New Therapies in Cancer and Implications for the Critical Care Community

Laveena Munshi, MD, MSc
Interdepartmental Division of Critical Care Medicine
Mount Sinai Hospital
University of Toronto
Toronto, Canada
I have nothing to disclose.

Within the last 12 months I have not had any type of financial arrangement or affiliation with commercial interests related to the content of this continuing education activity that requires disclosure.
Since the 1990s, cancer mortality has progressively declined despite increasing incidence of cancer.
It is not uncommon for patients with cancer to develop critical illness...

Oncologic Critical Care Mortality Over Time

Incidence of ICU Admission (medical admissions)

- Solid Tumor*
- Acute Myeloid Leukemia
- Hematopoietic Stem Cell Tx
- hematologic malignancies

Direct Tumor Effect/First Presentation

Infectious Treatment Toxicities

Non-Infectious Treatment Toxicities
This accelerating progress in Onc Critical Care attributable to

**Cancer-specific advancements**
- Better patient selection
- Earlier detection
- Targeted Therapy

**Infectious Disease Practices**
- Antimicrobial development
- Detection of viruses/fungi

**Infectious Control Practices**

**Critical Care Practices**
- Early recognition of disease
- Mechanical Ventilation Practices
- Mobility/Sedation Practices

Incidence of cancer will continue to rise and there are significant implications for the critical care community
There are many time points at which an Oncologic patient can interact with the ICU.
Type of Critical Illness that Oncology Patients Present with Is Evolving (complexity increasing)

Intensivists Expression at Time of Consultation:
What does “metastatic cancer” even mean anymore?

“Metastatic Breast Cancer”

“Metastatic Melanoma”

“Metastatic Ovarian Ca”

“Treatment Refractory B Cell Lymphoma”

Precision Medicine/Immunotherapy

10-year survival?

5-year survival?

1-year survival?

In the Future:
Will cancer be a chronic disease?
Revolution in cancer therapeutics

Precision medicine
Reprogramming Immune System to Recognize and Attack Cancer Cells
Complex toxicities that require critical care support

Immune Checkpoint Inhibitors
CAR-T
Outline

Immunotherapy 101

Immune effector cell therapies

Immune check point inhibitors

Implications for the critical care community
In the early 2000s, there was an effort to map out the genomic landscape of human cancers.

MacConaill, L, et. al., J Mol Diagn 2014, 16: 660-672
…this has laid the foundation for precision medicine with some very promising early results in cancer…
Precision medicine has led to a paradigm shift in cancer care taking our primary focus off of targeting the tumor.
Precision medicine has led to a paradigm shift in cancer care taking our primary focus off of only targeting the tumor

- **Target the Tumor**
  - Chemotherapy
  - Auto HCT
  - Radiation Therapy
  - Surgery
  - Checkpoint Blockade

- **Target the Tumor**
  - Allo HCT
  - Immune Effector Cell Therapy (CART)

- **Target the Host**
  - Immuno-modulators
  - Immune Checkpoint Inhibitors
  - CART
What is immunotherapy
What is Immunotherapy?

Cancer cells should be recognized as non-self and attacked.

A synchronized attack against a tumor requires a complex and rapidly evolving interaction between various immune cell types.

One component of this is the T cell.
What is immunotherapy

Cancer-Immunity Cycle:
T cell should recognize and eradicate cancer cells.

Immune Editing:
The ability of cancer cells to delete or avoid T cell targets

End Result:
The failure of the immune protection via T cell responses

Immunotherapy: Any medication that facilitates activating the immune system by re-exposing/uncovering T cell targets on cancer cells
Outline

Immunotherapy 101

Immune effector cell therapies: CART cell therapy

Immune check point inhibitors

Implications for the critical care community
Chimeric Antigen Receptor T Cell Therapy

- Genetically engineered T cells
- Modified using a virus, to have a chimeric antigen receptor attached
- Chimeric antigen receptor recognizes the (tumor) target
- Mediates T cell activation and co-stimulation
- Results in immune mediated tumor cell destruction
CART: INDICATIONS and EVIDENCE

Refractory B cell ALL (adults and children)
Relapsed or Refractory Diffuse Large B cell Lymphoma
Refractory Follicular Lymphoma
# Outcomes after CART

## Table 1. Responses to CAR T-Cell Therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Response Rate</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B-cell acute lymphoblastic leukemia (in adults)</td>
<td>83–93</td>
<td>High initial remission rates; unresolved issue is whether CAR T-cell therapy is definitive therapy or should be followed by allogeneic hematopoietic stem-cell therapy</td>
<td>Park et al.,\textsuperscript{35} Davila et al.,\textsuperscript{36} Turtle et al.\textsuperscript{37}</td>
</tr>
<tr>
<td>B-cell acute lymphoblastic leukemia (in children)</td>
<td>68–90</td>
<td>Approximately 25% of patients reported to have a relapse with CD19-negative or CD19-low leukemia; CD22 CAR T cells may improve survival among some patients with CD19 relapses</td>
<td>Maude et al.,\textsuperscript{34} Maude et al.,\textsuperscript{38} Fry et al.,\textsuperscript{39} Lee et al.\textsuperscript{40}</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>57–71</td>
<td>Relapse is rare in patients who have a complete response; ibrutinib appears to increase response rates</td>
<td>Porter et al.,\textsuperscript{41} Turtle et al.\textsuperscript{42}</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>64–86</td>
<td>Approximately 40–50% of patients reported to have a durable complete response</td>
<td>Turtle et al.,\textsuperscript{43} Kochenderfer et al.,\textsuperscript{44} Schuster et al.,\textsuperscript{45} Neelapu et al.\textsuperscript{46}</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>71</td>
<td>At a median follow-up of 28.6 mo, the response was maintained in 89% of patients who had a response</td>
<td>Schuster et al.\textsuperscript{45}</td>
</tr>
<tr>
<td>Transformed follicular lymphoma</td>
<td>70–83</td>
<td>A total of 3 of 3 patients with transformed follicular lymphoma had a complete response</td>
<td>Turtle et al.,\textsuperscript{43} Schuster et al.,\textsuperscript{45} Neelapu et al.\textsuperscript{46}</td>
</tr>
</tbody>
</table>
CART: CRITICAL CARE COMPLICATIONS

1. Tumor lysis Syndrome
2. Cytokine release syndrome (CRS)
3. Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)
4. Cytopenias
   - Macrophage Activation Syndrome (MAS)/HLH
5. B cell aplasia and hypogammaglobulinemia
1. Tumor lysis Syndrome
2. Cytokine release syndrome (CRS)
3. Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)
4. Cytopenias
   • Macrophage Activation Syndrome (MAS)/HLH
5. B cell aplasia and hypogammaglobulinemia
Cytokine Release Syndrome

During the process of immune activation, there is an exaggerated proliferation and cytokine release → activates T cells, B cells, NK cells, and macrophages

↑CRP, ferritin, IFN-γ and TNF-α, ILD6, IL10, TNF alpha,
Cytokine Release Syndrome Grading

<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>Fever AND</td>
<td>Temp≥38.0°C</td>
<td>Temp≥38.0°C</td>
<td>Temp≥38.0°C</td>
<td>Temp≥38.0°C</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>None</td>
<td>Requiring low flow nasal cannula or blow-by</td>
<td>Requiring high flow nasal cannula, facemask, nonrebreather, or Venturi mask</td>
<td>Requiring positive pressure (CPAP&lt; BiPAP, IMV)</td>
</tr>
</tbody>
</table>

Increasing Severity of Illness

Typically occurs within the first week (late presentations up to 10 weeks have been described)

Severity increases with larger tumor burden and cell dosing

Gutierrez CCM 2019 in press
60-90% of patient develop CRS, 10-30% severe (grade 3) CRS

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>CD19</td>
<td>CD19</td>
<td>CD19</td>
<td>CD19</td>
<td>CD19</td>
<td>CD19</td>
<td>BCMA</td>
<td>CD19</td>
<td>CD19</td>
</tr>
<tr>
<td>Disease</td>
<td>B-ALL</td>
<td>B-ALL</td>
<td>DLBCL/FL</td>
<td>DLBCL/FL</td>
<td>CLL</td>
<td>B-ALL</td>
<td>MM</td>
<td>MM</td>
<td>B-ALL</td>
</tr>
<tr>
<td>%CRS</td>
<td>77</td>
<td>85</td>
<td>93</td>
<td>57</td>
<td>83</td>
<td>93</td>
<td>50</td>
<td>18</td>
<td>66</td>
</tr>
<tr>
<td>% ≥ grade 3 CRS</td>
<td>46</td>
<td>26</td>
<td>13</td>
<td>18</td>
<td>8</td>
<td>23</td>
<td>17</td>
<td>9</td>
<td>32</td>
</tr>
</tbody>
</table>

Low attributable deaths as this is reversible but mortality is incompletely defined in the real world outside of clinical trials.
Mainstay's of treatment: Tocilizumab (IL6 receptor inhibitor), Corticosteroids

**Grade 1 CRS**
Monitor on wards Supportive care-treatment with antipyretic, hydration, microbiologic cultures, imaging to rule out infectious cause, empiric antibiotics

- **Persistence of Grade 1 symptoms**
  - Continue monitoring and supportive care

- **Deterioration**
- **Resolution of Grade 1 symptoms**
  - Continue monitoring

**Grade 2 CRS**
Increase monitoring of vital signs
Consider ICU admission if high risk patient

- **Persistence of Grade 2 symptoms**
  - Repeat Tocilizumab (maximum of 3 doses)
- **Deterioration**

**Grade 3 CRS**
Admit to the ICU for hemodynamic monitoring and supportive interventions, arterial and central venous catheterization
Continue Tocilizumab (8 mg/kg) q6h (maximum of 3 total doses)
Corticosteroids: dexamethasone 10 mg-20 mg IV q6h or equivalent dosing

- **Persistence of Grade 3 symptoms**
  - Repeat anti-IL6 treatment (tocilizumab maximum of 3 doses) and corticosteroids
  - Consider increased dose of corticosteroids if patient shows no signs of improvement
- **Deterioration**

**Grade 4 CRS**
ICU admission and supportive ICU care for organ failure
Anti-IL 6 treatment: Tocilizumab (maximum 3 doses) or anakinra or siltuximab, plus Methylprednisolone Pulse 1 gm

- **Persistence of Grade 4 symptoms**
  - Consider siltuximab or anakinra (anti IL-1 receptor antagonist)
- **Deterioration**

- **Improvement of symptoms to Grade 2 or less for 24-48h**
  - Consider rapid steroid taper
  - Monitor for signs of deterioration

- **Improvement of symptoms to Grade 2 or less for 24-48h**
  - Consider slow steroid taper
  - Monitor for signs of deterioration

*proposed algorithm, timing of tocilizumab and admission to ICU may vary between institutions depending upon resources, Gutierrez CCM 2019 in press*
CART: Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

Acute (concurrent with CRS)

Delayed (days to weeks without CRS)

Pathophysiology? Cytokines in the brain vs. trafficking of CARs across BBB

40-60% of patients; 20-30% severe

Symptoms: tremors, headache, mild aphasia, confusion, dysgraphia → status epilepticus, paresis and cerebral edema

Usually reversible but can be life-threatening

Gutierrez CCM 2018
## CART: Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorientation(^b)</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Dysgraphia(^b)</td>
<td>Present</td>
<td>Present</td>
<td>Limited assessment</td>
<td>Limited assessment</td>
</tr>
<tr>
<td>Aphasia(^b)</td>
<td>Word finding difficulty</td>
<td>Moderate aphasia</td>
<td>Severe global aphasia</td>
<td>Severe global aphasia</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>Mild tremor</td>
<td>Intermittent facial twitching, tremors, or myoclonus</td>
<td>Continuous facial twitching and myoclonus</td>
<td>Continuous facial twitching and myoclonus requiring airway protection</td>
</tr>
<tr>
<td>Attention and consciousness(^b)</td>
<td>Inattentive or mild delirium</td>
<td>Lethargic or moderate delirium</td>
<td>Obtundation/stupor or severe delirium</td>
<td>Coma or severe delirium requiring airway protection</td>
</tr>
<tr>
<td>Seizure</td>
<td>None</td>
<td>None</td>
<td>Partial seizures, nonconvulsive or convulsive seizures</td>
<td>Convulsive or nonconvulsive status epilepticus</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>None</td>
<td>None</td>
<td>Grades 1–2 papilledema and associated headache, nausea, and vomiting</td>
<td>Grades 3–5 papilledema, or clinical signs of herniation such as Cushing’s triad, posturing, cranial nerve VI palsy, and diabetes insipidus</td>
</tr>
<tr>
<td>Motor strength</td>
<td>5/5</td>
<td>5/5</td>
<td>3–4/5</td>
<td>0–2/5</td>
</tr>
</tbody>
</table>
# CART: Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) Treatment

<table>
<thead>
<tr>
<th>Supportive Care</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work up and monitoring</td>
<td>Monitored Setting Work up cause of encephalopathy (imaging, delirium work up)</td>
<td>Monitored Setting Work up cause of encephalopathy (imaging, delirium work up)</td>
<td>Consider transfer to ICU Monitored Setting Work up cause of encephalopathy (imaging, delirium work up) Treat seizures with benzodiazepines, levetiracetam or other AED, *previously some programs prophylactically treated with levetiracetam</td>
<td>Consider transfer to ICU Monitored Setting Work up cause of encephalopathy (imaging, delirium work up) Treat seizures with benzodiazepines, levetiracetam or other AED</td>
</tr>
<tr>
<td>Treatment</td>
<td>Close monitoring for progression</td>
<td>Consider corticosteroids if symptoms are persistent</td>
<td>Corticosteroids: dexamethasone 10mg IV q6 hr or equivalent to methylprednisolone</td>
<td>Consider high dose corticosteroids (methylprednisolone IV 1 g/day) Consider cyclophosphamide or other immunosuppressive agents</td>
</tr>
</tbody>
</table>

- **Adopt an evaluation tool to identify subtle signs of neurotoxicity (CARTOX)**
- **Utility of tocilizumab is only in the setting where it is associated with CRS, otherwise, IL-6 blockade does not seem to work**

Neelapu Nat Rev Clin Onc 2018; Gutierrez CCM 2019 in press
Outline

Immunotherapy 101

Immune effector cell therapies

Immune check point inhibitors

Implications for the critical care community
3 Classes of Immune Check Point Inhibitors

T cell binds to abnormal protein on tumor cell

If PD-1 binds PD-L1, T cell ignores tumor cell

PD1 is an inhibitor receptor on T cells
Binds to PD-L1 expressed on many cell types (including tumors)

When PD-1:PDL1 interaction:
• T cell no longer sees the tumor cell
  • Prevents tumor apoptosis
  • Promotes T cell exhaustion
**PD-1 inhibitors** – blocks PD-1 & PD-L1 binding, T cell recognition of cancer cell

**PDL1 inhibitors** - blocks PD-1 & PD-L1 binding, T cell recognition of cancer cell

**CTLA-4 checkpoint** that prevents dendritic cells from activating T cells

**CTLA-4 inhibitors** - Enables dendritic cells to activate T cells
### Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Non–small-cell lung cancer, urothelial carcinoma</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Merkel-cell carcinoma, urothelial carcinoma</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>Urothelial carcinoma</td>
</tr>
</tbody>
</table>

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.
Overall Survival Metastatic Melanoma
1-year OS Phase III Studies

1990
25–35%

2010
2011
2012
2013
2014
2015
2016

24%
29% Ipi
45% Dab
53% Dab + Tram
42% Nivo (Ph I)
42% Nivo (Ph I)

29% Ipi
58% Nivo
58% Nivo
58% Nivo
58% Nivo

46%
47%
56%
70%
71%

71% Pembro
74% Dab + Tram
75% Vem + Cobi
75% Vem + Cobi
75% Vem + Cobi

73% Nivo+Ipi (Ph II)
73% Nivo+Ipi (Ph II)
73% Nivo+Ipi (Ph II)
73% Nivo+Ipi (Ph II)
73% Nivo+Ipi (Ph II)

15%
15% 2-year OS
22% Ipi
18% Ipi

3-year OS
3-year OS

5-year OS
5-year OS

PRESENTED AT: ASCO ANNUAL MEETING '16
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Presented by Georgina V. Long
ICI Adverse Events: On Target but Off Tumor Effects

Encephalitis, aseptic meningitis
Hypophysitis
Uveitis
Dry mouth, mucositis
Thyroiditis, hypothyroidism, hyperthyroidism
Rash, vitiligo
Pneumonitis
Thrombocytopenia, anemia
Hepatitis
Myocarditis
Pancreatitis, autoimmune diabetes
Adrenal insufficiency
Nephritis
Colitis
Vasculitis
Enteritis
Arthralgia
Neuropathy
# ICI: Critical Care Toxicities

## Pulmonary

| Incidence       | All grades: 2-10%  
                   | Grade 3-4: 2-9%    |
|-----------------|-------------------|
| Risk Factors    | PD1/PDL1, combination |
| Time to Onset   | 2-3 months (May be earlier with dual) |
| Work Up         | Non-specific AHRF  
                   | Work up (CXR, CT, FOB, cultures) |
| Management      | Hold ICI  
                   | Corticosteroids grade ≥ 2 (P 1-2mg/kg/d)  
                   | Corticosteroids grade ≥ 3 (MP 1-2mg/kg/d) |
|                 | Consider escalation to additional immunosuppressants if worsening or not improving by 48 hours (infliximab, cyclophosphamide, IVIG, MMF) |
| Mortality       | ?14% if severe    |

## Neuro

# ICI: Critical Care Toxicities

## Neuro

| Incidence | All grades: 1-14%  
| Grade 3 or 4: 1-2% |
| Risk Factors | PD1/PDL1, combination |
| Time to Onset | Can present within 1 week |
| Work Up | Non-specific neurologic changes (ocular/mild weakness-unilateral/bilateral weakness, GBS, MG, aseptic meningitis)  
| Work up (CT, cultures. Consider LP) |
| Management | Hold ICI  
| If Grade 3-4 consider corticosteroids  
| Consider IVIG or plasmapheresis (if MG/GBS pattern)  
| If myositis present, consider rituximab or infliximab |

## Pulmonary

Outline

Immunotherapy 101

Immune effector cell therapies

Immune check point inhibitors

Implications
Implications and Considerations of Cancer Therapy-Critical Care Toxicities
Implications and Considerations for the Patient

1. Does the presence of CRS or ICI toxicity imply better anti-tumor effects? (Unclear, those who do not develop severe toxicities do demonstrate good response)

2. Does the administration of corticosteroids blunt the effectiveness of the therapy? (Currently debated but no evidence of this, since timing of corticosteroid durations not defined, we try to rapidly taper for CRS, slower tapers may be needed for ICI)

3. If my patient presents with grade 4 ICI pulmonary toxicity, is it correct to assume they will never be eligible for the drug again and should be palliated?
   (No – but speak to pt/family/oncologist/palliative care)
   Treatment may still be effective even if it needs to stop (ICI)
   70% of those with dual ICI’s stopped due to AEs received a response
   Safety of re-treatment or changing classes likely depends on severity of AE
Implications for Critical Care

Oncology will see a surge in patients receiving CART/ICI and the Critical Care community will need to be prepared for the volume of associated toxicities.
Implications for Critical Care:

It is imperative that we **liaise with our Oncology colleagues** to ensure we understand best case/worse case scenario prognosis in these patients (as well as palliative care where appropriate).

There were more than 60 new therapeutic indications approved in 2018 in hematologic oncology alone!
Implications for health care system

What is the impact of critical illness on their disease trajectory? Ongoing cancer care?

What are their patient–centered outcomes and symptom burden following critical illness

What is the health care resource utilization associated with these medications?
Implications for health care system

Price Tag CART construct: $475,000 US

(Price does not include cost of inpatient care, lymphodepleting chemotherapy, toxicity management, critical care admission etc)
In Conclusion

• New era of immuno-oncology requires intensivists to become familiar with treatment related toxicities

• Most of these toxicities are time limited and reversible

• Need to maintain a high index of suspicion of alternative causes of critical illness (ie. sepsis)

• Institution specific guidelines should be established if commencing a CART program

• There are many important questions that remain surrounding interaction between critical care and CART/ICI therapies
“Today in oncology, serious illness in cancer patients no longer means end of life”
Thank you,

Acknowledgements:
Colleen McEvoy, MD, Washington University
Michael Detsky, MD, University of Toronto

Laveena.munshi@sinahealthsystem.ca
@laveenamunshi
Neurotoxicity

➢ confusion
➢ word-finding difficulty
➢ aphasia
➢ paresis, cranial nerve palsies

vascular leakage with pulmonary edema

coagulopathy and DIC

DIC

vascular leakage with pulmonary edema

Any CTCAE grade 3 toxicity, grade 4 transaminases

Seizures

Fever

Fatigue, headache

Arthralgia, rigor

Nausea, vomiting

Tachypnea

Hypotension (responding to fluids or low dose vasopressor)

Hypoxia

Diagnostic features

Pancytopenia

Acute kidney injury

CRP >150-200 mg/dl

Ferritin (>10,000 mg/l)

Troponin elevations

stress cardiomyopathy

QTc prolongation

Prolonged aPTT

Hypofibrinogenemia

Troponin elevations

stress cardiomyopathy

QTc prolongation

Prolonged aPTT

Hypofibrinogenemia

Any CTCAE grade 4 lab finding

EEG

Grade 1

Grade 2

Grade 3

Grade 4

Therapeutic approach

Symptomatic support
➢ Fluids
➢ Antipyretics

Anti-infective therapy

Oxygen supply (< 40% FiO2)

Low dose vasopressors

(< 1000ug/h norepinephrine equivalent)

Tocilizumab
➢ 4-8 mg/kg BW, max. 800 mg/day
➢ Insufficient response: repeat once after 24-72 hrs

Oxygen supply (< 40% FiO2)

High dose vasopressors

(> 1000ug/h Norepinephrine equivalent)

Mechanical ventilation

Methylprednisolone
➢ 2 mg/kg BW

If refractory consider
➢ TNF-α blocker, anakinra
➢ Siltuximab
➢ Cyclophosphamide
➢ ATG, alemtuzumab

Differential diagnosis

Anaphylactic Reaction
➢ Prior exposure?
➢ Response to antihistamines?

Tumor lysis syndrome (TLS)
➢ hyperuricemia, hyperkalemia
➢ hyperphosphatemia, hypocalcemia

Sepsis
➢ Positive blood cultures, X-ray etc.
➢ Response to anti-infective therapy?

MAS/HLH
➢ family history of MAS/HLH?
➢ genetic aberrations associated with HLH/MAS (PRF1, STX11, STXB2, MUNC13-4)?
<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.
CARTOX 10

Orientation: year, month, city, hospital, prime minister (5 points)
Name 3 objects (3 points)
Writing of sentence (1 point)
Count backwards from 100 by 10 (1 point)
Recently Approved CART therapies in Canada

Tisagenlecleucel (Kymriah®) for multiply relapsed or refractory B-cell ALL & adults with relapsed or refractory large B-cell lymphoma

Axicabtagene ciloleucel (Yescarta®): adults with relapsed or refractory large B-cell lymphoma

Kymriah, a CD19-directed genetically modified autologous T-cell immunocellular therapy, is approved to treat two life-threatening cancers that have limited treatment options and historically poor outcomes, demonstrating the critical need for new therapies for these patients.
BETWEEN BEDSIDE AND BENCH

The sepsis seesaw

Adapted from Hotchkiss et al., Nat Med 2009

Adapted from Pedersen BK & Febbraio MA Physiol Rev 2008