8 mg/kg IV q 6h for up to 3 doses / 24 h if not administered previously  
• Consider corticosteroids (e.g. dexamethasone 10mg IV q6h or methylprednisolone 1 mg/kg IV q 12h) for worsening symptoms despite tocilizumab; Continue steroids until reversal of toxicity and taper over 2 weeks  
• Low grade (1 & 2) papilledema with CSF op < 20 mm Hg  
• Consider ICU transfer if associated with Grade 2 or greater CRS  
• Consider repeat neuro-imaging (CT or MRI) q 2-3 days if persistent neurotoxicity ≥ grade 3 |
| **Grade 4** | • Manage as per Grade 3  
• ICU monitoring  
• High-dose corticosteroids (e.g. Methylprednisolone IV 1 g/day x 3 days followed by rapid taper at 250 mg q12 h x 2 days, 125 mg q12 h x 2 days, and 60 mg q12 h x 2 days); Continue until reversal of toxicity and taper over 2 weeks  
• For convulsive status epilepticus, treat as per algorithm  
• High grade (3, 4, & 5) papilledema, CSF op ≥ 20 mm Hg, or cerebral edema |
Patient Care Tools for Toxicity Management
### CARTOX FYI flag

**Type of cell therapy**

**Date of cell therapy**

<table>
<thead>
<tr>
<th>Date and Time</th>
<th>Contact</th>
<th>User</th>
<th>Type</th>
<th>Summary</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/02/16 10:09</td>
<td></td>
<td></td>
<td>CARTOX</td>
<td>THIS PATIENT IS CURRENTLY ON CELL THERAPY</td>
<td>Active</td>
</tr>
</tbody>
</table>

**CARTOX**

**THIS PATIENT IS CURRENTLY ON CELL THERAPY**

- **Protocol #**: 2015-1234
- **Date**: 10/11/16
- **Principal Investigator**: MDA PI
  - **Phone**: 01062
  - **Pager**: 12345
- **Co-Principal Investigator**: MDA Co PI
  - **Phone**: 01062
  - **Pager**: 12345
- **Research Nurse**: MDA RN
  - **Phone**: 01062
  - **Pager**: 12345

**Type of cell therapy**

**Date of cell therapy**
### CARTOX flow sheet

<table>
<thead>
<tr>
<th>CRS Syndrome</th>
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<tbody>
<tr>
<td>Temp</td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td></td>
</tr>
<tr>
<td>SpO2</td>
<td></td>
</tr>
<tr>
<td>FiO2 (%)</td>
<td></td>
</tr>
<tr>
<td>SP02/Fi02 (Calculated)</td>
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</tr>
<tr>
<td>Cardiac</td>
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<tr>
<td>Respiratory</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Hepatic</td>
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<tr>
<td>Renal</td>
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<tr>
<td>Coagulopathy</td>
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<tr>
<td>CRS Syndrome Grade</td>
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</table>

<table>
<thead>
<tr>
<th>Neurotoxicity</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Level of Consciousness</td>
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</tr>
<tr>
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<tr>
<td>Orientation</td>
<td></td>
</tr>
<tr>
<td>Ability to Write</td>
<td></td>
</tr>
<tr>
<td>Name 3 Objects</td>
<td></td>
</tr>
<tr>
<td>Count 10 Backwards</td>
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</tr>
<tr>
<td>MDACC Neuro Scale Score</td>
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<tr>
<td>Neurotoxicity Grade Final</td>
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</table>

<table>
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<tr>
<th>Physician Notified</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician Notified</td>
<td></td>
</tr>
</tbody>
</table>
## CARTOX CRS order set

### General (no defaults and keep all options viewable):
- **Vital Signs** – Routine, Q2h
- **Strict intake and output** – Routine, every 8 hours
- **Titrate oxygen to SPo2 greater than** – Routine; SPO2 greater than 93
- **Nasal cannula oxygen** – Routine, Continuous; Rate in liters per minute: 2L/M
- **Blood Culture, peripheral** – STAT for 1 occurrence
- **Blood culture, central** – STAT for 1 occurrence
- **X-ray Chest 1 view** – STAT, 1 time imaging for 1 occurrence
- **X-ray Chest 2 view** – STAT, 1 time imaging for 1 occurrence
- **EKG, 12-Lead (portable)** – STAT, once for 1 occurrence

### Consults (no defaults and keep all options viewable):
- **Infectious Disease**
- **Neurology**
- **Cardiology**
- **Nephrology**

### Medications (no defaults and keep all options viewable):
- **“OK to give” order for tocilizumab** (doing this b/c tocilizumab lives as a prn order on the MAR) (order # BCN1045)
- **Acetaminophen 650 mg po q6h prn temp >/= 38.5 x 48 hrs**
- **Acetaminophen (Ofirmev) 650 mg IV Q6h prn temp >/= 38.5 X 48 hrs**
- **_____ mL NS IV bolus x 1 dose – once, STAT (no default) (order # 40800000205)**
- **Apply cooling blanket** – Routine, Until discontinued
- **Dexamethasone 10 mg IV – Once, STAT (this is default, keep other frequencies as an option)**
- **Methylprednisolone 1 gram IV – once, STAT -- followed by—**
- **Methylprednisolone 250 mg IV q6h x 8 doses -- followed by—**
- **Methylprednisolone 250 mg IV Q12h x 4 doses -- followed by—**
- **Methylprednisolone 125 mg IV Q12h x 4 doses -- followed by—**
- **Methylprednisolone 60 mg IV q12h x 4 doses -- followed by—**
### General (no defaults and keep all options viewable):
- Aspiration Precautions
- Neuro/vascular checks - Daily
- Neuro/vascular check
- MRI brain, ONCE - STAT
- MRI spine, ONCE – STAT
- EEG – STAT and then DAILY
- Elevate head to 30 degrees

### Consults (no defaults and keep all options viewable):
- Neurosurgery
- Neurology
- Ophthalmology

### Medications (no defaults and keep all options viewable):
- “OK to give” order for tocilizumab (doing this b/c tocilizumab lives as a prn order on the MAR) (order # BCN1045)
- Lorazepam ___ mg IV x 1 STAT (leave options for 0.5, 1 mg or 2 mg dose buttons)
- Levatiracetam 500 mg IV x 1 STAT
- Phenobarbital 60 mg IV once – STAT (order ID 40840000910)
- Phenobarbital 15 mg/kg mg IV once – STAT (order # 40840001779) --followed by—
- Phenobarbital 1 mg/kg IV q12h – STAT
  - Add comment – dose is 1 to 3 mg/kg q12h
- Dexamethasone 10 mg IV Q6h - STAT
- Methylprednisolone 1 gram IV – once, STAT --followed by— (order # 40840000639)
  - Methylprednisolone 250 mg IV q6h x 8 doses --followed by—
  - Methylprednisolone 250 mg IV Q12h x 4 doses --followed by—
  - Methylprednisolone 125 mg IV Q12h x 4 doses --followed by—
  - Methylprednisolone 60 mg IV q12h x 4 doses --followed by—
- Acetazolamide 1000 mg IV x 1 – STAT -- followed by—
- Acetazolamide 250 mg IV q12h
  - Mannitol 0.5 gm/kg x 1 STAT (order # 40840000926) – followed by—
  - Mannitol 0.25 gm/kg IVQ6h (order # 40840000926)
  - Add to comment – hold mannitol if serum osmolality greater than or equal to 320 mOsm/kg or osmol gap greater than or equal to 40
    - LINK ORDER to labs: Complete metabolic profile q6h and serum osmolality q6h
- Sodium Chloride 3% (Hypertonic) 250 mL IV x 1 STAT--followed by— (order # 7321)
  - Sodium Chloride 3% (hypertonic) at 50 ml/hr
  - Add to comment – hold infusion if serum sodium greater than or equal to 155 mEq/L
    - LINK ORDER to labs: electrolytes q4h
• Cellular therapy
  – Goals of care
  – Requirements for institution
• Manufacture and administration of cellular therapy products
  – CAR
• Oversight of trials
  – CARTOX
• Management of cost??
Costs

- Median cost of allogeneic SCT within first 100 days $200,000\(^1\), and within 1 year $500,000\(^2\)
- Median cost of autologous SCT within first 100 days: $100,000\(^1\)
- Cost of 1 vial of tocilizumab $1000
- Cost of cellular product??

1. Majhail NS, BMT, 2013
Conclusions I

• Non-HSC cellular therapies are increasingly being explored.
• Unique set of clinical toxicities.
• Broadly used across disease types.
• Accurate cost determinations, and patient charges, need to be made.
  – Health services research
Conclusions II

• Hematopoietic SCT provides framework, experience for implementing increasing use of non-HSC cellular therapy products.

• Database infrastructure through the leadership of CIBMTR provides opportunity to carefully study these new therapies.

• The SCT community needs to take leadership.
**It Takes a Village…**

<table>
<thead>
<tr>
<th><strong>Adult Transplant Faculty</strong></th>
<th><strong>Pediatric Transplant Faculty</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Richard Champlin</td>
<td>Borje Andersson</td>
</tr>
<tr>
<td>Elizabeth Shpall</td>
<td>Simrit Parmar</td>
</tr>
<tr>
<td>Katy Rezvani</td>
<td>Stefan Ciurea</td>
</tr>
<tr>
<td>Amanda Olson</td>
<td>Roy Jones</td>
</tr>
<tr>
<td>Yago Nieto</td>
<td>Nina Shah</td>
</tr>
<tr>
<td>Qaiser Bashir</td>
<td>Sairah Ahmed</td>
</tr>
<tr>
<td>Jeffrey Molldrem</td>
<td>Paolo Anderlini</td>
</tr>
<tr>
<td>Ben Valdez</td>
<td>Chitra Hosing</td>
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<tr>
<td>Martin Korbling</td>
<td>Issa Khouri</td>
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<tr>
<td>Uday Popat</td>
<td>Amin Alousi</td>
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<td>Rima Saliba</td>
<td>Gabriela Rondon</td>
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<tr>
<td>Gheath Al-Atrash</td>
<td>Rohtesh Mehta</td>
</tr>
<tr>
<td>Betul Oran</td>
<td>Muzaffar Qazilbash</td>
</tr>
<tr>
<td>David Marin</td>
<td></td>
</tr>
</tbody>
</table>

**GMP**

- Clinical and regulatory teams
- Clinical and research nurses