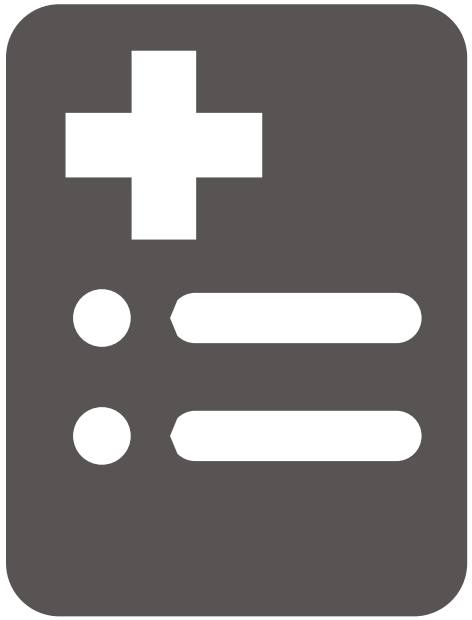
CAR T Case Simulator

Bristol Myers Squibb™

Melissa: Patient History

Patient History

- 60-year-old black woman
- Married, retired
- Refractory disease after treatment with 3 other classes of therapy
- Eligible for CAR T therapy based on evaluation by her oncology team



Eligibility Criteria for CAR T Cell Therapy

General eligibility requirements for CAR T cell therapy[1,2]

- Adequate numbers of T cells for collection
- No active, uncontrolled infections, including hepatitis B, hepatitis C, or HIV
- Adequate performance status and organ function
- Absence of clinically relevant comorbidities (eg, select cardiovascular, neurologic, or immune disorders)

Precise criteria for eligibility vary by:[1]

- Malignancy
- Treatment regimen or protocol
- CAR T cell product

HIV, human immunodeficiency virus.

References: 1. Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. 2018. **2.** Beaupierre A et al. *Clin J Oncol Nurs*. 2019;23:27-34.

Melissa: Pre-infusion

Leukapheresis

- Completed without incident and cells sent to manufacturer

Bridging Therapy

- Completed 16 days prior to lymphodepleting chemotherapy

Lymphodepleting (LD) Chemotherapy

- Fludarabine + cyclophosphamide over 3 days

Management Question 1

A couple of days before Melissa is scheduled to receive lymphodepleting chemotherapy, she tests positive for an active infection. What should happen next?

A. Proceed with LD chemo as planned

B. Delay LD chemo until the infection has been treated or resolved

LD, lymphodepleting.

Management Question 1

A couple of days before Melissa is scheduled to receive lymphodepleting chemotherapy, she tests positive for an active infection. What should happen next?

A. Proceed with LD chemo as planned

B. Delay LD chemo until the infection has been treated or resolved

Correct answer:
B. Delay LD chemo until the infection has been treated or resolved

LD, lymphodepleting.

Delivery of Lymphodepleting Chemo

- Patients are treated with LD chemo several days before CAR T cells are infused[1]
- Coordinated by the treating facility, and can be delivered in the inpatient or outpatient setting[2]
- **Active infection must be excluded or under control prior to the start of LD chemo[3]**

Patients should have a caregiver that meets certain expectations[2]

Expectations for Caregivers During LD Chemo[2]

- Be at least 18 years old
- Be able to drive
- Stay with the patient 24 hours/day in the outpatient setting
- Live with the patient at a place within safe proximity of the treating facility
- Transport patient to/from appointments
- Actively engage with the medical team
- Manage and administer the patient's medications
- Practice good home precautions
- Contact the medical team with any questions or regarding any symptoms or adverse events

LD, lymphodepleting.

References: 1. Perica K et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141. **2.** Beaupierre A et al. *Clin J Oncol Nurs*. 2019;23:27-34. **3.** Yakoub-Agha I et al. *Haematologica*. 2020;105(2):297-316.

Melissa: CAR T Cell Infusion

Leukapheresis

- Completed without incident and cells sent to manufacturer

Bridging Therapy

- Completed 16 days prior to lymphodepleting chemotherapy

Lymphodepleting Chemotherapy

- Fludarabine + cyclophosphamide over 3 days

CAR T cell Infusion

- Infection cleared
- CAR T cells infused (Day 1)
- Patient was monitored with no signs of acute reactions

Melissa: Acute Toxicities

18 Hours

- Fever (39.5ºC or 103.1ºF) + rigors
- No hypotension or hypoxia

Management Question 2

Given Melissa's signs and symptoms, which of the following is the most important next step (of the options listed)?

A. Workup for CRS

B. Workup for neurologic toxicity

C. Workup for hypogammaglobulinemia

D. Both B and C

CRS, cytokine release syndrome.

Management Question 2

Given Melissa's signs and symptoms, which of the following is the most important next step (of the options listed)?

A. **Workup for CRS**

B. Workup for neurologic toxicity

C. Workup for hypogammaglobulinemia

D. Both B and C

Correct answer:
A. Workup for CRS

CRS, cytokine release syndrome.

CRS Clinical Presentation

- Not all patients will develop CRS, but when it occurs the severity can range from mild to life-threatening or fatal[1]
  - Severity may but does not always correlate with disease burden[2]
- Typical onset is within 1 to 5 days, but varies[1]
  - Time-to-onset can be delayed and can present beyond 14 days[3]

The first symptom is typically fever, which can be high grade (>40°C or >104°F)[1]

- Additional signs and symptoms may include respiratory distress,[1] hypotension,[1] tachycardia[2] and neurologic symptoms[1]
- Although fever is a key indicator of CRS, other AEs, such as infection, should also be assessed and ruled out when fever arises

AE, adverse event; CRS, cytokine release syndrome.

References: 1. Oluwole OO, Davila ML. *J Leukoc Biol*. 2016;100:1265-1272. **2.** June CH et al. *Science*. 2018;359:1361-1365. 3. Lee DW et al. Biol Blood Marrow *Transplant*. 2019;25:625-638.

CRS Recognition

The importance of timely recognition of CRS cannot be overstated given the potential for mortality. Note that CRS and neurologic toxicity can occur simultaneously[1,2]

Routine Monitoring

- Vital signs (temperature, O_2 saturation, etc)[1]
- Review of systems and physical exam[1]
  - Focus on cardiovascular, pulmonary, and neurologic systems
  - Survey for occult infection
- Laboratory monitoring of inflammatory markers[1,2]
  - CRP
  - Cytokines*
  - Ferritin
  - LDH

Focused Assessment Based on Symptoms

- **Fever[1]**
  - **Blood and urine culture**
  - **Targeted imaging to assess for potential sources of infection**
- Tachycardia[1]
  - Electrocardiogram to assess for arrhythmia
- Hypotension/persistent tachycardia[1]
  - Echocardiogram to assess for decreased ejection fraction

*May be sent out for testing.
CRP, C-reactive protein; CRS, cytokine release syndrome; LDH, lactate dehydrogenase.

References: 1. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019:34:45-55. **2.** Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Management Question 3

Using ASTCT guidelines, how would you manage Melissa's side effects given their severity?

A. Watch and wait

B. Basic supportive care (eg, antipyretics)

C. Tocilizumab

D. Corticosteroids

E. Tocilizumab + corticosteroids

ASTCT, American Society for Transplantation and Cellular Therapy.

Management Question 3

Using ASTCT guidelines, how would you manage Melissa's side effects given their severity?

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B. Basic supportive care (eg, antipyretics)

C. Tocilizumab

D. Corticosteroids

E. Tocilizumab + corticosteroids

Correct answer:
B. Basic supportive care (eg, antipyretics)

ASTCT, American Society for Transplantation and Cellular Therapy.

ASTCT Consensus Grading for CRS Associated With CAR T Cell Therapy

Definition

"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"

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

The patient currently has grade 1 CRS in accord with the American Society for Transplantation and Cellular Therapy (ASTCT) CRS grading system.

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome.

Reference: 1. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

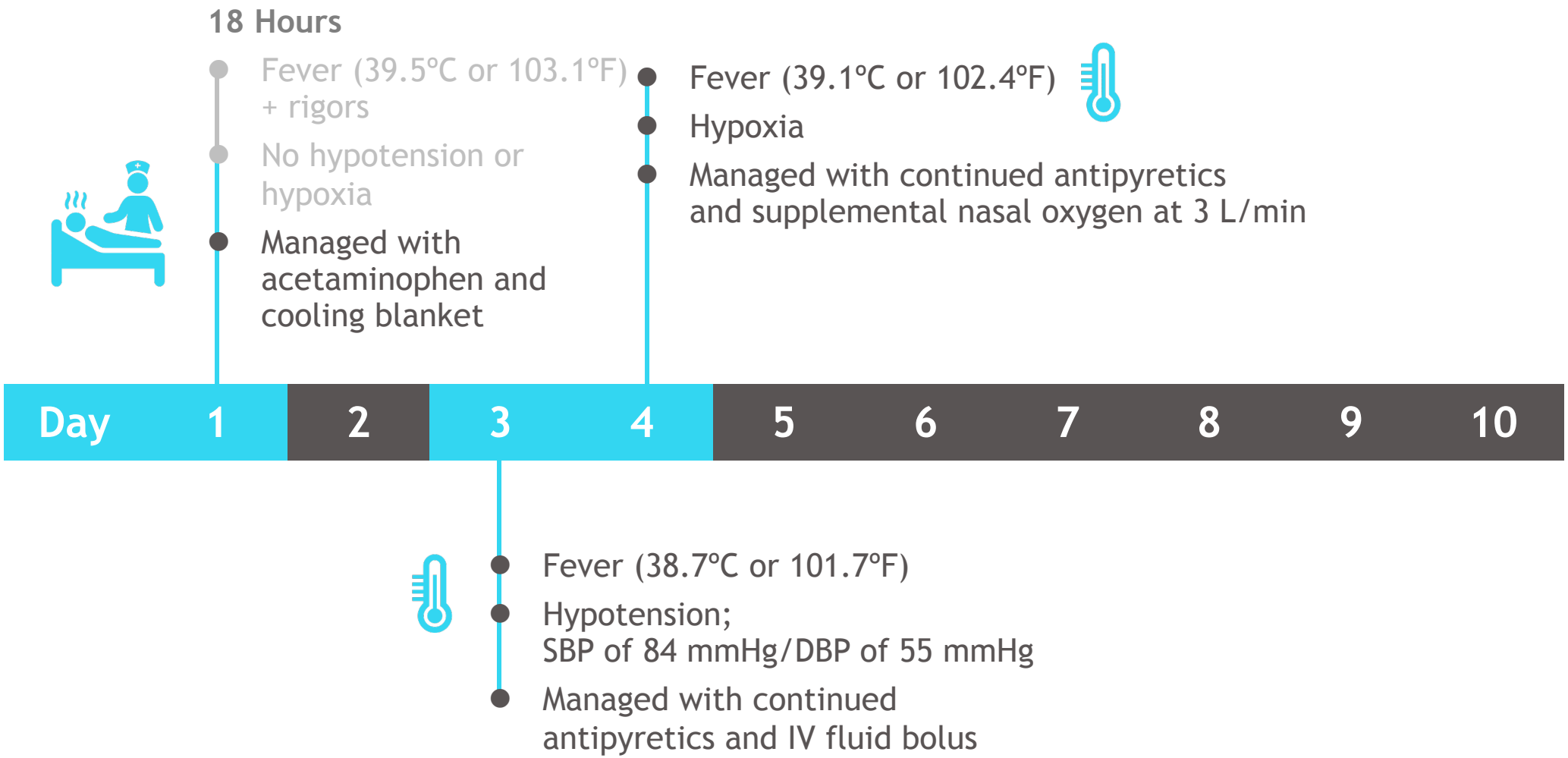
Management of CRS According to ASTCT Grade

Grade 1	Grade 2	Grade 3	Grade 4
• **Antipyretics and IV hydration**	• Supportive care as for grade 1	• Supportive care as in grade 1	• Supportive care as in grade 1
• Diagnostic work-up to exclude infection	• IV fluid boluses and/or supplemental oxygen	• Vasopressor support and/or supplemental oxygen	• Vasopressor support and/or supplemental oxygen via positive pressure ventilation
• Growth factors and antibiotics if neutropenic (optional)	• Tocilizumab ± dexamethasone (or methylprednisolone equivalent)	• Tocilizumab + dexamethasone 10-20 mg IV q6h (or methylprednisolone equivalent)	• Tocilizumab + methylprednisolone 1000 mg/day
		• Consider ICU monitoring (optional)	• ICU monitoring

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICU intensive care unit; IV, intravenous; q6h, every 6 hours

Reference: 1. Neelapu SS. *Hematol Oncol*. 2019;37(S1):48-52.

Melissa: Acute Toxicities



DBP, diastolic blood pressure; IV, intravenous; SBP, systolic blood pressure

Management Question 4

According to ASTCT guidelines, should tocilizumab also be administered on Days 3 and 4 to manage hypotension and hypoxia, or are IV fluid bolus and supplemental oxygen sufficient?

A. Tocilizumab should also be administered

B. IV fluid bolus and supplemental oxygen are sufficient

ASTCT, American Society for Transplantation and Cellular Therapy; IV, intravenous.

Management Question 4

According to ASTCT guidelines, should tocilizumab also be administered on Days 3 and 4 to manage hypotension and hypoxia, or are IV fluid bolus and supplemental oxygen sufficient?

A. **Tocilizumab should also be administered**

B. IV fluid bolus and supplemental oxygen are sufficient

Correct answer:
A. Tocilizumab should also be administered

ASTCT, American Society for Transplantation and Cellular Therapy; IV, intravenous.

ASTCT Consensus Grading for CRS Associated With CAR T Cell Therapy

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And/or hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

The patient now has grade 2 CRS in accord with the American Society for Transplantation and Cellular Therapy (ASTCT) CRS grading system

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome.

Reference: 1. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Management of CRS According to ASTCT Grade

Grade 1	Grade 2	Grade 3	Grade 4
• Antipyretics and IV hydration	• Supportive care as for grade 1	• Supportive care as in grade 1	• Supportive care as in grade 1
• Diagnostic work-up to exclude infection	• IV fluid boluses and/or supplemental oxygen	• Vasopressor support and/or supplemental oxygen	• Vasopressor support and/or supplemental oxygen via positive pressure ventilation
• Growth factors and antibiotics if neutropenic (optional)	• **Tocilizumab ± dexamethasone (or methylprednisolone equivalent)**	• Tocilizumab + dexamethasone 10-20 mg IV q6h (or methylprednisolone equivalent)	• Tocilizumab + methylprednisolone 1000 mg/day
		• Consider ICU monitoring (optional)	• ICU monitoring

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICU intensive care unit; IV, intravenous; q6h, every 6 hours

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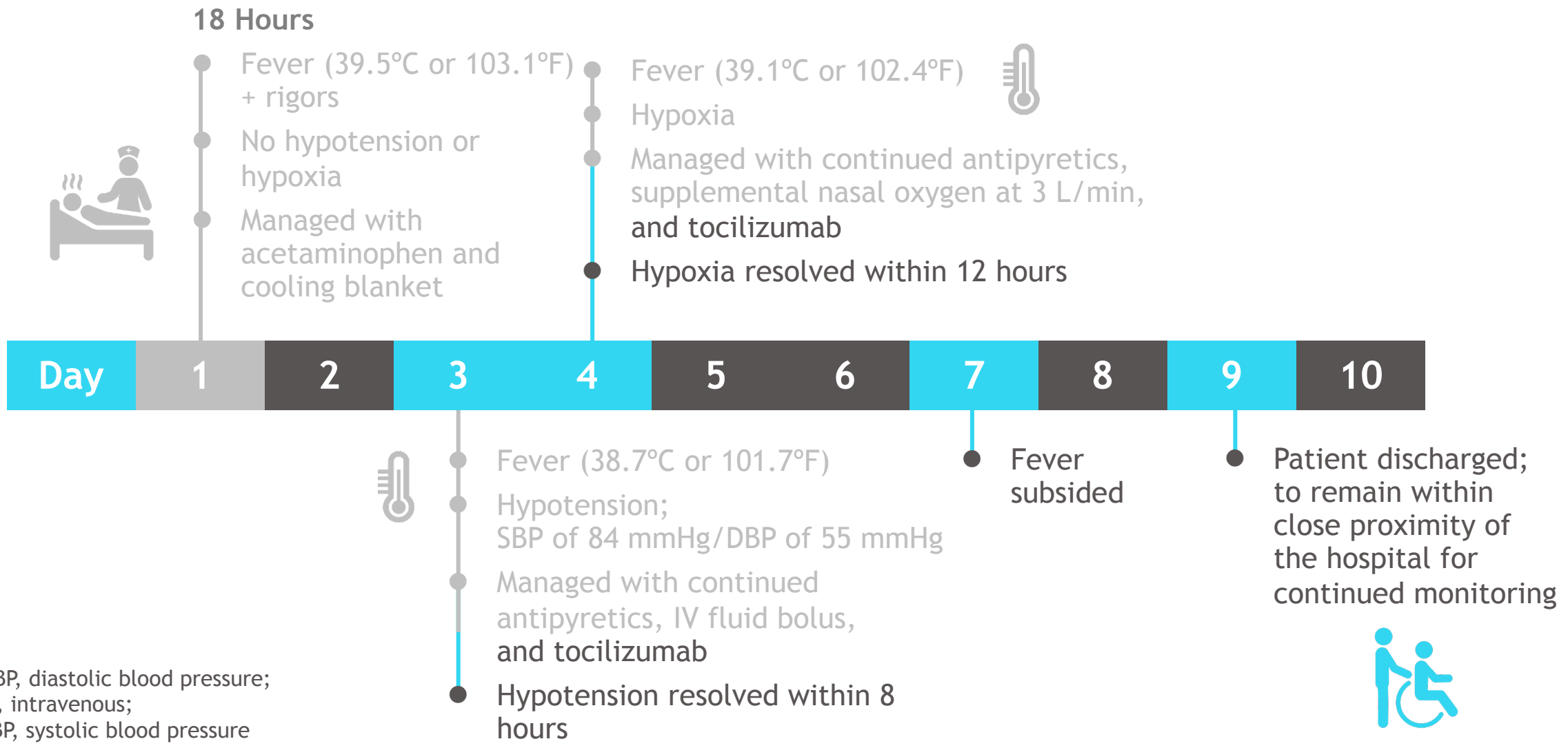
Melissa: Acute Toxicities



DBP, diastolic blood pressure;
IV, intravenous;
SBP, systolic blood pressure

Management Question 5

Melissa is being discharged. How long must she stay within close proximity of the treatment center?

A. 4 days

B. 2 weeks

C. At least 4 weeks

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A. 4 days

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C. At least 4 weeks

Correct answer:
C. At least 4 weeks

Inpatient vs Outpatient Post-infusion Monitoring

The practice of inpatient versus outpatient monitoring varies, depending on institutional guidelines and CAR T cell products[1]

- **Patients must remain within close proximity to the treatment center for at least 4 weeks to have quick access to care, regardless of whether patient received CAR T infusion inpatient or outpatient[2]**
- Depending on the patient, product, and center, inpatient administration and monitoring may be required for a period of time[1,3]
- Under certain circumstances, outpatient administration and monitoring may be appropriate[1]
  - When this occurs, patients are usually observed in the treating center for a few hours to monitor for acute reactions; if none occur, they are permitted to leave the treatment center[4]
  - Hospitalization is necessary if toxicities develop[4]

References: 1. Brudno JN, Kochenderfer JN. *Blood* Rev. 2019:34:45-55. **2.** Taylor L et al. *Clin J Onc Nurs*. 2019;23(2):20-26. **3.** Neelapu SS et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62. **4.** Maus MV, Levine BL. *Oncologist*. 2016;21:608-617.

Melissa: Response and Post-infusion Toxicities

After she is discharged, Melissa experiences no symptoms for a few days. At day 14 post-infusion, she starts to experience tremors and confusion.

Workup for Neurotoxicity:

- ICE score: 5 points
- No signs of seizure or depressed level of consciousness
- No deep focal motor weakness detected
- No edema detected on neuroimaging

Melissa shows no signs of concurrent CRS.

CRS, cytokine release syndrome; ICE, Immune Effector Cell-Associated Encephalopathy.

Management Question 6

According to ASTCT recommendations, which option may be used to manage Melissa's neurotoxicity?

A. Antiepileptic medication

B. Tocilizumab

C. Systemic corticosteroids

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B. Tocilizumab

C. Systemic corticosteroids

Correct answer:
C. Systemic corticosteroids

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ICE Scoring Is Used in the ASTCT Consensus Grading for Neurologic Toxicity

Using the 10-point Immune Effector Cell-Associated Encephalopathy (ICE) Screening Tool, cognitive function is assessed across 5 domains for a maximum possible score of 10 points

Domain	Definition	Points
Orientation	Orientation to: year, month, city, hospital	4 total (1 point for each item)
Naming	Ability to name 3 objects (eg, point to clock, pen, button)	3 total (1 point for each item)
Following commands	Ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1
Writing	Ability to write a standard sentence (eg, "Our national bird is the bald eagle")	1
Attention	Ability to count backwards from 100 by 10	1

ASTCT, American Society for Transplantation and Cellular Therapy

References: 1. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

ASTCT Consensus Grading for Neurologic Toxicity Is Based on Several Factors

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous/repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness (eg, hemiparesis or paraparesis)
Elevated ICP / cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

The final neurotoxicity grade is determined by the most severe event across the different domains

ASTCT, American Society for Transplantation and Cellular Therapy; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; N/A, not applicable.

Reference: 1. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Management of Neurologic Toxicity According to ASTCT ICANS Grade

Grade 1	Grade 2	Grade 3	Grade 4
• Aspiration precautions and IV hydration • Seizure prophylaxis with levetiracetam • EEG • Brain imaging • Consider tocilizumab if there is concurrent CRS	• Supportive care as in grade 1 • **Dexamethasone or methylprednisolone equivalent (optional)**	• Supportive care as in grade 1 • Dexamethasone 10-20 mg IV q6h (or methylprednisolone equivalent) • Seizure control with benzodiazepines (short-term) and levetiracetam ± phenobarbital and/or lacosamide • High-dose methylprednisolone 1000 mg/day for focal/local edema	• Supportive care as in grade 1 • High-dose methylprednisolone 1000 mg/day • Seizure control with benzodiazepines (short-term) and levetiracetam ± phenobarbital and/or lacosamide • Spine imaging for focal motor weakness • Lower ICP by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema

ASTCT, American Society for Transplantation and Cellular Therapy; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICP, intracranial pressure; q6h, every 6 hours

Reference: 1. Neelapu SS. *Hematol Oncol*. 2019;37(S1):48-52.

Melissa: Response and Post-infusion Toxicities

Response

- Day 30: CR
- Month 6: CR
- Follow-up ongoing

Adverse Events Following Infusion

- 14 days post-infusion
  - Tremors and confusion
  - Resolved following management
- 28 days post-infusion
  - ANC: 700/µL
- Month 4 post-infusion
  - Rhinovirus

Note: This patient case serves as an example, and results with CAR T cell therapy will vary.

ANC, absolute neutrophil count; CR, complete response.

Management Question 7

Melissa's IgG level was 360 mg/dL at her fourth monthly evaluation. What type of care should be considered?

A. Intravenous IgG infusions

B. Growth factors

C. No treatment needed

IgG, immunoglobulin G.

Management Question 7

Melissa's IgG level was 360 mg/dL at her fourth monthly evaluation. What type of care should be considered?

A. **Intravenous IgG infusions**

B. Growth factors

C. No treatment needed

Correct answer:
A. Intravenous IgG infusions

IgG, immunoglobulin G.

Hypogammaglobulinemia

Understanding the Risk

- B cells produce antibodies that recognize foreign antigens and protect against infection[1]
- CAR T cells can kill healthy B cells in addition to malignant B cells (on-target, off-tumor effect)[1]
- This activity can lead to B-cell aplasia, chronic immunodeficiency, and hypogammaglobulinemia (IgG <400 mg/dL)[1]
- Two studies have suggested that ~25%-75% of patients have hypogammaglobulinemia at 30 days postinfusion, up to day 90 and beyond[2,3]
- B-cell aplasia and hypogammaglobulinemia can last months to years after treatment and predispose patients to infection[1,5]

Monitoring and Follow-up Care

- Check IgG levels monthly[4]
- **Consider monthly immunoglobulin infusions for patients who develop frequent infections, especially those with IgG <400 mg/dL[1]**
- **Given how long this complication can last, IgG replacement may be necessary[1]**

Note: Institutional and product guidelines may vary.[1]

IgG, immunoglobulin G.

References: 1. Buitrago J et al. *Clin J Onc Nurs*. 2019;23(2):42-48. **2.** Hill JA et al. *Blood*. 2018;131(1):121-130. **3.** Cordeiro A et al. *Biol Blood Marrow Transplant*. 2020;26(1):26-33. **4.** Callahan C et al. *Clin J Onc Nurs*. 2019;23(2):35-41. **5.** Beaupierre A et al. *Clin J Oncol Nurs*. 2019;23(2):27-34.

Key Points

- Patients may be considered for CAR T cell therapy if they have adequate T cell count, no active/uncontrolled infections, sufficient performance status and organ function, and no clinically relevant comorbidities
  - Exact criteria may also vary based on the malignancy, treatment, and CAR T cell product
- Following CAR T cell administration, CRS is a serious, potentially life-threatening toxicity that requires careful monitoring, along with neurologic toxicity
- Several long-term toxicities may be associated with CAR T cell therapy, including cytopenias, infections, hypogammaglobulinemia, and others, which require periodic long-term monitoring
  - Severe cytopenias may be treated with transfusion and/or growth factor support, when appropriate

CRS, cytokine release syndrome.

Thank you for completing this module of CAR T Academy

We hope you found it informative and educational

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