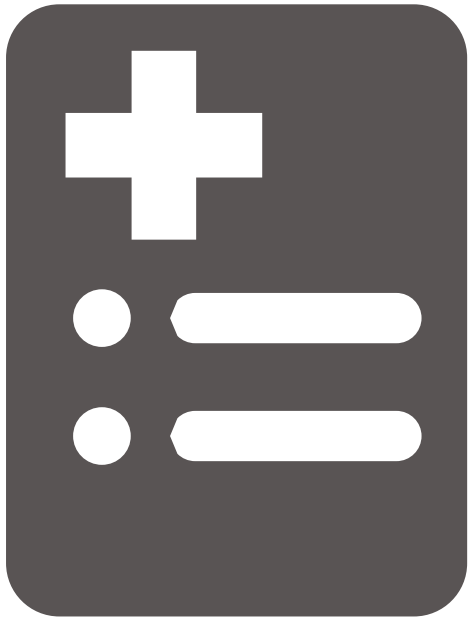
CAR T Cell Therapy Case Simulator

Bristol Myers Squibb™

Melissa[a]: Patient History

Patient History

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



[a]Hypothetical patient case.

Eligibility Criteria for CAR T Cell Therapy

General eligibility requirements for CAR T cell therapy[1-3]

- Have a disease as defined in commercial indication or in clinical trial
- Adequate numbers of T cells
- 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. **3.** Taylor L, et al. *Clin J Oncol Nurs.* 2019;23:20-26

Melissa[a]: 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

[a]Hypothetical patient case.
LD, lymphodepleting.

Management Question 1

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

A. Proceed with LD chemotherapy as planned

B. Delay LD chemotherapy 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 chemotherapy as planned

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

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

Delivery of Lymphodepleting Chemotherapy

- Patients are treated with LD chemotherapy 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 chemotherapy[3]**

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

Expectations for Caregivers During LD Chemotherapy[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
- Contact the medical team with any questions or regarding any symptoms or adverse events

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[a]: 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 over the next several hours with no signs of acute reactions

[a]Hypothetical patient case.

Melissa: Acute Toxicities

18 hours after CAR T cell infusion

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

Day	1	2	3	4	5	6	7	8	9	10

Management Question 2

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

A. Workup for cytokine release syndrome (CRS)

B. Workup for infection

C. Workup for neurotoxicity

D. Both A and B

Management Question 2

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

A. Workup for cytokine release syndrome (CRS)

B. Workup for infection

C. Workup for neurotoxicity

D. Both A and B

Correct answer:
D. Both A and B – workup for both CRS and infection

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.

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 to assess possible infections**
  - **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; 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.

CRS Grading Scales: Lee, ASTCT, Penn, and CARTOX

The patient currently has **grade 1** CRS in accord with **Lee, ASTCT, Penn, and CARTOX criteria**

Grade	Lee Criteria[1]	ASTCT Criteria[2]	Penn Criteria[3]	CARTOX Criteria[4]
1	Symptoms are not life threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgias, malaise)	Fever (≥ 38°C)[b]	• Mild reaction: treated with supportive care such as antipyretics, antiemetics	• Temperature ≥38 °C and/or grade 1 organ toxicity[d]
2	Symptoms require and respond to moderate intervention: • O_2 requirement <40% FiO_2, **OR** • Hypotension responsive to IV fluids or low dose of one vasopressor, **OR** • Grade 2 organ toxicity[a]	Fever (≥ 38°C)[b], not requiring vasopressors, and/or[c] requiring low-flow nasal cannula or blow-by	• Moderate reaction: Some signs of organ dysfunction (eg, grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition • Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for IV therapies (not including fluid resuscitation for hypotension)	• Hypotension responds to IV fluids or low-dose vasopressors • Hypoxia requiring FiO_2 <40% • Grade 2 organ toxicity[d]
3	Symptoms require and respond to aggressive intervention: • O_2 requirement ≥40% FiO_2, **OR** • Hypotension requiring high dose or multiple vasopressors, **OR** • Grade 3 organ toxicity[a] or grade 4 transaminitis	Fever (≥ 38°C)[b], requiring vasopressor with or without vasopressin, and/or[c] requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	• More severe reaction: hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition • Hypotension treated with multiple fluid boluses or low-dose vasopressors • Coagulopathy requiring FFP, cryoprecipitate, or fibrinogen concentrate • Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	• Hypotension needing high-dose or multiple vasopressors • Hypoxia requiring FiO_2 ≥40% • Grade 3 organ toxicity[d] or grade 4 transaminitis
4	Life-threatening symptoms: • Requirement for ventilator support, **OR** • Grade 4 organ toxicity[a] (excluding transaminitis)	Fever (≥ 38°C)[b], requiring multiple vasopressors (excluding vasopressin), and/or[c] requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	• Life-threatening complications such as hypotension requiring high-dose vasopressors • Hypoxia requiring mechanical ventilation	• Life-threatening hypotension • Needing ventilator support • Grade 4 organ toxicity[d] except grade 4 transaminitis
5	Death	Death	Death	Death

CRS grading and treatment recommendations may differ by scale and by product. Treating HCPs should refer to the product specific information and utilize their best medical judgement to determine the best course of treatment for a particular patient

[a]As per CTCAE Version 4.0.[b]Not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. [C]CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. [d]Cardiac (tachycardia, arrhythmias, heart block, low ejection fraction), respiratory (tachypnea, pleural effusion, pulmonary edema), gastrointestinal (nausea, vomiting, diarrhea), hepatic (increased serum ALT, AST, or bilirubin levels), renal (acute kidney injury, increased serum creatinine, decreased urine output), dermatological (rash), and coagulopathy (disseminated intravascular coagulation), as per CTCAE Version 4.03.

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; FFP, fresh frozen plasma; FiO_2, fraction of inspired oxygen; IV, intravenous; LFT, liver function test.

References: **1.** Lee DW, et al. *Blood*. 2014;124:188–195. **2.** Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **3.** Porter D, et al. *J Hematol Oncol*. 2018;11:35. **4.** Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47–62.

Management of Grade 1 CRS According to Different CRS Grading Scales

Lee[1]	ASTCT[2]	Penn[3]	CARTOX[4]
• Vigilant supportive care • Assess for infection • Treat fever and neutropenia if present • Monitor fluid balance • Antipyretics, analgesics as needed	• Antipyretics and IV hydration • Diagnostic work-up to exclude infection • Growth factors and antibiotics if neutropenic (optional)	• Treated with supportive care such as antipyretics, antiemetics	• Acetaminophen and hypothermia blanket for the treatment of fever • Ibuprofen can be used as second treatment option for fever, if not contraindicated • Assess for infection using blood and urine cultures, and chest radiography • Empiric broad-spectrum antibiotics and filgrastim if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Consider tocilizumab or siltuximab[a] for persistent (lasting >3 days) and refractory fever

CRS grading and treatment recommendations may differ by scale and by product. Treating HCPs should refer to the product specific information and utilize their best medical judgement to determine the best course of treatment for a particular patient

[a]Siltuximab is not currently indicated for treatment of CRS for CAR T cell therapy.

References: 1. Lee DW, et al. Blood. 2014;124(2):188-195. **2.** Neelapu SS. *Hematol Oncol*. 2019;37(S1):48-52. **3.** Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139. **4.** Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62.

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

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)

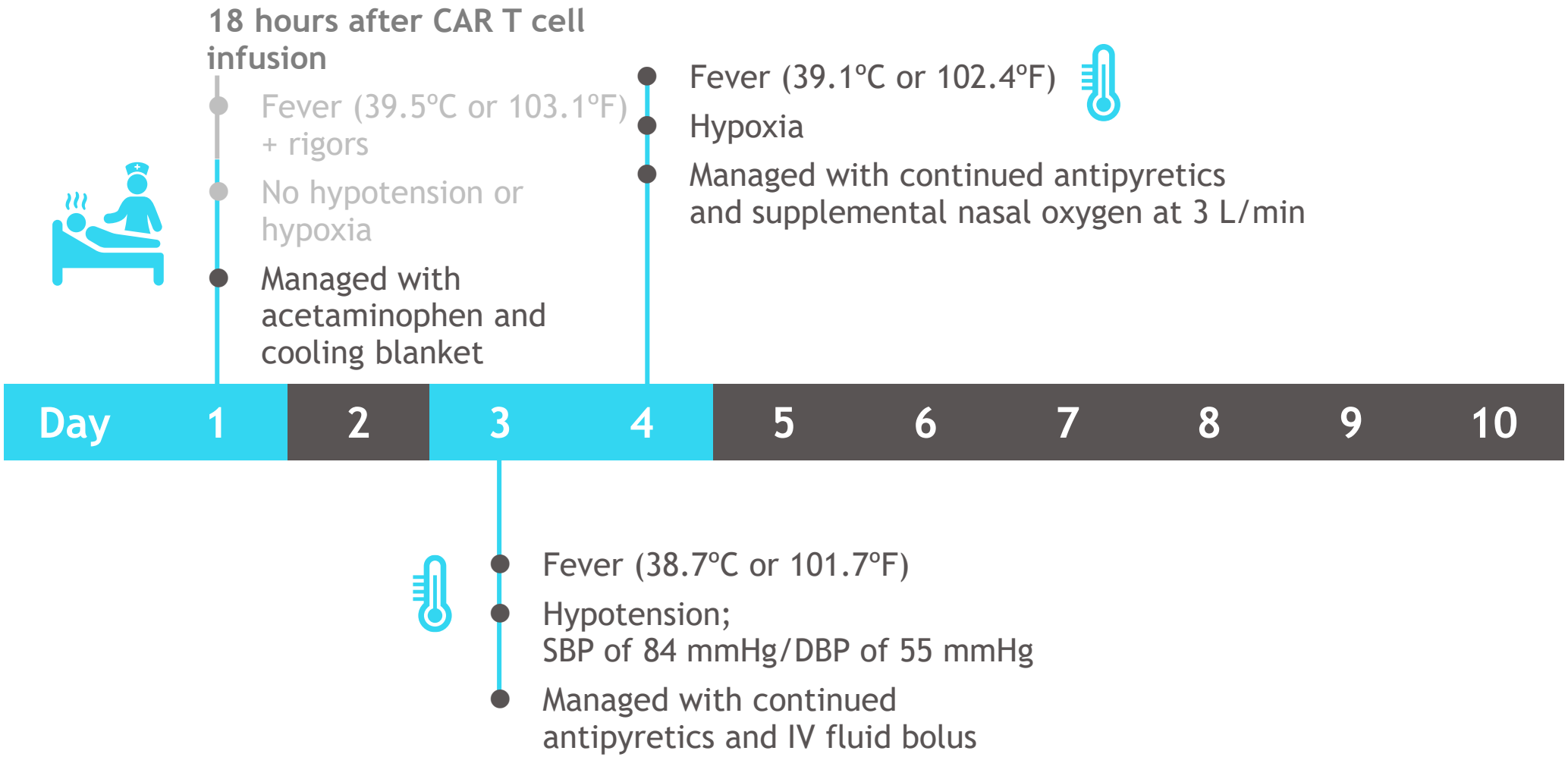
C. Tocilizumab

D. Corticosteroids

E. Tocilizumab + corticosteroids

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

Melissa[a]: Acute Toxicities



[a]Hypothetical patient case.
DBP, diastolic blood pressure; IV, intravenous; SBP, systolic blood pressure

CRS Grading Scales: Lee, ASTCT, Penn, and CARTOX

The patient currently has **grade 2** CRS in accord with **Lee, ASTCT, and CARTOX criteria** and **grade 3** in accord with **Penn criteria**

Grade	Lee Criteria[1]	ASTCT Criteria[2]	Penn Criteria[3]	CARTOX Criteria[4]
1	Symptoms are not life threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgias, malaise)	Fever (≥ 38°C)[b]	• Mild reaction: treated with supportive care such as antipyretics, antiemetics	• Temperature ≥38 °C and/or grade 1 organ toxicity[d]
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3	Symptoms require and respond to aggressive intervention: • O_2 requirement ≥40% FiO_2, **OR** • Hypotension requiring high dose or multiple vasopressors, **OR** • Grade 3 organ toxicity[a] or grade 4 transaminitis	Fever (≥ 38°C)[b], requiring vasopressor with or without vasopressin, and/or[c] requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	• More severe reaction: hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition • Hypotension treated with multiple fluid boluses or low-dose vasopressors • Coagulopathy requiring FFP, cryoprecipitate, or fibrinogen concentrate • Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	• Hypotension needing high-dose or multiple vasopressors • Hypoxia requiring FiO_2 ≥40% • Grade 3 organ toxicity[d] or grade 4 transaminitis
4	Life-threatening symptoms: • Requirement for ventilator support, **OR** • Grade 4 organ toxicity[a] (excluding transaminitis)	Fever (≥ 38°C)[b], requiring multiple vasopressors (excluding vasopressin), and/or[c] requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	• Life-threatening complications such as hypotension requiring high-dose vasopressors • Hypoxia requiring mechanical ventilation	• Life-threatening hypotension • Needing ventilator support • Grade 4 organ toxicity[d] except grade 4 transaminitis
5	Death	Death	Death	Death

CRS grading and treatment recommendations may differ by scale and by product. Treating HCPs should refer to the product specific information and utilize their best medical judgement to determine the best course of treatment for a particular patient

[a]As per CTCAE Version 4.0.[b]Not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. [C]CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. [d]Cardiac (tachycardia, arrhythmias, heart block, low ejection fraction), respiratory (tachypnea, pleural effusion, pulmonary edema), gastrointestinal (nausea, vomiting, diarrhea), hepatic (increased serum ALT, AST, or bilirubin levels), renal (acute kidney injury, increased serum creatinine, decreased urine output), dermatological (rash), and coagulopathy (disseminated intravascular coagulation), as per CTCAE Version 4.03.

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; FFP, fresh frozen plasma; FiO_2, fraction of inspired oxygen; IV, intravenous; LFT, liver function test.

References: 1. Lee DW, et al. *Blood*. 2014;124:188–195. **2.** Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **3.** Porter D, et al. *J Hematol Oncol*. 2018;11:35. **4.** Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47–62.

Management of Grade 2 (Lee, ASTCT, CARTOX) or Grade 3 (Penn) CRS Grading Scales

Lee[1] Grade 2	ASTCT[2] Grade 2	Penn[3] Grade 3	CARTOX[4] Grade 2
• Vigilant supportive care • IV fluids or one low dose pressor for hypotension • Oxygen for hypoxia • For pts without extensive comorbidities or younger pts: monitor cardiac and other organ function closely • For older pts or pts with extensive comorbidities: tocilizumab ± corticosteroids	• Supportive care as for grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab ± dexamethasone (or methylprednisolone equivalent)	• Hospitalization to manage symptoms related to organ dysfunction • Manage hypotension with IV fluids or low-dose vasopressors • Fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate for coagulopathy • Supplemental oxygen	• Supportive care – Manage fever and constitutional symptoms as in grade 1 – Supplemental oxygen – One or more IV fluid bolus of normal saline • Tocilizumab or siltuximab[a] for the treatment of hypotension that is refractory to fluid boluses – Vasopressors if hypotension persists after 2 fluid boluses and anti-IL-6 therapy, consider transfer to ICU, obtain echocardiogram, and initiate other methods of hemodynamic monitoring • Dexamethasone for high-risk pts or pts with persistent hypotension • Tocilizumab or siltuximab[a] ± corticosteroids and supportive care, as recommended for the management of hypotension, for hypoxia, and/or organ toxicity • Symptomatic management of organ toxicities, as per standard guidelines

CRS grading and treatment recommendations may differ by scale and by product. Treating HCPs should refer to the product specific information and utilize their best medical judgement to determine the best course of treatment for a particular patient

[a]Siltuximab is not currently indicated for treatment of CRS for CAR T cell therapy.

References: 1. Lee DW, et al. Blood. 2014;124(2):188-195. **2.** Neelapu SS. *Hematol Oncol*. 2019;37(S1):48-52. **3.** Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139. **4.** Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62.

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

IV, intravenous.

Management Question 4

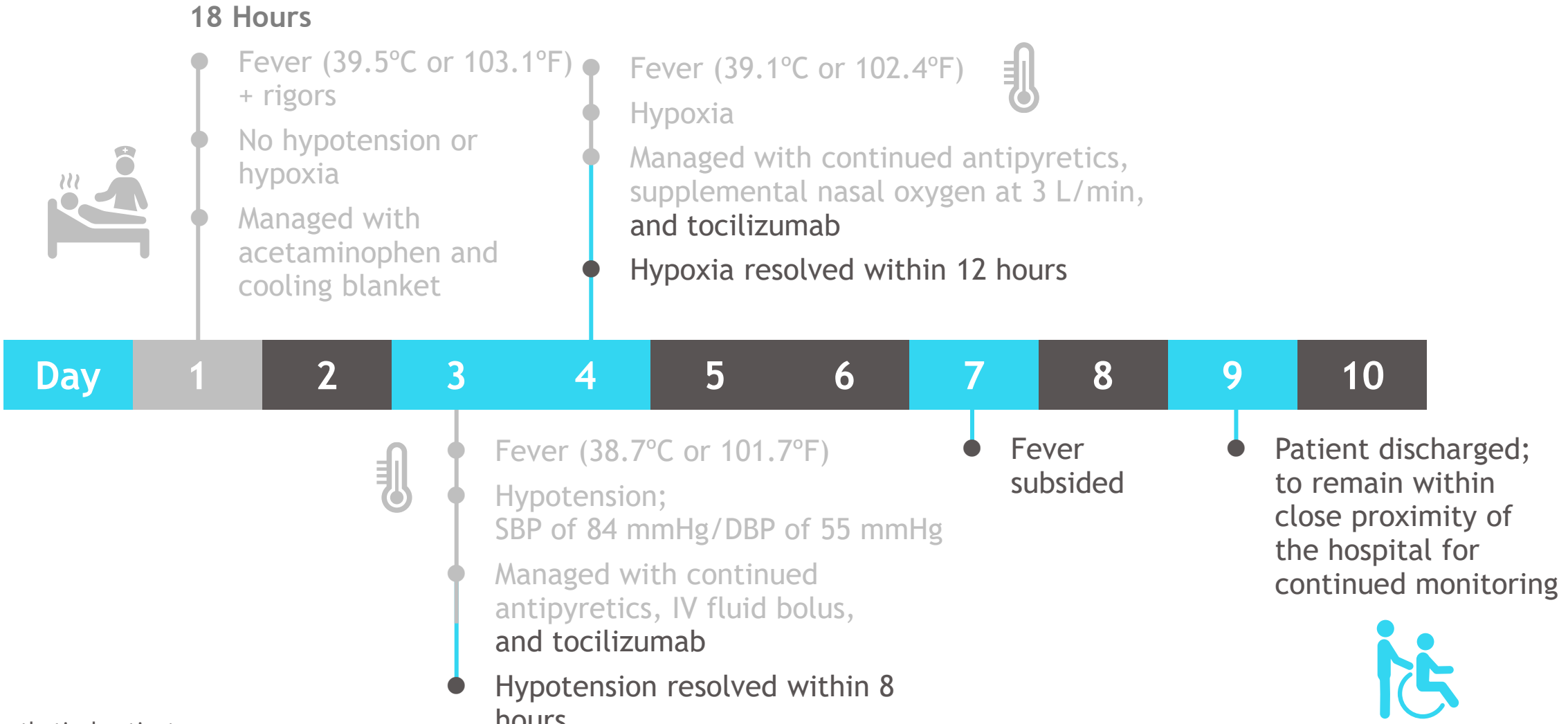
According to ASTCT guidelines, should tocilizumab also be administered on Days 3 and 4 to manage hypotension and hypoxia, or are IV fluid bolus and supplemental oxygen sufficient?

A. **Tocilizumab should also be administered**

B. IV fluid bolus and supplemental oxygen are sufficient

Correct answer:
A. Tocilizumab should also be administered

Melissa[a]: Acute Toxicities



[a]Hypothetical patient case.
DBP, diastolic blood pressure; SBP, systolic blood pressure.

Inpatient vs Outpatient Post-infusion Monitoring

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

- **Patients must remain within close proximity to the treatment center for at least 4 weeks to ensure quick access to care, regardless of whether the patient received CAR T cell therapy as an inpatient or outpatient[2]**
- Depending on the patient, product, and center, inpatient monitoring may be required for a period of time[1,3]
- Under certain circumstances, outpatient administration and monitoring may be appropriate per the treating physician's discretion[1]
  - When this occurs, patients are usually observed in the treating center for a few hours after the CAR T cell therapy infusion to monitor for acute reactions; if none occur, they are permitted to leave the treatment center[4]
  - Hospitalization may be 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.

Management Question 5

Melissa is being discharged after her CAR T cell therapy infusion. How long must she stay within close proximity of the treatment center?

A. 4 days

B. 2 weeks

C. At least 4 weeks

Management Question 5

Melissa is being discharged after her CAR T cell therapy infusion. How long must she stay within close proximity of the treatment center?

A. 4 days

B. 2 weeks

C. At least 4 weeks

Correct answer:
C. At least 4 weeks

Melissa[a]: 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
- CARTOX-10 score: 5
- 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.

[a]Hypothetical patient case.
ICE, Immune Effector Cell-Associated Encephalopathy.

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

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

CARTOX-10 Scoring Is Used in the CARTOX Grading for CRES

CARTOX-10 uses a 10-point scale to assess alterations in concentration, speech, and writing ability that are associated with CAR-T-cell-related encephalopathy syndrome (CRES)

Task	Points
Orientation to: year, month, city, hospital, and President/Prime Minister of country of residence	5 total (1 point for each item)
Ability to name 3 objects (e.g., point to clock, pen, button)	3 maximum points
Ability to write a standard sentence (e.g., "Our national bird is the bald eagle")	1
Ability to count backwards from 100 by 10	1

Reference: Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47–62.

Neurotoxicity[a] Grading Scales: ASTCT, CARTOX, CTCAE

The patient currently has **grade 2** neurotoxicity in accord with **ASTCT and CARTOX** criteria and **grade 1** neurotoxicity in accord with **CTCAE** criteria

Grade	ASTCT Criteria[1,b]	CARTOX Criteria[2]	CTCAE, Version 5.0[3]
1	• ICE score: 7-9 • Awakens spontaneously	• CARTOX-10 score: 7-9 (mild impairment)	• Mild symptoms of encephalopathy or tremor • Brief partial seizure and no loss of consciousness • Awareness of receptive or expressive characteristics • Not impairing ability to communicate • Mild headache, mild disorientation, decreased level of alertness
2	• ICE score: 3-6 • Awakens to voice	• CARTOX-10 score: 3-6 (moderate impairment)	• Moderate encephalopathy, tremor, and/or pain symptoms limiting instrumental ADL • Brief generalized seizure • Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously • Moderate disorientation and/or slow response to stimuli limiting instrumental ADL; sedation
3	• ICE score: 0-2 • Awakens only to tactile stimulus • Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention • Focal/local edema on neuroimaging[c]	• CARTOX-10 score: 0-2 (severe impairment) • Stage 1-2 papilledema[d] or CSF opening pressure <20 mmHg • Partial seizure or nonconvulsive seizures on EEG with response to benzodiazepine	• Severe encephalopathy, tremor, pain, or disorientation symptoms limiting self-care ADL • New-onset seizures (partial or generalized) • Multiple seizures despite medical intervention • Severe receptive or expressive characteristics, impairing ability to read, write or communicate intelligibly • Difficult to arouse • New onset cerebral edema/worsening from baseline
4	• ICE score: 0 (unarousable and unable to perform ICE) • Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma • Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between • Deep focal motor weakness such as hemiparesis or paraparesis • Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad	• Critical condition, and/or obtunded and cannot perform assessment of CARTOX-10 tasks • Stage 3-5 papilledema[d] or CSF opening pressure ≥20 mmHg, or cerebral edema • Generalized seizures or convulsive or nonconvulsive status epilepticus, or new motor weakness	• Life-threatening consequences from encephalopathy, seizure, confusion, depressed level of consciousness and/or cerebral edema; coma; prolonged repetitive seizures • Urgent intervention indicated
5	• Death	• Death	• Death

NOTE: CTCAE criteria are graded for each neurotoxicity domain (encephalopathy, seizure, dysphasia, tremor, headache, confusion, depressed level of consciousness, cerebral edema)

Neurotoxicity grading and treatment recommendations may differ by scale and by product. Treating HCPs should refer to the product specific information and utilize their best medical judgement to determine the best course of treatment for a particular patient

[a]ASTCT guidelines refer to neurotoxicity as immune effector cell-associated neurotoxicity syndrome (ICANS); CARTOX guidelines refer to neurotoxicity as CAR T cell-related encephalopathy syndrome (CRES). [b]Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication). Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading. [c]Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0. [d]Papilledema grading is performed according to the Modified Frisén scale.

References: 1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **2.** Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47-62. **3.** US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). V5.0. Accessed Aug 5, 2021. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. 4. Frisen L. *J. Neurol. Neurosurg. Psychiatry*. 1982;45:13-18.

Management of Neurotoxicity[a,b]: ASTCT and CARTOX

The patient currently has **grade 2** NT in accord with **ASTCT and CARTOX** criteria

Grade	ASTCT [1]	CARTOX[2]
1	• Aspiration precautions and IV hydration • Seizure prophylaxis w/ levetiracetam • EEG • Brain imaging • Consider tocilizumab if there is concurrent CRS	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing; convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam or haloperidol can be used, with careful monitoring, for agitated patients • Neurology consultation; fundoscopic exam to assess for papilledema • MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI spine if patient has focal peripheral neurological deficits; CT scan can be performed if MRI is not feasible • Daily 30 min EEG until toxicity symptoms resolve; if no seizures are detected on EEG, continue levetiracetam; if EEG shows non-convulsive status epilepticus, treat as per CARTOX recommendations • Consider anti-IL-6 therapy with tocilizumab or siltuximab, if CRES is associated with concurrent CRS
2	• Supportive care as in grade 1 • Consider dexamethasone or methylprednisolone equivalent	• Supportive care and neurological work-up as described for grade 1 CRES • Tocilizumab or siltuximab if associated with concurrent CRS • Dexamethasone or methylprednisolone if refractory to anti-IL-6 therapy, or for CRES without concurrent CRS • Consider transferring patient to ICU if CRES associated with grade ≥2 CRS
3	• Supportive care as in grade 1 • Dexamethasone (or methylprednisolone equivalent) • Seizure control with benzodiazepines (short-term) and levetiracetam ± phenobarbital and/or lacosamide • High-dose methylprednisolone for focal/local edema	• Supportive care and neurological work-up as indicated for grade 1 CRES; ICU transfer is recommended • Anti-IL-6 therapy if associated with concurrent CRS, as described for grade 2 CRES and if not administered previously • Corticosteroids as outlined for grade 2 CRES if symptoms worsen despite anti-IL-6 therapy, or for CRES without concurrent CRS; continue corticosteroids until improvement to grade 1 CRES and then taper • Stage 1 or 2 papilledema with CSF opening pressure <20 mmHg should be treated as CARTOX recommendations • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 CRES
4	• Supportive care as in grade 1 • High-dose methylprednisolone • Seizure control as per grade 3 • Spine imaging for focal motor weakness • Lower intracranial pressure by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema	• Supportive care and neurological work-up as outlined for grade 1 CRES • ICU monitoring; consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for grade 3 CRES • High-dose corticosteroids continued until improvement to grade 1 CRES and then taper • For convulsive status epilepticus or stage ≥3 papilledema, with a CSF opening pressure ≥20 mmHg or cerebral edema, treat as per CARTOX recommendations

Neurotoxicity grading and treatment recommendations may differ by scale and by product. Treating HCPs should refer to the product specific information and utilize their best medical judgement to determine the best course of treatment for a particular patient

[a]CTCAE guidelines do not provide management strategies for neurotoxicities; [b]ASTCT guidelines refer to neurotoxicity as immune effector cell-associated neurotoxicity syndrome (ICANS); CARTOX guidelines refer to neurotoxicity as CAR T cell-related encephalopathy syndrome (CRES).
CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging.
References: 1. Neelapu SS. *Hematol Oncol*. 2019;37 Suppl 1:48-52. **2.** Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47-62.

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

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

Correct answer:
C. Systemic corticosteroids

Melissa[a]: 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
  - IgG level 360 mg/dL

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

[a]Hypothetical patient case.
ANC, absolute neutrophil count; CR, complete response.

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 post-infusion, 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.

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

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

Key Points

- Patients may be considered for CAR T cell therapy if they have a disease as defined in commercial indication or in clinical trial, 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
- CRS and neurotoxicity are serious, potentially life-threatening toxicities that require careful monitoring
- Several long-term toxicities may be associated with CAR T cell therapy, including cytopenias, infections, hypogammaglobulinemia, and others, which require periodic long-term monitoring and appropriate management
  - Severe cytopenias may be treated with transfusion and/or growth factor support, when appropriate

Thank you for completing this module of CAR T Academy

We hope you found it informative and educational

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