Management of Toxicities Associated with Bispecific Immune Cell Engager Monoclonal Antibodies - Adult - Inpatient/Ambulatory/Emergency Department Consensus Care Guideline

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Content Expert:
Mike Fallon, PharmD, BCOP - Pharmacy
Phone Number: (608) 263-7230
Email Address: Mike Fallon

Contact for Changes:
Jason Bergsbaken, PharmD, BCOP - Pharmacy
Phone Number: (608) 265-0341
Email Address: Jason Bergsbaken

Guideline Authors:
Mike Fallon, PharmD, BCOP - Pharmacy
Cameron Ninos, PharmD, BCOP - Pharmacy
Harpreet Sandhu, PharmD - Pharmacy

Workgroup Members
Jason Bergsbaken, PharmD, BCOP - Pharmacy
Julie Chang, MD - Medicine, Hematology/Oncology
Elizabeth Dow-Hillgartner, PharmD, BCPS, BCOP - Pharmacy
Vaishalee Kenkre, MD - Medicine, Hematology/Oncology
Tim Schmidt, MD - Medicine, Hematology/Oncology
Elaine Stenstrup, MSN, RN - Nursing
Nataliya Uboha, MD, PhD - Medicine, Hematology/Oncology

Reviewers:
Natalie Callander, MD - Medicine, Hematology/Oncology
Aric Hall, MD - Medicine, Hematology/Oncology
Ryan Mattison, MD - Medicine, Hematology/Oncology
Linda Eckstein, NP - Medicine, Hematology/Oncology
Christopher Nemergut, PharmD - Center for Clinical Knowledge Management
Jennifer Trott, NP - Medicine, Hematology/Oncology

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Introduction

Bispecific immune cell engager monoclonal antibodies are novel immunotherapeutics designed to bind two different antigens simultaneously to activate immune cells leading to subsequent lysis and death of targeted cells. Currently all FDA-approved products are bispecific T-cell engaging (BiTE) agents, but development continues for products that engage other immune cells such as macrophages, natural killer cells, or dendritic cells. Administration of these products may be accompanied by cytokine release which can evolve to a potentially severe and life-threatening inflammatory syndrome.

Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are supraphysiologic responses following an immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.[1-3] The supraphysiologic response is related to increased levels of several cytokines including IL-2, IL-5, IL-6, IL-8, IL-10, IFN-γ, and TNF-α as well as granulocyte macrophage-colony stimulating factor (GM-CSF). The predominate cytokine primarily implicated in CRS toxicity is IL-6 that initiates a proinflammatory response at elevated levels. CRS symptoms can be progressive, must include fever at onset, and may include hypotension, capillary leak (hypoxia), and end organ dysfunction requiring urgent medical attention and supportive care based on presenting signs and symptoms.[3] ICANS symptoms may range from subtle inattention, dysgraphia, language disturbance, confusion, altered mental status, and may progress to seizures or cerebral edema. CRS and ICANS can occur concomitantly. UW Health Hematology/Oncology practitioners have agreed to endorse recommendations from the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for CRS and ICANS associated with immunotherapeutics including BiTE agents.

There is significant variation in the incidence, onset, and time to resolution of CRS among available products (See Appendix). Site of care coordination will be optimized based on product-specific CRS and ICANS features.[4-7] While there is a unified grading system for CRS and ICANS, the optimal management strategies for BiTE products are less well defined. The efficacy of bispecific immune cell engager monoclonal antibodies in combination with "off-the-shelf" convenience has led to increased use and rapid development of multiple products. Recent advances in both solid tumor and hematologic malignancy immunotherapies have demonstrated the need for guidance on CRS and ICANS management in non-cellular therapies. Other BiTE adverse effects (e.g., infections, cytopenias, and hemophagocytic lymphohistiocytosis) are outside the scope of this guideline but also require vigilant monitoring.[1]

Scope

Intended Users: Physicians, Advanced Practice Providers, Pharmacists, Nurses, Technical Support

Objective: To provide guidance on the grading and prompt management of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome arising from bispecific immune cell engager monoclonal antibody therapy in adult patients based on manufacturer recommendations and evidence-based interventions

Target Population: Adult patients with toxicities associated with bispecific immune cell engager monoclonal antibody therapies in the inpatient, emergency department, or ambulatory setting

Clinical Questions Considered:

- What clinical assessment should be conducted when evaluating a patient with suspected CRS and/or ICANS?
- How long should patients be monitored after receiving bispecific immune cell engager monoclonal antibody therapies for CRS and/or ICANS? When is it safe to administer therapy as in the outpatient setting?
- How are toxicities classified for CRS and/or ICANS and what are the appropriate treatments for the various levels of severity?
- When should tocilizumab be used for the treatment of CRS and/or ICANS?

Definitions

- **ASTCT**: American Society for Transplantation and Cellular Therapy
- **BiTE**: Bispecific T-cell Engager
- **CTCAE**: Common Terminology Criteria for Adverse Events
- **CAR-T**: Chimeric antigen receptor T cell
- **CRS**: Cytokine release syndrome. 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.
- **HLH/MAS**: Hemophagocytic lymphohistiocytosis/macrophage activation syndrome
- **ICANS**: Immune effector cell-associated neurotoxicity syndrome. A disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.
- Organ specific toxicity is defined according to CTCAE

Recommendations

1. Therapy Coordination
   - 1.1. Bispecific T-cell engager medication prior authorization approval should be completed prior to therapy start. If needed, home health infusion coverage prior authorization also must be completed. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
   - 1.2. Timely patient scheduling should include clear site of care (i.e. ambulatory, inpatient, or a mix of ambulatory/inpatient) and length of required monitoring communication to the patient and clinical care team.[4-7] Refer to product-specific details (Refer to Appendix) for clinical site of administration and post-infusion monitoring time recommendations. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   - 1.3. Ambulatory post-dose monitoring plan should be established with patients and caregivers prior to the first dose. Plan should support reasonable access to continuous adverse event monitoring during the first cycle and reliable transportation to a medical facility that can support adverse effect management if needed.[1-3] An appropriate emergency department should be identified. If needed, home health infusion staff travel limits should also be assessed (e.g., some providers will only travel up to two hours). (*UW Health Strong Recommendation, High Quality of Evidence*)
   - 1.4. The Hematology or Oncology attending physician will maintain primary responsibility for patient and provide oversight to other providers and specialties to provide prompt evaluation and treatment of side effects. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
     - 1.4.1. The Hematology or Oncology attending physician should be notified whenever care is escalated, and prior to administering tocilizumab, anakinra, siltuximab, and/or corticosteroids. Order sets should be utilized for management of adverse effects. (*UW Health Strong Recommendation, Low Quality of Evidence*)
   - 1.5. Nurses are responsible for providing patient wallet cards and educating patients/families/caregivers regarding CRS and ICANS symptom monitoring and reporting upon administration of the first dose of therapy.[1,4-6] (*UW Health Strong Recommendation, High Quality of Evidence*)
   - 1.6. Ambulatory patient management[1,3-6]
     - 1.6.1. Patients should be monitored for signs/symptoms of CRS and ICANS on days of therapy and at least twice weekly during weeks 1 and 2 and at least weekly during weeks 3 and 4 with increased monitoring as clinically appropriate. Monitoring after week 4 will be based on provider discretion. (*UW Health Strong Recommendation, High Quality of Evidence*)
     - 1.6.2. Patients should be instructed to take their temperature twice daily and call their clinic/provider immediately for a fever greater than or equal to 100.4 °F (38 °C), or any other signs/symptoms of CRS or ICANS. (*UW Health Strong Recommendation, High Quality of Evidence*)

1.6.3. Patients should be provided a dexamethasone 8 mg once if needed prescription for severe CRS (e.g. shaking chills, difficulty breathing, feeling severely ill, etc.) to take at home if instructed prior to travel to the Emergency Department. (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

1.6.4. Consider inpatient admission for patients who develop CRS or ICANS. (*UW Health Strong Recommendation, High Quality of Evidence*)

1.7. Inpatients patient management[1,3-6]

1.7.1. Admission order sets should be utilized to ensure standardized monitoring. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

1.7.2. Patients should be monitored daily to every eight hours for signs/symptoms of CRS and daily at a minimum for signs/symptoms of ICANS with increased monitoring as clinically appropriate. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

1.7.3. Guidelines for transfer to a higher level of care.[1-3] (*UW Health Strong Recommendation, Moderate Quality of Evidence*):

1.7.3.1. Monitoring required more frequently than every 4 hours

1.7.3.2. Persistent hypotension (SBP below 90 mmHg) after 500 to 1000 mL normal saline bolus

1.7.3.3. Low-dose vasopressor support required

1.7.3.4. Oxygen needs greater than 6 L nasal cannula or oxymask, rapidly increasing oxygen needs, or inability to keep oxygen saturation greater than 90%

1.7.3.5. Neurologic changes (ICE less than 7, Grade 3 or higher ICANS, moderate somnolence or encephalopathy limiting instrumental ADLs, moderate disorientation or confusion, seizures, moderate dysphagia impairing ability to communicate spontaneously, deep focal motor weakness such as hemiparesis or paraparesis or focal/local edema on neuroimaging)

2. Cytokine Release Syndrome (CRS) Monitoring and Treatment

2.1. CRS Grade Monitoring[1,3]

2.1.1. CRS grading should be determined using criteria from Table 1 (*UW Health Strong Recommendation, High Quality of Evidence*)

2.1.2. Timing of CRS grading should occur during ambulatory clinic visits or every eight hours to daily in the inpatient setting or based on manufacturer recommendations if specified and/or as clinically appropriate. Monitoring after week 4 will be based on provider discretion. (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

2.1.3. Ambulatory patients should be instructed to take their temperature twice daily and call their clinic/provider immediately for a fever greater than or equal to 100.4 °F (38 °C), or any other signs/symptoms of CRS. Patients should be directed to seek emergency room care if clinically appropriate. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

2.1.4. CRS grading will be determined by the most severe event: hypotension or hypoxia not attributable to other causes. (*UW Health Strong Recommendation, High Quality of Evidence*)

2.1.5. CRS can contribute to systemic multiorgan dysfunction which should be graded according to CTCAE v 5.0 guidelines; consider treating as severe CRS as clinically appropriate.[1,3,8] (*UW Health Strong Recommendation, High Quality of Evidence*)

2.1.6. Early treatment escalation may be considered for elderly patients or those with considerable comorbidities.[1,4-7] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

Table 1. ASTCT CRS Consensus Grading

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C
		With	**With**	**With**
Hypotension	None	Hypotension, not requiring vasopressors	Requiring vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or	**And/or**	**And/or**
Hypoxia	None	Requiring low-flow nasal cannula[A] or blow-by	Requiring high-flow nasal cannula[B], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (i.e., CPAP, BiPAP, intubation and mechanical ventilation)

[A] Low-flow nasal cannula defined as oxygen delivered at ≤6 L/minute

[B] High-flow nasal cannula defined as oxygen delivered at >6 L/minute

[C] Vasopressors: Norepinephrine, Dopamine, Phenylephrine, Epinephrine, Vasopressin

Table 2. CRS Management and Treatment[1,3,8-19]

All Grades Management	• Hold BiTE infusion or hold further doses until CRS resolves • Evaluate for infection (e.g., pan-culture, respiratory viral panel, CXR and/or non-contrast CT) • Monitor CMP, CBC ferritin, C-reactive protein, and coagulation lab panels daily at a minimum or more frequently if clinically appropriate • Monitor pulmonary, renal, and hepatic function closely • If no improvement within 24 to 72 hours or ferritin rising despite management assess for HLH/MAS and treat separately if clinically indicated • Assess product specific package insert for guidance on subsequent dosing following CRS including: timing to next dose, infusion time and dose modifications, premedication recommendations, and hospitalization requirements

CRS grade	Assessment/Monitoring	Supportive care	Tocilizumab	Corticosteroids
1	• Follow All Grades management • Consider telemetry and/or continuous pulse oximetry • Vitals every 2-4 hours or as clinically appropriate	• Consider hospitalization until symptoms resolve • Antipyretics per provider discretion: acetaminophen preferred as primary treatment option for fever • Intravenous fluids per provider discretion; judicious use encouraged given vascular leak etiology of CRS related hypoxia • Consider empiric broad spectrum antibiotics	• If no improvement after 24 to 48 hours, consider tocilizumab 8 mg/kg IV (maximum 800 mg). Consider earlier use if significant symptoms, comorbidities, and/or over 65 years old. If concurrent ICANS give corticosteroids prior to tocilizumab. • If no clinical improvement in CRS after the first dose, repeat tocilizumab 8 mg/kg IV (maximum) once	• If no resolution of fever after 48 to 72 hours, consider one dose of dexamethasone 10 mg IV
2	• Follow All Grades management • Telemetry and continuous pulse oximetry • Vitals every 2-4 hours or as clinically appropriate	• Supportive measures as above • Hospitalize until symptoms resolve • Administer 1L normal saline fluid bolus over 1 hour; repeat as needed for up to 3L to maintain systolic BP ≥90 mm Hg • Supplemental oxygen as needed • If recurrent Grade 2 consider treating as Grade 3	• Give tocilizumab 8 mg/kg IV (maximum 800 mg). If concurrent ICANS give corticosteroids prior to tocilizumab. • If no clinical improvement in CRS after the first dose, may repeat tocilizumab every 8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	• If no improvement within 24 hours of starting tocilizumab, consider dexamethasone 10 mg IV daily • If improving, continue corticosteroids use until the event is Grade 1 or less, then quickly taper as clinically appropriate • If no improvement, manage as per Grade 3
3	• Follow All Grades management • If patient transferred to higher acuity unit, increase frequency of monitoring as clinically appropriate • If recurrent grade 3 consider permanently discontinue offending BiTE therapy	• Supportive measures as above • May consider ICU transfer • May require vasopressor • Continue as needed IV fluid bolus to maintain perfusion	• Give tocilizumab 8 mg/kg IV (maximum 800 mg) • If no clinical improvement in CRS after the first dose, repeat tocilizumab every 8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. • If no improvement or rapid progression after 2 doses of tocilizumab/escalation of steroids, consider alternative immunosuppressants (e.g., anakinra 8-10 mg/kg/day IV in 3 to 4 divided doses, siltuximab 11 mg/kg IV once)	• Administer dexamethasone 10 mg IV every 8 hours • If improving, continue corticosteroids use until the event is Grade 1 or less, then quickly taper as clinically appropriate • If no improvement within 24 hours or rapid progression of CRS, administer dexamethasone 20 mg IV every 6 hours. If no improvement within 24 hours or continued rapid progression switch to high-dose methylprednisolone 1000 mg IV daily for 3 days.
4	• Follow All Grades management • If patient transferred to higher acuity unit, increase frequency of monitoring as clinically appropriate • Permanently discontinue offending BiTE therapy	• Supportive measures as above • Transfer to ICU • May utilize multiple vasopressors as appropriate • Continue as needed IV fluid bolus to maintain perfusion	• Give tocilizumab per Grade 3 • If no improvement or rapid progression after 2 doses of tocilizumab/escalation of steroids, consider alternative immunosuppressants (e.g, anakinra 8-10 mg/kg/day IV in 3 to 4 divided doses, siltuximab 11mg/kg IV once)	• As above or administer high dose methylprednisolone 1000 mg IV daily for 3 days • If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate

3. Immune Effect Cell-Associated Neurotoxicity Syndrome (ICANS) Management
   3.1. ICANS Grade Monitoring[1,3]
      3.1.1. ICANS grading may be determined using criteria from Table 5. (*UW Health Strong Recommendation, High Quality of Evidence*)
      3.1.2. Timing of ICANS grading should occur on the day of ambulatory visits or at least daily in the inpatient setting or based on manufacturer recommendations if specified and/or as clinically appropriate. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
      3.1.3. Ambulatory patients should be instructed to call their clinic/provider immediately for any signs/symptoms of ICANS and should be directed to seek Emergency Departmenmt care if appropriate. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
      3.1.4. To determine ICANS grading, encephalopathy must be evaluated using BOTH neurotoxicity clinical assessment AND the Immune Effector Cell-Associated Encephalopathy (ICE) score (*UW Health Strong Recommendation, High Quality of Evidence*)
         3.1.4.1. ICE scores should be documented using the Cellular Therapy Toxicity [HL 511]: Encephalopathy Assessment Tool Flowsheet.
      3.1.5. Management is determined by the most severe event, not attributable to any other cause. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

Table 3. ASTCT ICANS Consensus Grading for Adults[1,3]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0
Depressed level of consciousness not attributable to another cause	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	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 such as 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

Table 4. ICE Scoring Tool (Total of 10 points)

Category	Tasks	Associated Points
Orientation	Orientation to year, month, city, hospital	4 points
Naming	Ability to name 3 objects	3 points
Following commands	Ability to follow simple commands	1 point
Writing	Ability to write a standard sentence	1 point
Attention	Ability to count backwards from 100 by 10	1 point

Table 5. Management and Treatment and of ICANS[2,3,9,12-19]

Grade	If concurrent CRS, manage CRS per above Section 2
1	• Monitor neurologic symptoms and consider Neurology consultation and evaluation • Consider anti-seizure prophylaxis (e.g., levetiracetam preferred)
2	• Consider anti-seizure prophylaxis (e.g., levetiracetam preferred) • Consider Neurology consultation and other specialists (e.g. Critical Care) for further evaluation, as needed • Administer dexamethasone 10 mg IV every 12 hours; if improvement not rapid consider dexamethasone 10 mg IV every 6 hours • Continue dexamethasone use until the event is Grade ≤1, then taper
3	• Consider anti-seizure prophylaxis (e.g., levetiracetam preferred) • Consult Neurology and other specialists (e.g. Critical Care) for further evaluation, as needed. • Administer dexamethasone 10 mg IV every 6 hours; if improvement not rapid consider dexamethasone 20 mg IV every 6 hours • Continue dexamethasone use until the event is Grade ≤1, then taper • If not improving consider methylprednisolone 1000 mg IV daily for up to 3 days and consider alternative immunosuppressants (e.g. anakinra 8-10 mg/kg/day IV in 3-4 divided doses)
4	• Consider anti-seizure prophylaxis (e.g., levetiracetam preferred) • Consult Neurology and other specialists (e.g. Critical Care) for further evaluation, as needed • Dexamethasone as above or consider administration of methylprednisolone 1000 mg IV per day for 3 days • Consider alternative immunosuppressants (e.g. anakinra 8-10 mg/kg/day IV in 3-4 divided doses); siltuximab 11 mg/kg IV once may be considered for Grade 4 ICANS refractory to high-dose methylprednisolone and anakinra • Continue dexamethasone use until the event is Grade ≤1, then taper

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology

Methods Used to Collect the Evidence:

The following criteria were used by the guideline authors and workgroup members to conduct electronic database searches in the collection of evidence for review.

Development of clinical question(s) and rationale: (From A3/PICOT)

- In patients receiving bispecific immune cell engager monoclonal antibody therapy (non-CAR-T therapy), how does standardized grading for CRS compare with manufacturer grading affect toxicity treatment within inpatient stays?

Literature Sources:

- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: Published articles after 2019 due to the novel nature of these medications and reactions

Search Terms:

- [(“cytokine release syndrome management” OR “CRS”)]
- [(“cytokine release syndrome”) AND [(“solid malignancy”)
- [(“cytokine release syndrome”) AND [(“bispecific t-cell engager”)
- [(“blinatumomab” OR “tebentafusp OR “mosunetuzumab” OR “teclistamab” OR “epcoritamab” OR “glofitamab” OR “talquetamab” AND “tocilizumab”)]
- [(“blinatumomab” OR “tebentafusp OR “mosunetuzumab” OR “teclistamab” OR “epcoritamab” OR “glofitamab” OR “talquetamab”) AND (“CRS” OR “Cytokine release syndrome”)
- [(“blinatumomab” OR “tebentafusp OR “mosunetuzumab” OR “teclistamab” OR “epcoritamab” OR “glofitamab” OR “talquetamab”) AND (“CRS management” OR “Cytokine release syndrome management”)
- [(“blinatumomab” OR “tebentafusp OR “mosunetuzumab” OR “teclistamab” OR “epcoritamab” OR “glofitamab” OR “talquetamab”) AND [(“side effect” or “adverse effect”)

Methods to Select the Evidence:

Describe the inclusion/exclusion criteria used for selecting the literature; include chosen variables such as language, study design, outcomes, and comparisons. Describe outcome measures and intervention selection criteria.

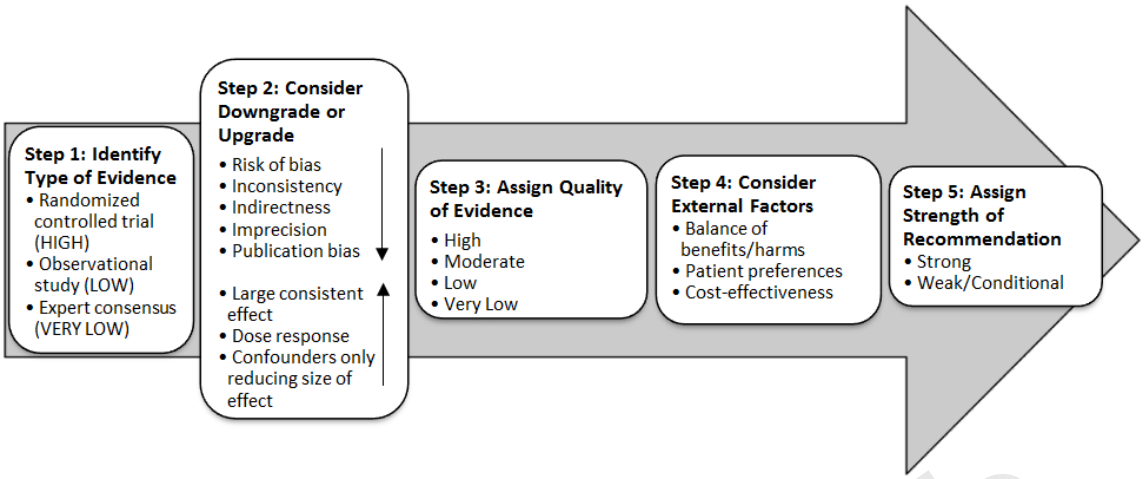
Methods Used to Formulate the Recommendations:

The workgroup members agreed on recommendations via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:

Internally developed recommendations were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1).[20]

Figure 1. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:
GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong (S)	Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision)
Conditional (C)	May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented)

ASTCT Grading Evidence
Experts from all aspects of the field met on June 20 and 21, 2018, at a meeting supported by the American Society for Transplantation and Cellular Therapy (ASTCT) in Arlington, VA. Here we report the consensus recommendations of that group and propose new definitions and grading for CRS and neurotoxicity that are objective, easy to apply, and ultimately more accurately categorize the severity of these toxicities.

Recognition of Potential Health Care Disparities:
Disparities in the treatment of patients with malignancies exist. The availability of novel diagnostic and therapeutic measures (novel chemotherapy) and the opportunity to participate in clinical trials may be affected by multiple factors (e.g., geographical location, socioeconomic status). Distrust of the health care system, stigmas related to cancer and death, literacy and language barriers, and poor expectations regarding the outcome from cancer care may also influence treatment outcomes. Barriers may include race/ethnicity, socioeconomic status, and distance.

Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics

- Utilization of tocilizumab per year for bispecific immune cell engager monoclonal antibodies (i.e., non-CAR-T products)
- Average tocilizumab use for tebentafusp
- Incidence of cytokine release syndrome Grade 1 or higher
- Number of cytokine release syndrome events per patient
- Incidence of siltuximab use for CRS management

Beacon Protocols

- CSC HEM INPT/OUTPT BLINATUMOMAB(42D:1-28) MRD- POSITIVE B-ALL AND PATIENT WEIGHT LESS THAN 45 KG VER: 5-19-22 [HL 7355]
- CSC HEM INPT/OUTPT BLINATUMOMAB(42D:1-28) MRD- POSITIVE B-ALL AND PATIENT WEIGHT GREATER THAN OR EQUAL TO 45 KG VER: 5-19-22 [HL 6970]
- CSC HEM INPT/OUTPT BLINATUMOMAB(42D:1-28) RELAPSED/REFRACTORY B-ALL VER: 5-19-22 [HL 5728]
- CSC HEM INPT/OUTPT EPCORITAMAB(28D) VER: 6-30-23 [HL 10023]
- CSC HEM INPT/OUTPT GLOFITAMAB(21D)/OBINUTUZUMAB(C1D1 ONLY) VER: 8-4-23 [HL 10082]
- CSC HEM MOSUNETUZUMAB(21D) VER: 4-6-23 [HL 9921]
- CSC MELANOMA TEBENTAFUSP VER: 4-12-22 [HL 9586]
- CSC HEM INPT/OUTPT TECLISTAMAB(28D) STEP-UP DOSING C1D1,3,5 VER: 1-6-23 [HL 9857]
- CSC HEM INPT/OUTPT TECLISTAMAB(28D) STEP-UP DOSING C1D1,4,7 VER: 1-6-23 [HL 9803]

HealthLink Flowsheets

- UW BMT CELLULAR THERAPY TOXICITY [HL 511]: Encephalopathy Assessment Tool

Order Sets & Smart Sets

- Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Management for Bispecific T-Cell Engager Agents [9887]
- IP - CAR-T Therapy - Adult - Admission [6804]

Patient Resources

- Blinatumomab Wallet Card
- Epcoritamab Wallet Card
- Glofitamab Wallet Card
- Mosunetuzumab Wallet Card
- Talquetamab Wallet Card: Navigate to *Resources for Prescribers* and then *Patient Wallet Card*
- Tebentafusp Patient Guide
- Teclistamab Wallet Card: Navigate to *Resources for Prescribers* and then *Patient Wallet Card*

Procedures

- Inventory Management of Tocilizumab for CAR-T Patients

References

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Appendix

Table. FDA-approved bispecific immune cell engager monoclonal antibodies[13-19]

Drug	Targets	Indication	CRS Incidence	Grade 3 or 4 CRS Incidence	Median Time to CRS Onset	Median Time to CRS Resolution
Blinatumomab	CD19 CD3	Treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children	7% to 15%	2% to 5%	3 days (range 1-22 days)	2 days (range 1-14 days)
Epcoritamab	CD20 CD3	Treatment of relapsed/refractory DLBCL adult patients	51%	2.5%	1 day (range 1-10 days)	2 days (range 1-27 days)
Glofitamab	CD20 CD3	Treatment of relapsed/refractory DLBCL adult patients	63%	4%	13.5 hours (range 6-52 hours)	1.3 days (range 0.02-13 days)
Mosunetuzumab	CD20 CD3	Treatment of relapsed/refractory follicular lymphoma adult patients	39%	2.5%	Cycle 1 Day 1: 5 hours Cycle 1 Day 8: 28 hours Cycle 1 Day 15: 25 hours Cycle 2 Day 1: 46 hours	3 days (range 1-29 days)
Talquetamab	GPRC5D CD3	Treatment of relapsed/refractory multiple myeloma adult patients	76%	1.5%	27 hours (range 0.1-167 hours)	0.7 days (range 0-26 days)
Tebentafusp	gp100 peptide CD3	Treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma	89%	1%	Within a few hours after administration of first 3 doses	2 days
Teclistamab	BCMA CD3	Treatment of relapsed/refractory multiple myeloma adult patients	72%	0.6%	2 days (range 1-6 days)	2 days (range 1-9 days)

Table. Monitoring for FDA-approved BsAb products[13-19]

Drug	UW Administration Location[A]	Recommendations for Initial and Subsequent Dosing[B]
Blinatumomab IV	• First 3 to 9 days of Cycle 1 and first 2 days of Cycle 2: Inpatient • Late Cycle 1/2 and additional Cycles: Ambulatory	• MRD-positive B-cell ALL / MRD-negative B-cell ALL o Hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle • Relapsed/refractory B-cell ALL o Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle • If patient develops Grade 3 CRS, admit to hospital to restart at 9 mcg/day, and escalate to 28 mcg/day after 7 days if tolerated
Epcoritamab SubQ	• Step-up dosing (Cycle 1 - Day 1, 8): Ambulatory • Step-up dosing (Cycle 1 - Day 15): Inpatient • Cycle 1 Day 22 and beyond: Ambulatory	• Cycle 1 ambulatory doses to include three CRS checks (pre-administration, 30 minutes post-dose, and prior to clinic discharge) o Hospitalization is recommended for 24 hours after administration of Cycle 1 Day 15 • If patient develops Grade 2 CRS following any dose, monitor more frequently and consider hospitalization for the next dose • If patient develops Grade 3 CRS following any dose, patient should be hospitalized for 24 hours following the subsequent dose; permanently discontinue if recurrent Grade 3 CRS
Glofitamab IV	• Initial dosing (Cycle 1 - Day 1): Ambulatory • Step-up dose #1 (Cycle 1 - Day 8): Inpatient • Step-up dose #2 (Cycle 1 - Day 15): Ambulatory unless CRS with step-up dose #1 • Cycle 2 and beyond: Ambulatory	• Hospitalization is recommended for 24 hours after administration of Cycle 1 Day 8 • If patient develops any grade CRS following Cycle 1 Day 8 they should be hospitalized for 24 hours following step-up dose #2 (Cycle 1 Day 15) • If patient develops Grade 2 or higher CRS with any previous infusion, they should be hospitalized for 24 hours for the subsequent infusion
Mosunetuzumab IV	Ambulatory	• Cycle 1 ambulatory doses to include three CRS checks (pre-administration, 30 minutes post-dose, and prior to clinic discharge) • If patient develops Grade 2 CRS, monitor more frequently and consider hospitalization for the subsequent dose • If patient develops Grade 3 CRS, hospitalize for the subsequent dose
Talquetamab SubQ	• Step-up dosing (Cycle 1 - Day 1, 3, 5): Inpatient • Subsequent Cycle 1 weekly doses: Ambulatory • Cycle 2 and beyond biweekly doses: Ambulatory	• Hospitalization is recommended for 48 hours after administration of the first three step-up doses • If patient experiences Grade 2 or 3 CRS during or after the third infusion, hospitalize for 48 hours following the subsequent dose
Tebentafusp IV	• Step-up dosing (Cycle 1 - Day 1, 8, and 15): Inpatient • Subsequent weekly doses: Ambulatory	• Hospitalization is recommended for at least 16 hours after administration of the first three step-up doses • If the patient does not experience Grade 2 or worse hypotension during or after the third infusion, administer subsequent doses in an appropriate ambulatory care setting
Teclistamab SubQ	• Step-up dosing (Cycle 1 - Day 1, 3, 5): Inpatient • Subsequent weekly doses: Ambulatory	• Hospitalization is recommended for 48 hours after administration of the first three step-up doses • If patient experiences Grade 2 or 3 CRS during or after the third infusion, hospitalize for 48 hours following the subsequent dose

[A] Hospital at home work flows may be utilized as clinically appropriate if staffing levels support

[B] See product specific package insert on need for step-up dosing restart if significant dose delays