“Cancer Care: The Rapidly Emerging World of Clinical Cellular Immunooncology and how it can integrate with community practices”

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- Consultancy: Novartis, Artiva Biotherapeutics, Intellia,
- ASTCT: Chair, Value & Health Econ interest group
Provider Principles

- Primary goal is the direct delivery of care to patients
- The patient is the center of our attention.
Cell Therapy 2022

- HCT remains the paradigm for clinical cell therapy
  - Continues to provide important treatment options for patients with hematologic malignancies, as well as other disorders
- Ongoing improvements in supportive care → expansion of application of a safer procedure
- Expansion of cell therapy options → further outcome improvement (adult stem cells, T regs, viral specific T cells, etc)
- Evidence based medicine → dictate expansion of procedures (MDS or NHL in the elderly; scleroderma; sickle cell; multiple sclerosis)
Annual Number of HCT Recipients in the US by Transplant Type

Number of Transplants


Autologous HCT
Allogeneic HCT
Trends in Survival after Allogeneic HCT for AML, ≥18, 2001-2017

2001-2005 (n=11,080)
2006-2010 (n=13,094)
2011-2017 (n=24,607)

p<0.0001
Trends in Survival after Autologous HCT for DLBCL, 2001-2017

- 2001-2005 (n=5,029)
- 2006-2010 (n=5,337)
- 2011-2017 (n=9,578)

p<0.0001
The Future is Now
Novel Therapeutic Interventions:
Vascularized Composite Allotransplantation
CELLS ARE DRUGS*

- **Autologous HCT-** PBSC are used to enhance Hematopoietic Recovery after high-dose chemoradiotherapy

- **Allogeneic HCT** - Allogeneic stem cells are used to enhance hematopoietic recovery after high-dose chemoradiotherapy and critical to the intervention, donor derived, adoptively transferred mature lymphocytes are used to establish a graft versus malignancy effect

- **Immune effector cells/ CAR–T** – Graft engineered autologous (or allogeneic) T cells targeting surface B-cell antigens that activate the cytotoxic capacity of the ex vivo manufactured, reintroduced T-cell products

- *Regulated by FDA- exempt or non-exempt (e.g. more than minimally manipulated; heterologous use)
Cancer Therapy Evolves

- Surgery
- Radiation
- Chemotherapy

- Immunotherapy/
  Cellular Therapy
History:

Do T cells really make an impact in a clinical scenario
Grade IV Acute GVHD of the G I Tract is a T cell Disease
Toxic Shock Syndrome: a T cell disorder of Superantigens

Fraser, PLOS Bio, 2011
Current Day: Immuno-oncology

- T cell therapies
  - Gene expression
  - Autologous vs allogeneic
  - Neoantigens
  - TILs
  - Tregs
- Natural Killer cells
- Vaccines- peptide, dendritic cell,
- Checkpoint blockade (inhibitors)
- Checkpoint agonists
- Humoral immune therapy
  - Monoclonal antibodies
  - lVlg
  - BITEs
- Cytokines
Pipeline of Cancer Immunotherapies—Commercialization

Cell Therapy Landscape: 2018-2021 View
Prediction: cell and gene landscape rapid growth

- Fewer than 10 cell and gene therapies currently approved and in use, but with another 10+ expected annually in 2021 and beyond
- 1,000+ clinical trials for cell and gene therapies underway in the U.S. (asgct.careboxhealth.com)
- 24+ conditions on the near-term pipeline and constantly changing
- Number of manufacturers in cell and gene therapy market growing exponentially including big players
- Constantly shifting market; Not all cancer

### Forecast (2021-2022 Pipeline)

#### Blood Disorders
- Hemophilia B (gene)
- Hemophilia A (gene)
- Transfusion dependant β-thalassemia (gene)

#### Cancer
- Follicular lymphoma (CAR-T expanded indications)
- Multiple myeloma (CAR-T)
- Bladder cancer (gene)
- Epstein-Barr virus-associated post-transplant lymphoproliferative disease (CTL)
- Cervical cancer (TIL)
- Metastatic melanoma (TIL)
- Marginal zone lymphoma (CAR-T expanded indications)
- Diffuse large B-cell lymphoma (CAR-T)
- Acute lymphoblastic leukemia (CAR-T)
- Synovial sarcoma (TCR T-Cell)

#### Ocular Disorders
- Choroideremia (gene)
- Leber hereditary optic neuropathy (gene)
- Wet & dry age-related macular degeneration (gene/cell)

#### Metabolic Disorders
- Cerebral adrenoleukodystrophy (gene)
- Mucopolysaccharidosis type III (gene)

#### Neurodegenerative
- Aromatic L-amino acid decarboxylase (AADC) deficiency (gene)
- Spinal muscular atrophy (expanded indications-gene)

#### Skin Disorders
- Recessive dystrophic epidermolysis bullosa (gene)
- Scleroderma (gene)

#### Inherited Immunodeficiencies
- Wiskott-Aldrich syndrome (gene)
- Leukocyte adhesion deficiency type I (gene)
Specifically, what we see coming includes

In 2022, US could see these annualized numbers of patients (or higher) in need of services:

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients / 50 Million Lives*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ Transplant</td>
<td>4,850</td>
</tr>
<tr>
<td>Bone Marrow Transplant</td>
<td>3,400</td>
</tr>
<tr>
<td>Leukemia / Lymphoma (CAR-T)</td>
<td>23,000</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy (SMA)</td>
<td>120</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>3,300</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>4,000</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>13,700</td>
</tr>
<tr>
<td>Total</td>
<td>52,370</td>
</tr>
</tbody>
</table>

*US population currently estimated at 333 million
What is CAR-T?

• CAR T therapy - chimeric antigen receptor (CAR) genetically modified T cells - designed to recognize Tumor specific antigens (TSA) → in vivo activation and proliferation → significant and durable malignant cell immunity

• CAR T cells : “living drug” – can persist for long periods of time

• CAR T cells - generally autologous product from patient’s own blood cells, although universal donor “off the shelf” CAR T cells emerging
CAR T-Cell Therapy: Underlying Principles

**Leukapheresis**
- Collect patient’s white blood cells

**Manufacturing**
- Isolate and activate T-cells
- Engineer T-cells with CAR gene
- Viral vector with CAR DNA
- CAR-engineered T-cell
- Median manufacturing time: 17-28 days
- Targeting element (eg, CD19, BCMA, CD20)
- Spacer
- Transmembrane domain
- Costimulatory domains (eg, CD28 or 4-1BB)
- CD3ζ (essential signaling domain)

**Infusion**
- Expand CAR T-cells
- Infuse same patient with CAR T-cells

**Activity**
- CD19

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

Rapid tumor elimination and recovery of normal bone marrow after 19-28z CAR T cell therapy
First 2 patients: Refractory CLL
Still alive and in CR, >10 yrs after single application

Decade-long leukaemia remissions with persistence of CD4+ CAR T cells,
Melenhorst et al, Nature. 2022 Feb;602(7897):503-509
CAR T vs Tx for NHL
| CAR-T therapy | Diffuse large B cell lymphoma/primary mediastinal B cell lymphoma- adult |
|----------------|
| Primary refractory, resistant (after 2 lines of therapy) | S |
| First relapse, resistant | S |
| Beyond second relapse | S |
| Relapse after autologous transplant | S |

| CAR-T therapy | High-grade B cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements |
|----------------|
| Primary refractory, resistant (after 2 lines of therapy) | S |
| First relapse, resistant | S |
| Beyond second relapse | S |
| Relapse after autologous transplant | S |

<table>
<thead>
<tr>
<th>Diffuse large B cell lymphoma</th>
<th>Allo</th>
<th>Auto</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 (PET negative)</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Primary refractory, sensitive</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Primary refractory, resistant</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>First relapse, sensitive</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>First relapse, resistant</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Second or greater relapse</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Relapse after autoHCT</td>
<td>S</td>
<td>N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diffuse large B cell lymphoma</th>
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<th>Auto</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 (PET negative)</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>Primary refractory, sensitive</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Primary refractory, resistant</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>First relapse, sensitive</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>First relapse, resistant</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>Second or greater relapse</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Relapse after autoHCT</td>
<td>R</td>
<td>N</td>
</tr>
</tbody>
</table>

Standard of care (S); Standard of care, clinical evidence available (C); Standard of care, rare indication (R); Developmental (D); Not generally recommended (N).
OHSU Pt: Relapsed, refractory DLBCL
**JULIET: Median Overall Survival**
Median OS not reached (95% CI, 21 months-NE) in patients in CR

- No patients proceeded to allogeneic SCT or auto-SCT while in remission

Auto-SCT, autologous stem cell transplant; CI, confidence interval; CR, complete response; NE, not evaluable; OS, overall survival; SCT, stem cell transplant.
Median OS in CR patients: not reached (95% CI, 21 months-NE).
ZUMA-1: Axicabtagene Ciloleucel in r/r DLBCL

Response Duration by Best Objective Response (ZUMA-1)

- **n = 101**
- **ORR/CR 82% / 54%**
- More than half of patients with PR progressed by month 3
- **12 mo PFS for CR/PR @ month 3**
  - CR = 79% (95% CI, 63-88)
  - PR = 78% (95% CI, 36-94)

Locke et al, Lancet Onc, 2019
Transform study, Lisocabtagene, Abramson et al, Lancet 2020
Potential Baseline Predictors of Efficacy
Clinical Trials and Real-World Evidence

- LDH
- Tumor burden
- CRP, ferritin, and serum cytokines
- ECOG PS and disease state
- Bridging vs no bridging chemotherapy
- Baseline platelet levels
- Baseline ALC

ALC, absolute lymphocyte count; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.
Adverse Events of Special Interest
CRS and Neurological Events after CAR-T Cells

Neurologic:
- Headaches
- Changes in level of consciousness
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dystonia
- Myoclonus
- Facial nerve palsy
- Seizures

Constitutional:
- FEVER
- Rigors
- Malaise
- Fatigue
- Anorexia
- Arthralgias

Cardiovascular:
- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fraction
- Troponinemia
- QT prolongation

Pulmonary:
- Tachypnea
- Hypoxia

Renal:
- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

Hepatic:
- Transaminitis
- Hyperbilirubinemia

Gastrointestinal:
- Nausea
- Vomiting
- Diarrhea

Musculoskeletal:
- Myalgias
- Elevated creatine kinase
- Weakness

Hematologic:
- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile neutropenia
- Lymphopenia
- B-cell aplasia
- Prolonged prothrombin time
- Prolonged activated partial thromboplastin time
- Elevated D-Dimer
- Hypofibrinogenemia
- Disseminated intravascular coagulation
- Hemophagocytic lymphohistiocytosis

## Risk Factors for Severity of CRS and Neurological Events

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor burden</td>
<td>Higher activation and proliferation of CAR T cells is observed with high tumor burden leading to an exaggerated inflammatory response and higher toxicity (4, 5, 9, 13, 16).</td>
</tr>
<tr>
<td>Cell dosing</td>
<td>A higher dose of cells can lead to increased cytokine release and therefore greater toxicities once these cells are activated (18, 24).</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Higher number of comorbidities has been associated with increased risk and severity of CRS (17).</td>
</tr>
<tr>
<td>Age</td>
<td>Although there are no definitive studies, older patients may have a lower tolerance to CRS and neurotoxicity (4, 17).</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>The chemotherapy regimen prior to cell infusion is important to ensure replication and survival of CAR T cells. A regimen that leads to severe immunosuppression and therefore an exaggerated proliferation of CAR T cells can result in increased toxicity (9, 18, 24).</td>
</tr>
<tr>
<td>Timing of onset of symptoms</td>
<td>Early onset of symptoms is associated with worse toxicity and should lead to more aggressive monitoring and treatment (5, 24).</td>
</tr>
<tr>
<td>Cell product</td>
<td>Variabilities of the cell construct between protocols can potentially have an effect on cell proliferation and activity. Some factors include the costimulatory domain used, vector used, time in culture, and type of culture (9).</td>
</tr>
</tbody>
</table>

CAR = chimeric antigen receptor, CRS = cytokine release syndrome.

<table>
<thead>
<tr>
<th>CRS Parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong>‡</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
</tr>
<tr>
<td><strong>With either:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring one vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td><strong>And/or‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypoxia</strong></td>
<td>None</td>
<td>Requiring low-flow nasal cannula(^\wedge) or blow-by</td>
<td>Requiring high-flow nasal cannula(^\wedge), facemask, non-rebreather mask, or Venturi mask</td>
<td>Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 liters/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 liters/minute.
How to improve on outcomes?
Potential trial candidates

There is an internal message: CAR T does not cure all!!!!!!
- Day 30 PET-CT will be centrally reviewed (72 hours turn around time) – response criteria per Lugano
- Treatment vs observation (1:1:1:1 randomization)
- 1 year PFS: 20.0% (observation) vs 44.7% (consolidation) \(\rightarrow\) 120 patients (30 per arm)
Progress continues on CAR-T cell therapy
Approved CAR-T Products & Indications

- R/R DLBCL - 3rd line- Tisagenlecleucel, Axicabtagene, Lisocabtagene
- R/R Follicular Lymphoma- 3rd line Axicabtagene
- Mantle cell lymphoma- Brexucabtagene
- Pediatric/young adult- > 2nd line- Tisagenlecleucel
- Adult ALL- Brexucabtagene
- Myeloma- Beyond 4th line- Idecabtagene, Ciltacabtagene

Anticipated 2022:

**R/R – 2nd line- Axicabtagene, Lisocabtagene**
R/R Follicular Lymphoma- Tisagenlecleucel

Anticipated 2023- TIL for Advanced Melanoma- Lifileucil
Open/ Pending Clinical Trials with Cell Therapy

- Universal donor CD19 CAR T for DLBCL & ALL- CRSPR
- Universal donor CD19 NK-CAR T for NHL, CLL, ALL- Fate
- Autologous Dual Targeted CD19/CD20 for DLBCL- Miltenyi
- Autologous CAR T for BCMA+ Myeloma
- Autologous ROR1 CAR-T for advanced solid tumor malignancies expressing ROR-1
- Autologous GD2 CAR-T for osteosarcoma
- Allogeneic CART for advanced ovarian cancer
- Universal donor NK cells for R/R lymphoma (including CAR T failure)
  - Autologous HLA A2.01 restricted, WT1 peptide specific T cells for AML
  - HLA restricted, EBV specific donor T cells for EBV+ PTLD
  - HLA restricted, NY ESO specific autologous T cells for Synovial Cell Sarcoma
  - HLA restricted, NY ESO specific autologous T cells for overexpressed NY ESO in advanced Ca
- Autologous TIL for R/R NSCLC
- Autologous TIL for advanced malignancies
- HLA restricted, Virus Specific T cells for BK Cystitis and RSV/Parainfluenza/ Influenza Resp virus infections
- Her2/Neu-Macrophage CAR for overexpressed HER2/Neu malignancies
- HPV peptide loaded RBC + poly IC as systemic tumor vaccine for HPV+ malignancies
- Genetically engineered, immune activating RBC (sIL15+ 41BB+) for recurrent RCC, NSCLC
Number of CAR T cell infusions: 2016-2021
(5,364 patients and 5,625 infusions)
Can we deliver cell therapy everywhere?
Where do we begin? At the beginning, of course
Cell Therapy Program Management
Patient Readiness / Logistics

- Referral
- Eligibility evaluation
  - Path review critical
- Clinical Trial Considerations
- Payer authorization support
- Leukapheresis
- Manufacturing time
- Bridging chemotherapy
- Infusion
- Short and long term management
Program Implementation

• Certification
• Preparation
  – Stakeholders
  – Training
  – Documentation
  – Management guidelines
FACT/JACIE

- Primary objective of standards - promote quality medical and laboratory practice

- FACT - standards specific to the use of Hematopoietic Cell Therapy & Immune Effector Cells (IEC).
  - Specify clinical and quality infrastructure
    - Purpose: facilitate safe administration of IECs
    - Formalize monitoring and reporting of outcomes

- Option for IEC therapy only – IEC standards manual

- For both HSCT and IEC therapies –
  - Product Collection, Processing, and Administration standards
Unanticipated Challenges

- Need for expanded access protocols
  - Access to manufactured commercial products that do not meet release criteria
  - Requires IRB/regulatory approval for use
- Patient scheduling with short notice:
  - Apheresis unit
  - Outpatient infusion room
- On-going training for nurses and physicians – due to turnover
- Different processes for commercial products and clinical trial products
- Payment for services
- Medicare reimbursement
Outcomes Dashboard Metrics

- Infusion date
- Status (A/D)
- 30 day survival
- 100 day survival
- Diagnosis and Histology
- Discharge date (if inpatient for infusion)
- LOS (if inpatient for infusion)
- CRS max grade
- Time to CRS max grade
- Number of doses of Tocilizumab
- ICANS max grade
- Time to ICANS max grade
- Days to readmission post discharge (if inpatient for infusion)
- Number inpatient days within 30 days
- Number of inpatient days within 100 days
- Number of ICU days
- Clinical status at day 90
Growth of Cell Therapy being Addressed at National/International Level

• Access to care
• Cost of care
• Logistics of care
Launch of a Commercial Cell Therapy Product at a Clinical Site is a Complex Process

<table>
<thead>
<tr>
<th>Commercial Partner/Manufacturer</th>
<th>Internal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Standard Operating Procedures</td>
<td>• Buy in from Center Leadership</td>
</tr>
<tr>
<td>• Clinical standards for toxicity management</td>
<td>• Submission to Pharmacy &amp; Therapeutics</td>
</tr>
<tr>
<td>• Initiation and auditing of a REMS program</td>
<td>• Financial Due Diligence</td>
</tr>
<tr>
<td>• Adverse event and data reporting under REMS</td>
<td>• EMR record order sets/ treatment plans</td>
</tr>
<tr>
<td>• Implementation of Product Application (IT)</td>
<td>• Informed Consents</td>
</tr>
<tr>
<td></td>
<td>• Cell Therapy Coordinator Training and Resources</td>
</tr>
<tr>
<td></td>
<td>• Patient education and wallet card workflow</td>
</tr>
<tr>
<td></td>
<td>• Payor Strategies</td>
</tr>
<tr>
<td></td>
<td>• Education of consulting services and ancillary staff</td>
</tr>
</tbody>
</table>

This process can take 3-9 months with countless hours of effort
Specific Start-up Qualification and Tasks

Apheresis
- Machine Operation
- COC/COI
- QC System
- 2 vs 3 BVs
- +/- Plasma addition
- Company-specific Portal

Cell Processing
- 15-20 SOPs
- PMs on Equipment
- LN storage monitors
- COC/COI
- Packing and Sterile Technique
- Vials/Syringes vs Bags
- +/- Dosing
- Company-specific Portal

Pharmacy
- Drug Logs
- Toci Stock
- Toci Delivery Time

Nursing
- LD Chart
- FACT
- Toci
- Infusion
- Reaction Management
- Syringes vs Bags

Contracting

Company-specific Portal

FACT
NMDP
AABB
**Defining resource utilization:**

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>236</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>62.5 (19-82)</td>
</tr>
<tr>
<td>Female sex</td>
<td>91 (38.6)</td>
</tr>
<tr>
<td>White race*</td>
<td>218 (92.4)</td>
</tr>
<tr>
<td>Relationship status</td>
<td></td>
</tr>
<tr>
<td>Married/Life partner</td>
<td>163 (69.1)</td>
</tr>
<tr>
<td>Single</td>
<td>40 (17.0)</td>
</tr>
<tr>
<td>Divorced/Legally separated</td>
<td>13 (5.5)</td>
</tr>
<tr>
<td>Widowed</td>
<td>13 (5.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (3.0)</td>
</tr>
</tbody>
</table>

**CAR T-cell product**

- Axicabtagene ciloleucel 183 (77.5)
- Tilisagenleucel 36 (15.3)
- Axicabtagene ciloleucel combined with immunotherapy 9 (3.8)
- KTE-X19 7 (3.0)
- Lisocabtagene maraleucel 1 (0.4)

**Lymphoma subtype**

- DLBCL/Grade 3B follicular lymphoma 107 (45.3)
- Indolent lymphoma transformed to DLBCL 40 (17.0)
- HGBCL with MYC and BCL2 and/or BCL6 rearrangements 40 (17.0)
- Follicular lymphoma 22 (9.3)
- Primary mediastinal large B-cell lymphoma 12 (5.1)
- Other 15 (6.4)

### Table 1. Patient Characteristics (cont.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>194 (82.2)</td>
</tr>
<tr>
<td>2-4</td>
<td>38 (16.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Received bridging therapy</td>
<td></td>
</tr>
<tr>
<td>Prior lines of therapy, median (range)</td>
<td>3 (0-10)</td>
</tr>
<tr>
<td>Prior autologous stem cell transplant</td>
<td>65 (27.5)</td>
</tr>
<tr>
<td>Days from relapse to CAR T-cell therapy, median (range)</td>
<td>58 (11-391)</td>
</tr>
<tr>
<td>Toxicity and response</td>
<td></td>
</tr>
<tr>
<td>Cytokine release syndrome (any grade)</td>
<td>183 (77.5)</td>
</tr>
<tr>
<td>ICANS (any grade)</td>
<td>126 (53.4)</td>
</tr>
<tr>
<td>Received tocilizumab</td>
<td>120 (50.9)</td>
</tr>
<tr>
<td>Received corticosteroids</td>
<td>107 (45.3)</td>
</tr>
<tr>
<td>Overall response</td>
<td>201 (85.2)</td>
</tr>
<tr>
<td>Complete response</td>
<td>152 (64.4)</td>
</tr>
<tr>
<td>Survival</td>
<td>184</td>
</tr>
<tr>
<td>Alive 1 year after CAR T-cell therapy</td>
<td>116 (63.0)</td>
</tr>
</tbody>
</table>

### Table 2. Healthcare Utilization Among CAR T-Cell Therapy Patients (n=236)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay for CAR T-cell hospitalization, median (range), d</td>
<td>15 (7-91)</td>
</tr>
<tr>
<td>ICU admission during admission for CAR T-cell therapy</td>
<td>30 (12.7)</td>
</tr>
<tr>
<td>Any ICU admission within 3 mo of CAR T-cell infusion^a</td>
<td>36 (15.5)</td>
</tr>
<tr>
<td>Any hospital readmission within 3 mo of CAR T-cell infusion^b</td>
<td>65 (28.1)</td>
</tr>
<tr>
<td>Number of hospital readmissions within 3 mo of CAR T-cell infusion</td>
<td>1 (1-4)</td>
</tr>
<tr>
<td>Days from discharge to first readmission, median (range) (n=65 readmissions)</td>
<td>18 (1-91)</td>
</tr>
</tbody>
</table>

**Reason for first hospital readmission (n=64 readmissions)**

- Symptoms 22 (34.4)
- Noncancer medical condition 10 (15.6)
- Cancer progression 8 (12.5)
- Infections 6 (9.4)
- Febrile neutropenia 5 (7.8)
- Neurotoxicity 5 (7.8)
- Cytokine release syndrome 2 (3.1)
- Other 6 (9.4)
CAR T Cell Toxicities in the real world

- Overall rates of toxicities in the real world are comparable to clinical trials.
- Toxicity rates vary by product (construct), by indication, age and other factors.
  - Improvement in management → reduction in higher grade CRS among patients with lymphoma.
- Toxicities are correlated with each other and impact overall patient outcomes.
Requirements for community treatment:

- Sufficient logistical coordination for delivery of complex care (or not).
- Sufficient resources to support patient care.
  - What happens when things go awry?
- Sufficient staffing for regulatory commitments.
- Sufficient patient volume to warrant investment and maintenance of the above components.
A need for efficiencies and standardization across the cell therapy workflow – Order management platform technology
Program Onboarding

- Program Quality Control
- Toxicity Management
- Chemotherapy
- Cell Therapy Infusion
- Consent Forms

Clinical Management Approaches

- Documentation
- Toxicity Grading
- Tocilizumab use
- Steroids use
- ID prophylaxis
- Apheresis

Data Reporting

Tension between REMS guidelines and Apheresis Manual vs institutional standards
Educational requirements differ by group/sub-specialty

- Reporting Requirements
  - Patient Wallet Cards
  - Patient Education
  - Clinical Site Education
  - Length of Stay
  - Institutional Toxicity Management Algorithms

Do differences in REMS guidelines for management impact site practice?
Collaboration needs to maximize community care

• Identification of partners
• Shared care models
• Flow models
• How to get a patient to OHSU: intake center or CALL ME
• How to get a patient home: pt education, recommended mgmt. of long term issues, FDA requirements of 15yr follow-up, CALL ME

• HOW TO CALL ME: CELL is 503-805-1965
National CAR-T Landscape

- Clintrials.Gov - >1000 trials planned, ongoing, completed
- Disease targets:
  - Lymphoma - NHL and HD; MM; Neuroblastoma; ALL; CLL; Mesothelioma; Ovarian ca; Pancreatic ca; AML; Glioblastoma; Prostate ca; HCC: MUC 1+ Lung CA & triple (-) Breast Ca; Colorectal Ca; H/N Ca; SLE; other autoimmune disease
  - Targets include Her2/Neu, mesothelin, EGFRvIII, GD2 ganglioside
  - CD19/CD22 bispecific CAR-T (generated by bicistronic insertion)
  - CD19/CD20 bispecific CAR-T
  - Multi-CAR T trials
  - CAR-T with checkpoint inhibitors
CAR T & Transplant: the work evolves

Thanks to all for joining; Here to help!!!

Dawn over Mt Hood near Portland, OR