Cell Therapy Registry Update

2021 DM/CRP Virtual Conference – Transplant and Cellular Therapy Meeting

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Agenda

• Cell Therapy Registry updates
• Revie the latest form revisions
• Toxicity reporting examples
Timeline and Milestones of CT Registry

- **2015**: Establish the CT Task Force
- **2016**: NCI funded CT Registry Pilot
- **2017**: First CT Registry Annual Forum
- **2018**: Approval of Kymriah
- **2018**: Approval of Yescarta
- **2019**: Launch of the Cellular Therapy Registry
- **2019**: CIBMTR LTFU for Axi-cel
- **2019**: CIBMTR LTFU for Tisagenleclecel
- **2020**: Forms Harmonization with EBMT
- **2020**: 2,000 CAR T-cell Infusions reported
- **2021**: Accrual completion of the first Post Approval Safety Study (Yescarta)
- **2021**: Approval of Tecartus
- **2021**: Japanese Platform to capture CT Data
## Industry-sponsored Projects

<table>
<thead>
<tr>
<th>Project</th>
<th>Sponsor</th>
<th>Objective</th>
<th>Timeline/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yescarta LTFU</td>
<td>Kite</td>
<td>Safety and efficacy outcomes (PASS) N=1,500 (Completed 07/2020) Diseases: NHL</td>
<td>07/2018 2 years of accrual 15 years of follow up</td>
</tr>
<tr>
<td>(Axicabtagene ciloleucel)</td>
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<tr>
<td>Kymriah LTFU</td>
<td>Novartis</td>
<td>Safety and efficacy outcomes (PASS) N=2,500 (Current N=1000) Diseases: NHL and ALL</td>
<td>08/2018 5 years of accrual 15 years of follow up</td>
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<tr>
<td>Lisocabtagene maraleucel</td>
<td>BMS</td>
<td>Safety and efficacy outcomes (PASS) N=1,000 Disease: NHL</td>
<td>5 years 15 years of follow up</td>
</tr>
<tr>
<td>Idecabtagene veceleucel</td>
<td>BMS</td>
<td>Safety and efficacy outcomes (PASS) N=1,000 Diseases: Multiple Myeloma</td>
<td>5 years 15 years of follow up</td>
</tr>
<tr>
<td>Tecartus</td>
<td>Kite</td>
<td>Safety and efficacy outcomes (PASS) N=500 Disease: Mantle Cell Lymphoma</td>
<td>5 years 15 years of follow up</td>
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<td>(Breuxucatagene autoleucel)</td>
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<tr>
<td>Ciltacabtagene autoleucel</td>
<td>Janssen/ Legend</td>
<td>Safety and efficacy outcomes (PASS) N=TBD Disease: Multiple Myeloma</td>
<td>5 years 15 years of follow up</td>
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**Under Development**

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<tr>
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CRP/DM CONFERENCE 2021 | 4
Number of CAR T cell infusions: 2016-2020
(3,488 patients and 3,665 infusions)
CAR T cell Indications Annually: 2016-2019

- Non Hodgkin Lymphoma
- Acute Lymphoblastic Leukemia
- Other Indications
CAR T Cell Indications: 2016-2020 (N=3,488)

- **NHL**: 74%
- **ALL**: 20%
- **Multiple Myeloma**: 5%
- **Other**: 1%

Centers: 148
Median age: 59 y (<1-91)y
Prior HCT: 33%

- **Commercial**: 79%
- **Noncommercial**: 21%
Prior HCT to CAR T-cell by Indication: 2017-2020

**Acute Lymphoblastic Leukemia**

- No Prior HCT
- Prior AutoHCT
- Prior AlloHCT

**Non Hodgkin Lymphoma**

- No Prior HCT
- Prior AutoHCT
- Prior AlloHCT
Cell Therapy Form Revisions: The Highlights
## Winter (January) 2021 Release

<table>
<thead>
<tr>
<th>Forms</th>
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<tr>
<td>Pre-Cellular Therapy Essential Data (4000)</td>
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<tr>
<td>Cellular Therapy Product (4003)</td>
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<tr>
<td>Cellular Therapy Infusion (4006)</td>
</tr>
<tr>
<td>Cellular Therapy Essential Data Follow-up</td>
</tr>
<tr>
<td>(4100)</td>
</tr>
</tbody>
</table>
Check all that Apply

- Continue to implement where applicable
- F4003:
  - Manipulation methods
  - Genetic manipulation methods
- F4006:
  - Product ID
  - Cells infused
- F4100:
  - Current heme findings
  - Symptoms of CRS
  - Symptoms of Neurotoxicity (ICANS)
  - Max lab values
F4000 Recipient Data

- Added new questions to capture:
  - Country of primary residence
  - State/province/territory of Brazil/Canada/US
  - Zip code (US/Canada)
- Aligns with Pre-TED
New Consent Tool!

More information to be given during “Consent and You” on February 2nd
F4000 Name of Product

• Added additional product names
• This question will no longer be answered for DLIs
F4000 Indication

Indication for Cellular Therapy

58. What was the primary indication for performing treatment with cellular therapy?

- Cardiovascular disease
- GVHD prophylaxis *(with HCT)*
- GVHD treatment *(post-HCT)*
- Immune reconstitution *(post-HCT)*
- Infection prophylaxis
- Infection treatment
- Malignant hematologic disorder - Also complete CIBMTR Form 2402
- Musculoskeletal disorder
- Neurologic disease
- Non-malignant disorder - Also complete CIBMTR Form 2402
- Ocular disease
- Prevent disease relapse *(post-HCT)*
- Pulmonary disease
- Solid tumor - Also complete CIBMTR Form 2402
- Suboptimal donor chimerism *(post-HCT)*
- Other indication
F4000 Indication

• New indications
F4000 Disease Assessment

- Removed disease assessment section
- Information captured on disease specific forms
F4000 Lymphodepleting (LD) Therapy

- Moved height & weight to Lymphodepleting Therapy section
F4000 Toxicity prophylaxis and Heme Findings

2 new sections:
• Toxicity prophylaxis
• Hematologic findings prior to LD therapy
F4003 Out of Spec Products

- According to the product label, indicate if the product met specification release criteria.
F4003 Tissue Source and Cell Type

- Expanded the option values for tissue source and cell type
F4003 Pharmaceutical/Biotech Company

- Added additional sponsors
F4003 Manipulation methods

• Updated an expanded the option values for:
  – Gene edited
  – CAR construct
  – Suicide gene
  – Viral targets
  – Tumor/cancer antigen
F4100 Best response and Recovery

- Best response
  - Added CCR
  - Not answered if disease forms are also being completed
- Peripheral blood count recovery
  - Additional questions to capture subsequent decline
F4100 B-cell aplasia

- Updated B-cell aplasia questions
- Validation against product name
F4100 Macrophage Activation Syndrome and hemophagocytic lymphohistiocytosis

- severe systematic inflammatory syndromes
- within the spectrum of CRS
Reporting toxicities:
Don’t fall into these traps
CAR T cell Toxicities: CRS, ICANS and other related organ toxicities

**Neurologic**
- Headaches
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Headaches
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial Nerve palsy
- Seizures

**Hepatic**
- Transaminitis
- Hyperbilirubinemia

**Hematologic**
- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile Neutropenia
- Lymphopenia
- B-Cell Aplasia
- Prolonged Prothrombin time
- Prolonged Activated Partial Thromboplastin time
- Hypogammaglobulinemia
- Elevated D-Dimer
- Hypofibrinogenemia
- Disseminated Intravascular Coagulation
- Hemophagocytic Lymphohistiocytosis

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

**Constitutional**
- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Arthralgias

**Pulmonary**
- Tachypnea
- Hypoxia

**Gastrointestinal**
- Nausea
- Eructation
- Diarrhea

**Musculoskeletal**
- Myalgias
- Weakness
- Elevated creatine kinase

©2016 by American Society of Hematology
Common Toxicities of CD19 CAR T Cells

Cytokine Release Syndrome

- Fever
- Hypotension
- Capillary leak
- Respiratory insufficiency
- Multi-organ failure (+/- neurotoxicity)
- HLH/MAS
- Coagulopathy/DIC

Symptoms rapidly resolve with IL-6R blockade (Tocilizumab)

Neurotoxicity (Immune Effector Cell Associated Neurotoxicity Syndrome – ICANS)

- Global encephalopathy
- Aphasia
- Seizure, seizure like activity
- Obtundation
- Tremor/myoclonus
- Hallucinations
- (Rapid onset of brain edema)

Severe symptoms do not resolve with IL-6R blockade (Tocilizumab)
Cytokine Release Syndrome (CRS)

• “.. a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells…”

“…Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction…” (ASTCT criteria).

Lee DW et al 2019, BBMT

Figure: Varadajan et al, CAR T cell Therapies for Cancer, A practical Guide 2020
Elements

Cytokine Release Syndrome (CRS)

Did the recipient experience Cytokine Release Syndrome (CRS)?
- Yes
- No

Specify therapy given for CRS (check all that apply)
- Anti-IL-6R
- Anti-IL-1β
- Anti-IFN-γ
- Anti-TNF-α
- Corticosteroids
- Other

Indicate the symptoms of CRS (check all that apply)
- Fever (> 100.4°F or > 38°C)
- Tachycardia
- Hypotension requiring therapy
- Other

Specify details about the occurrence of CRS
- Date started: ___-___-___
- Doses of tocilizumab:
  - 1
  - 2

Did cytokine release syndrome resolve?
- Yes
- No

Date resolved: ___-___-___

Were there features related to macrophage activation syndrome (MAS) / hemophagocytic lymphohistiocytosis (HLH)?
- Yes
- No

Date of MAS / HLH onset: ___-___-___

Did the recipient have splenomegaly?
- Yes
- No

Was MAS / HLH confirmed by a bone marrow biopsy?
- Yes
- No

Values collected (check all that apply)

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New- capturing prophylactic treatment

- Not yet routinely performed
- Practices are evolving
- Tociluzumab may be given preemptively to high risk patients

Toxicity Prophylaxis

- Therapy given for the prevention of CRS (prophylactic therapy)
- Tocilizumab
- Other
- None

Specify other therapy given:_________
Factors Associated with CRS

- Disease burden
- High peak CAR T cell expansion
- High IL6 levels at baseline
- CAR construct
- High cytokine levels post infusion
Macrophage Activation Syndrome (MAS) / Hemophagocytic Lymphohistiocytosis (HLH)?

- Severe and often uncontrolled systemic supra-inflammatory response rarely associated with CAR T cell related CRS

- Features:
  - High fevers, cytopenias, hyperferritenemia, organomegaly, coagulopathy, organ failure, high triglycerides.
  - Pathologic diagnosis (bone marrow or tissue biopsy) → confirmation
Elements

Were there features related to macrophage activation syndrome (MAS) / hemophagocytic lymphphhistiocytosis (HLH)?
- Yes
- No

Date of MAS / HLH onset: ___ ___ ___ ___  ___  ___  ___  ___

- YYYY  MM  DD

Did the recipient have splenomegaly?
- Yes
- No

Was MAS / HLH confirmed by a bone marrow biopsy?
- Yes
- No

Specify the laboratory values collected (check all that apply)

- Fibrinogen
- Triglyceride
- None

Lowest fibrinogen level: ___ ___ ___ ___
- mg/dL
- mg/L

Date fibrinogen sample collected: ___ ___ ___ ___  ___  ___  ___  ___

- YYYY  MM  DD

Highest triglyceride level: ___ ___ ___ ___
- mg/dL
- mmol/L

Date triglyceride sample collected: ___ ___ ___ ___  ___  ___  ___  ___

- YYYY  MM  DD
Reporting MAS/HLH

- the first symptom of MAS/HLH was documented by either the date of the pathological confirmation of MAS/HLH (bone marrow or other organ biopsy)
- the first date of a ferritin level $\geq 100,000$ ng/mL among patients without pathologic confirmation but with high clinical suspicion (persistent high fevers, ongoing cytopenias, high triglyceride levels, low fibrinogen levels or organomegaly)
# ASTCT Neurotoxicity Consensus Grading for Adults - Immune effect Cell-Associated Neurotoxicity Syndrome (ICANS)

<table>
<thead>
<tr>
<th>NT Domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro-Assessment ICE Score</td>
<td>7-9</td>
<td>3-6</td>
<td>0-2</td>
<td>0</td>
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<tr>
<td>Depressed level of consciousness</td>
<td></td>
<td></td>
<td></td>
<td>AND</td>
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<td></td>
<td>One of the events below</td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td>Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention</td>
<td>Life-threatening prolonged seizure (&gt;5 min); or Repetitive clinical or electrical seizures without return to baseline in between.</td>
</tr>
<tr>
<td>Motor findings</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Deep focal motor weakness such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Raised ICP / Cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/local edema with or without hemorrhage on neuroimaging</td>
<td>Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad</td>
</tr>
</tbody>
</table>

• NT grade is determined by the most severe event not attributable to any other cause.
• A patient with a neuro-assessment score of 3 who has a generalized seizure is classified as having Grade 3 NT.
• A patient with a neuro-assessment score of 0 may be classified as having Grade 3 NT if the patient is awake with global aphasia. But a patient with a neuro-assessment score of 0 may be classified as having Grade 4 NT if the patient is unarousable.
• Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)
• Tremors and myoclonus associated with NT may be graded according to CTCAE v5.0 but they do not influence NT grading.
CD19 CAR T cell Neurotoxicity events are almost always reversible

Park J et al. NEJM 2017
Santomasso B & Park J et al. Cancer Discovery 2018
Impaired handwriting is a sensitive sign of neurotoxicity

<table>
<thead>
<tr>
<th>Day 4</th>
<th>9 am</th>
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Day 4
9 am

Day 5
01:30 PM

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<th>MMSE score</th>
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Day 5
03:30 PM

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Day 6
9 am

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Factors associated with worse ICANS

- CAR T cell target (CD19>>CD22 or BCMA)
- Disease: ALL > NHL
- Disease Burden: ALL (High blast count)
- Early onset of fever
- High peak CAR T cell expansion
- High levels of cytokines
- Baseline low platelet count
- Break of the blood brain barrier
- High dose of lymphodepleting chemotherapy
Elements
New- capturing prophylactic treatment

- Anti-epileptic drugs may also be used to prevent ICANS
- Practices are evolving
Recipients of commercial CD19 CAR T-cells: 2016-2020

Patients with at least the first follow up: 3m

1647

CRS 71%

1181

ICANS 45%

736

Complete grading information N=1169

Complete grading information N=680

HLH reported in 3 patients
Lee DW, 2014 vs ASTCT Consensus Grading

- Lee 2014 and ASTCT consensus gradings are generally similar.
- There is upstaging of patients with grade 2 according to Lee 2014 to grade 3 using ASTCT Consensus criteria
  - Based on use of low dose or single vasopressor agent
- Patients with other grade 4 organ toxicities (excluding liver) are graded as 4 according to Lee 2014, even if there is no hypotension or hypoxia. The same would be grade 1 with ASTCT consensus
Distribution of manifestation by ASTCT grading

CRS Grade 2 (N=441)
- Hypotension: 30%
- Hypoxia: 20%
- Both: 50%

CRS Grade 3 (N=103)
- Hypotension: 30%
- Hypoxia: 20%
- Both: 50%

CRS Grade 4 (N=71)
- Hypotension: 100%

CRS Grade 5 (N=24)*
- Hypotension: 100%

Median Onset of CRS: 4 days (1-28d)
Median duration of CRS: 7 days (IQR 3-11d)
CRS resolution by 100 days: 94%

ICANS
- Grade 1: 2%
- Grade 2: 15%
- Grade 3: 27%
- Grade 4: 18%
- Grade 5: 38%
Hypogammaglobulinemia

- Controversial outcome as it is caused by the disease and by the treatment, not only CAR T cells
Hypogammaglobulinemia – Why is this important?

- It is accentuated by the CD19 or BCMA CAR T cells
- It requires immunoglobulin replacement therapy (IV or SQ) in order to prevent or treat infections.
- It is also a surrogate for CAR T cell persistence.

**Pitfalls:**
- Previously existence of hypogamma
- Variation in treatment practices
- When can we clearly state that it has resolved?
### Other toxicities

**Hypogammaglobulinemia**

- Yes
- No
- Unknown

**Was the date of onset previously reported?**

- Yes
- No

**Date of onset:**

```
YYYY  MM  DD
```

**Did hypogammaglobulinemia resolve?**

- Yes
- No

**Date resolved:**

```
YYYY  MM  DD
```

**Did recipient require immunoglobulin replacement therapy?**

- Yes
- No

**Is the recipient still requiring replacement therapy?**

- Yes
- No
When to report hypogammaglobulinemia

- If IgG dropped below 600 (or 500 for children ages 4 – 10) in the reporting period, regardless if the IgG was below 600 prior to infusion

OR

- if the IgG was below 600 (or 500 for children ages 4 – 10) and persistent into the current reporting period

- Diagnosis can be based on lab values
When to report hypogammaglobulinemia

- For an adult recipient, IgG levels were below 600 mg/dL pre-cellular therapy infusion and continue to be low post-infusion.
When to report hypogammaglobulinemia

• For an adult recipient, IgG levels were below 600 mg/dL pre-cellular therapy infusion and continues to be low post-infusion and immunoglobulin replacement therapy (IVIG) was given post-infusion
When not to report hypogammaglobulinemia

• For an adult recipient, IgG levels were never below 600 mg/dL, but levels were decreasing post-infusion and immunoglobulin replacement therapy (IVIG) was given.
When not to report hypogammaglobulinemia

• For an adult recipient, IVIG was administered prophylactically, but IgG levels were never below 600 mg/dL
Hypogammaglobulinemia onset date

- IgG levels were measured at 450 mg/dL on June 1; however, immunoglobulin replacement therapy (IVIG) was not given.
- June 15 IgG levels dropped to 400 mg/dL, immunoglobulin replacement therapy (IVIG) was given as this time.
Hypogammaglobulinemia onset date

- IgG levels were measured at 450 mg/dL on May 15, no immunoglobulin replacement therapy (IVIG) was given.

Other toxicities

- Hypogammaglobulinemia: Yes
- Date of onset: 2020-05-15
Hypogammaglobulinemia can be reported as resolved if there are sustained normal levels of IgG in the blood without the need for IVIG infusions for 3 consecutive months.

- Report the first date of that 3 month period.
Hypogammaglobulinemia resolution date

- IgG levels were measured at 450 mg/dL on June 1
- Immunoglobulin replacement therapy (IVIG) was given on June 15
- IgG levels were monitored for the next 4 months and no further immunoglobulin replacement therapy (IVIG) was given
- IgG levels went above 600 mg/dL on September 15 and continued to rise
Hypogammaglobulinemia resolution date

- IgG levels were measured at 450 mg/dL on May 15, no immunoglobulin replacement therapy (IVIG) is given.
- IgG levels were monitored and went above 600 mg/dL on June 3 and normal levels were sustained.

**Date resolved:** 2020-06-03

**Did hypogammaglobulinemia resolve?**

- Yes
- No

Did hypogammaglobulinemia resolve?

2020-06-03
Hypogammaglobulinemia resolution date

- IgG levels were measured at 450 mg/dL on June 1; immunoglobulin replacement therapy (IVIG) was given on June 15. IgG levels were not monitored, and the recipient has returned to their primary oncologist.
- In the absence of any testing, the resolution date can be reported as the date 3 months after the last IVIG infusion.
More training

• New eLearnings
• New manuals
• Your friendly CT coordinators are here to help 😊
  – Tiffany Hunt
  – Jaime Santi
  – Liz Bolton
Questions?