AE Toxicity Grading for Transplant Patients

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Objectives

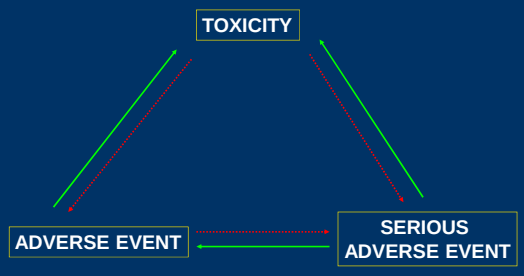
- Why do we care?????
- Toxicity vs Adverse Event vs Serious Adverse Event
- Importance of accurate toxicity grading
- Examples

Why is this relevant?

- Toxicities are common following transplant
- Knowledge about frequencies of certain toxicities allow us to better counsel our patients
- We can only learn about frequency of toxicity if we have data…

Toxicity vs AE vs SAE

- Toxicity ≈ Adverse Event
  - Toxicity: An unplanned, unwanted event which occurs following transplant
  - AE: An unplanned, unwanted event which is possibly related to clinical trial specific therapy
  - **EVENT….. Not a Cause!***
- SAE
  - An AE resulting in the following:
    - Death
    - Life-threatening
    - Hospitalization (or prolongation of)
    - persistent disability
    - birth defect



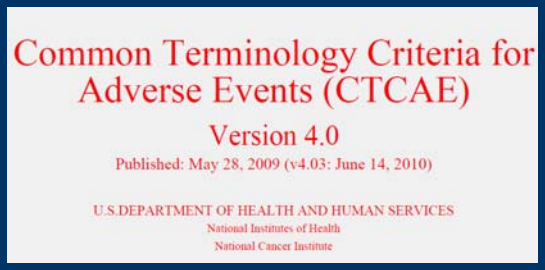
An SAE is always an AE and a Toxicity
A Toxicity may be an AE and/or SAE

Expectedness and Attribution

- Only for clinical trials
- Expected vs Unexpected
  - If it's listed in the trial protocol and/or the consent form ⟶ *expected*
- Attribution
  - Is it related to the investigational therapy of the trial?
    - Definite
    - Probable
    - Possible
    - Unlikely
    - Unrelated

Toxicity Grading

- Common Terminology Criteria Adverse Events
  - Developed by NCI
  - Currently on Version 4.03
    - Significantly different than v 3.0
  - Available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-4_QuickReference_5x7.pdf



Grading Scale

- 0: no AE or within normal limits
- 1: mild
- 2: moderate
- 3: severe
- 4: life-threatening/disabling
- 5: fatal

Common Toxicities after HCT

- "Common"—occur in >20% of patients
- Should be easily recognized and graded
- Examples:

Nausea	Neutropenic fever
Vomiting	Fatigue
Diarrhea	Electrolyte disturbances
Mucositis	
Pancytopenia requiring transfusions	

Grading Toxicities during Transplant

- Most toxicities change severity day to day…… sometimes hour to hour!
- Assessments often look for most severe in a block of time
  - Ex. Most severe grade of oral mucositis between day 0 – day 7
  - Ideally, assess about the same time each day during HCT
- Reporting differs based on indication for report: daily nurse assessments vs clinical research vs registry reporting

"Less Common" toxicities

- Many other issues with our transplant patients
- Consider assessment by organ systems
  - Pulmonary
  - Cardiac
  - Hepatic
  - GU
- Still assess with CTC AE criteria

Example

- 33 yo M with ALL now day +8 after MUD HCT with Flu/Bu conditioning and Tac/MTX for GvHD prophylaxis
- Temp 101.3F, BP 92/57, HR 124, RR 24, O2 sat 90% on RA and inc to 97% with 2 LPM/NC
- PE: A&O x4, tachycardic and tachypneic, crackles at the bases bilaterally, abdomen bland, no rash

What are the toxicities to be graded and what are the grades?

What other information do you need to assist in grading?

Toxicities which could be graded….

- Fever… is patient neutropenic?
  - ANC < 500/mcL
- Hypotension… what is the baseline BP?
  - 100's/60's
- Tachycardia
- Hypoxia

Example, cont

- Patient is now day +10
- He is unable to eat due to mouth pain and exam shows an ulcer on the tongue and some mild mucosal bleeding
- Blood cultures from day +8 grew Streptococcus viridans and he is on appropriate antibiotics without additional fevers and no longer requiring O2

CIBMTR Registry

- CIBMTR (registry)
  - Report the infection on form 2100

389. Did the recipient develop a clinically significant infection after the start of the preparative regimen?
1 ☐ yes → 2 ☐ no

Report each infection organism, site and date of diagnosis. *(see page 16 for organism and site codes)*

Organism ‡ § † ¤	Site *	Date of Diagnosis (Month / Day / Year)
390.	391. If other, specify:	392.	393.

167 Streptococcus (all species except Enterococcus)

1 Blood / buffy coat

Trial Reporting (CTN/RCI BMT)

- Does it fall into a "clinically significant" infection category?

Example, cont

- Now day +16 with an ANC of 600/mcL
- Bilirubin increasing to 3.4 with abdominal distension and weight has increased to 96kg from admission of 90kg
- A RUQ ultrasound demonstrates reversal of flow c/w VOD/SOS and ascites

CIBMTR Reporting

Liver Function

474. Did the recipient develop non-infectious liver toxicity (excluding GVHD) after the start of the preparative regimen to the date of last contact (question 1)?
1 ☐ yes → 2 ☐ no

475. Date of diagnosis: ☐☐ Month ☐☐ Day ☐☐☐☐ Year

Etiology:

476. 1 ☐ yes 2 ☐ no cirrhosis

477. 1 ☐ yes 2 ☐ no veno-occlusive disease (VOD) / sinusodial obstruction syndrome (SOS) →

478. Did the recipient receive treatment for VOD?
1 ☐ yes → 479. Specify: _____
2 ☐ no

480. Did VOD resolve by day 100?
1 ☐ yes
2 ☐ no

481. Maximum bilirubin in first 100 days: ☐☐☐

CIBMTR Reporting

482. 1 ☐ yes 2 ☐ no other → 483. Specify: _____
484. 1 ☐ yes 2 ☐ no unknown

Specify diagnosis of liver toxicity by clinical signs and symptoms / evaluation:

485. 1 ☐ yes 2 ☐ no ascites
486. 1 ☐ yes 2 ☐ no autopsy
487. 1 ☐ yes 2 ☐ no bilirubin > 2.0 mg
488. 1 ☐ yes 2 ☐ no biopsy
489. 1 ☐ yes 2 ☐ no elevated hepatic venous pressure gradient
490. 1 ☐ yes 2 ☐ no elevated liver enzymes (e.g., alkaline phosphatase, ALT, AST, LDH, GGT)
491. 1 ☐ yes 2 ☐ no hepatomegaly
492. 1 ☐ yes 2 ☐ no right upper quadrant pain or tenderness
493. 1 ☐ yes 2 ☐ no ultrasonography / doppler (abnormal portal vein flow)
494. 1 ☐ yes 2 ☐ no weight gain > 5%
495. 1 ☐ yes 2 ☐ no other → 496. Specify: _____

Trial Reporting (CTN/RCI BMT

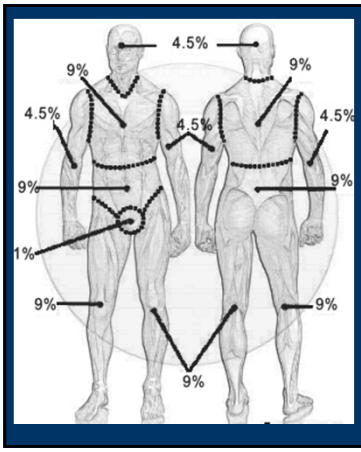
- Toxicity forms are time-point driven
  - D30, d60, d100, d180, etc
- Asks not only symptoms but requests potential etiologies

Example, cont

- On day +22, he develops a confluent maculopapular erythematous rash on his face, back, chest, abdomen, and arms
- His bilirubin is now 4.2 and his creatinine is 1.6
- He has started having diarrhea, about 6 stools per day, with a volume of about 800 mL

Example, cont

- Patient has a skin biopsy and EGD/Flex sig to assess for GVHD
  - Skin: consistent with GVHD
  - Rectal biopsy with path 3/4 GVHD
  - Gastric biopsy with path 1/4 GVHD
- Stool cultures are also sent for infectious etiology
  - Negative



Rule of Nines chart to assess percent BSA involved with a rash

CIBMTR Reporting

238. Did acute GVHD occur?
1 ☐ yes →
2 ☐ acute GVHD persists from prior HSCT / DCI
Continue with 240
3 ☐ no
Continue with 286
4 ☐ unknown
Continue with 286

239. Date of acute GVHD diagnosis: Month Day Year ☐ Date is greater than 100 days; date is correct

240. Was the diagnosis based on evidence from a biopsy (histology)?
1 ☐ yes →
2 ☐ no

Specify result(s):

	positive	negative	inconclusive	not tested	
241.	1 ☐	2 ☐	3 ☐	4 ☐	gastrointestinal (GI)
242.	1 ☐	2 ☐	3 ☐	4 ☐	liver
243.	1 ☐	2 ☐	3 ☐	4 ☐	lung
244.	1 ☐	2 ☐	3 ☐	4 ☐	skin
245.	1 ☐	2 ☐	3 ☐	4 ☐	other site → 246. Specify other site:

247. Is a copy of the pathology report attached?
1 ☐ yes
2 ☐ no

248. Was the diagnosis based on clinical evidence?
1 ☐ yes
2 ☐ no

249. Maximum overall grade of acute GVHD:
1 ☐ I
2 ☐ II
3 ☐ III
4 ☐ IV

Trial Reporting (CTN/RCI BMT)

- GVHD
  - Weekly assessments for reporting aGVHD
  - Clinical diagnosis with pathologic confirmation
  - Organ STAGE and Overall GRADE

Clinical Staging by Organ System of aGVHD

Stage	Skin	Liver/Bilirubin	Lower GI	Upper GI
0	no symptoms	bilirubin < 2mg/dL	no symptoms	no symptoms
1	rash <25% body surface area	bilirubin 2 - 3 mg/dL	diarrhea 500 - 1000mL/day	intractable nausea/vomiting
2	rash 25 - 50% body surface area	bilirubin >3 - 6 mg/dL	diarrhea 1000 - 1500 mL/day	
3	generalized rash	bilirubin >6 - 15mg/dL	diarrhea >1500 mL/day	
4	desquamation and bullae	bilirubin >15mg/dL	pain +/- ileus +/- bleeding	

Clinical Grading of aGVHD

Overall Grade	Skin	liver	Gut (Lower/Upper)	
0	stage 0	stage 0	stage 0/0	
I	stage 1-2	stage 0	stage 0/0	
II	stage 1-3	stage 1	stage1/1	
III	stage 2-3	stage 2-3	stage 2-3	
IV	stage 1-4	stage 2-4	stage 2-4	

Summary

- Toxicities
  - Signs and Symptoms
  - Not etiologies
- Clear criteria for assessment
  - Available on-line in a searchable PDF
- Reporting of toxicities varies based on reasons for assessment