Patient Self-Reporting and Cancer Drug Tolerability: Lessons Learned from the Adult Experience with PRO-CTCAE

Lori Minasian, MD

Deputy Director, Division of Cancer Prevention, NCI

NIH NATIONAL CANCER INSTITUTE

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CTCAE for Adverse Event Reporting in Cancer Clinical Trials

- CTCAE is the lexicon for adverse event reporting in cancer clinical trials.
  - ✓ Designed for cancer-specific adverse events and revised over time
  - ✓ Provides consistent method for reporting and publishing safety data
  - ✓ Grading of adverse events depends upon severity and functional interference
  - ✓ Not all adverse event items have all grades

- Vast majority of adverse event items are objective measures (labs, etc)
- 10% are subjective measures and are amenable to patient reporting
  - ✓ Real-time patient-reported symptomatic adverse events may improve the precision and reproducibility

Symptomatic Adverse Events

- Clinician reporting of symptomatic adverse events in cancer clinical trials underestimates the frequency and severity of symptoms compared to patient-reported outcome measures.

  (Basch NEJM 2010, Velikova JCO 2004, Fromme JCO 2004,)

- Agreement between patient and clinician reporting is moderate at best, with patients reporting greater severity of symptoms than reflected in clinician-graded events.

  (Atkinson Q Support Car Cancer 2016, Atkinson Qual Life Res 2012)

PRO-CTCAE™

- PRO-CTCAE is derived from the CTCAE version 4.0.
  - ✓ Designed specifically for patient-reported symptomatic adverse event in a manner consistent and complementary to clinician-reported CTCAE.
    - 78 symptomatic adverse event from CTCAE used for 124 items.
- It is an item bank that does not require that all items are used together.
  - ✓ Selection of items specific to those adverse events to capture at baseline and monitor over time.
- Publicly available since April 2016
  - ✓ Complete library of items: https://healthcaredelivery.cancer.gov/pro-ctcae
- Over 30 translated versions are available for use

Patient-Reported Outcomes version Of The Common Terminology Criteria For Adverse Events (PRO-CTCAE™)

QUICK GUIDE TO THE ITEM LIBRARY*

Oral	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

Gastrointestinal	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	SI
Cough	SI
Wheezing	S

Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

Cutaneous	
Rash	P
Skin dryness	S
Acne	S
Hair loss	A
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	SI
Fatigue	SI

Mood	
Anxious	FSI
Discouraged	FSI
Sad	FSI

Genitourinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	A
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	FI
Change in usual urine color	P
Urinary incontinence	FI

Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

Miscellaneous	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

Attributes	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence
A: Amount	

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Version date: 3/11/2020

CTCAE Grading versus PRO-CTCAE™ Scoring

- Clinician provides a single grade for each adverse event item
  - ✓ Grading requires the clinician bundle severity and interference together.
  - ✓ Distinction between grade 2 and 3 specific to medical interventions.

- Patients score severity, frequency, and interference separately

- Patient's scores do not equal clinician grades.
  - ✓ Currently, scores are only for descriptive reporting.
  - ✓ Ongoing work is evaluating composite scores.

CTCAE vs. PRO-CTCAE™ Item Structures

CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	-

PRO-CTCAE
Please think back over the past 7 days:
What was the severity of your MOUTH OR THROAT SORES at their WORST? None / Mild / Moderate / Severe / Very severe
How much did MOUTH OR THROAT SORES interfere with your usual or daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

Incorporation of PRO-CTCAE™ into Cancer Clinical Trials

- Systematic review of PROs from 2004 through 2018
  - ✓ PRO-CTCAE used in 2.2% of trials (*Giesinger Value Health 2021*)
- PRO-CTCAE is feasible in phase 3 trials.
  - ✓ Excellent patient compliance in rectal cancer trial *(Basch JCO 2018)*
  - ✓ Patient reported data improved accuracy of symptomatic adverse events in a metastatic phase 3 prostate cancer trial. (*Dueck, JAMA Oncol 2020*)
- PRO-CTCAE in phase 3 radiation trial showed better granularity of bothersome toxicity *(Yeung, JCO 2020)*
  - ✓ Patient-reported symptomatic adverse events showed a reduction in symptoms with intensity modulated radiation therapy in comparison to standard radiation whereas clinician safety data did not.

Tolerability of Cancer Treatment

- Current approach
  - ✓ Phase 1 dose escalation is based upon the most severe adverse events in the first cycle of treatment.
  - ✓ If no significant ≥ grade 3 adverse events, then considered tolerable regimen.
  - ✓ However, this approach does not capture the impact of chronic, low grade adverse events over time.

- NCI Moonshot for Tolerability of Cancer Treatment *(RFA CA-17-053)*
  - ✓ Analyzing clinician-reported CTCAE adverse events and patient-reported PRO-CTCAE data retrospectively along with other clinical data to develop new methods and approaches to understand tolerability of cancer treatment

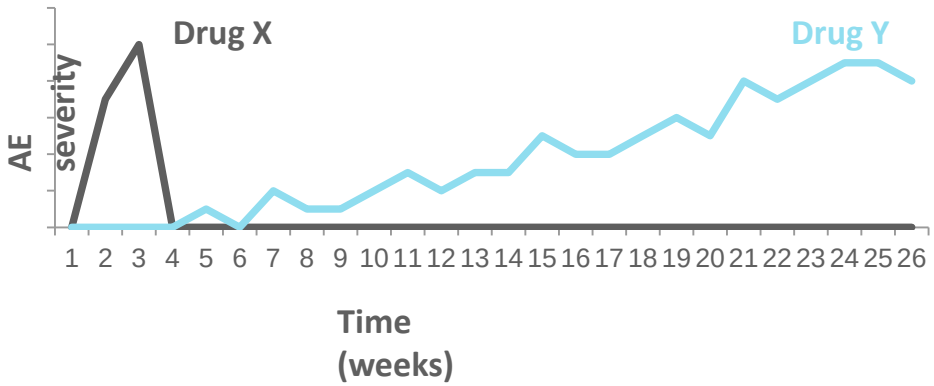
Relevance of AE time profile

(courtesy Gita Thanarajansingam)

Two grade 3+ AEs with similar incidence (conventional maximum grade reporting)

Grade 3 or higher	Drug X + standard regimen (n=463)	Drug Y + standard regimen (n=456)
Dyspnea	**25 (5%)**	10 (2%)
Peripheral neuropathy	6 (1%)	**24 (5%)**

Patient experience of AE: which is more burdensome?



NCI Moonshot Tolerability Consortium Approaches In Progress

- Assessing longitudinal toxicity (trajectory over time)
  - ✓ ToxT *(Thanarajasingam Lancet Hem 2020)*

- Identifying cumulative toxicity
  - ✓ Burden of multiple low-grade and sometimes, chronic, toxicities
  - ✓ Toxicity Index *(Gresham JNCI 2020, Razaee Stat Med 2021)*

- Evaluating baseline patient factors as predictors of tolerability
  - ✓ Risk for discontinuation of treatment based upon treatment emergent symptomatic adverse events *(Wagner Breast Cancer Res Treat 2018)*

Summary from PRO-CTCAE

- Feasible to incorporate into cancer clinical trials
- Patient reporting of symptomatic adverse events can complement clinician reporting and provide valuable insight into tolerability
- Standard approaches to the use and analysis of PRO-CTCAE are under development
- Tolerability methods are being developed and evaluated using retrospective trial data

Pediatric Module of the Patient-Reported Outcomes version Of The Common Terminology Criteria For Adverse Events (Ped-PRO-CTCAE™)

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Dry mouth	SI
Difficulty swallowing	S
Mouth/throat pain	FSI
Voice quality changes	PI
Hoarseness	FSI
Sore throat	SI

Gastrointestinal	
Taste changes	PI
Decreased appetite	F
Nausea	FSI
Vomiting	FI
Heartburn	FS
Gas	PI
Bloating	PI
Hiccups	FS
Constipation	FSI
Diarrhea	FI
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	FSI
Cough	FSI
Wheezing	SI
Sneezing	S

Cardio/Circulatory	
Swelling	SI
Heart palpitations	FS

Cutaneous	
Skin dryness	P
Acne	S
Hair loss	P
Itching	SI
Hives	P
Sensitivity to sunlight	P
Skin ulceration	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	PI
Flashing lights	FI
Watery eyes	FSI
Ringing in ears	SI
Dry eyes	FSI

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	FSI
Fatigue	SI

Mood	
Anxious	FSI
Sad	SI
Suicidal ideation	P

Genitourinary	
Painful urination	SI
Urinary urgency	FI
Urinary frequency	FI
Change in usual urine color	P
Urinary incontinence	FI

Miscellaneous	
Bruising	P
Chills	FS
Increased sweating	FSI
Hot flashes	FSI
Nosebleed	FSI
Falls	F
Muscle weakness	FSI
Restlessness	SI

Attributes	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence

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