Response evaluation and adverse events

Part 2 of 2

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*** Japan Clinical Oncology Group** (https://jcog.jp/en/)

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ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

Today's contents

- Response evaluation and
  Response Evaluation Criteria in Solid Tumors (RECIST)
  - Accuracy and precision
  - Basic logic of RECIST
  - Hypothetical example of response evaluation of a lesion

- Adverse events and
  Common Terminology Criteria for Adverse Events (CTCAE)
  - What is an adverse event?
  - Reporting adverse events
  - History and structure of CTCAE
  - Evaluation of adverse events using CTCAE

- Common Terminology Criteria for Adverse Events
  - Exhaustive list of adverse events produced by the National Cancer Institute (NCI)
    - Corresponds to any adverse event regardless of the modality such as chemotherapy, radiation therapy, or surgery
  - Comprises common adverse event names and common grade criteria
  - These are the adverse event evaluation criteria themselves
  - Not used in cases other than those of cancer
    - Surgical trials may use different adverse event criteria (e.g., Clavien-Dindo classification)

✓ Universal scale for evaluating adverse events

What is an adverse event?

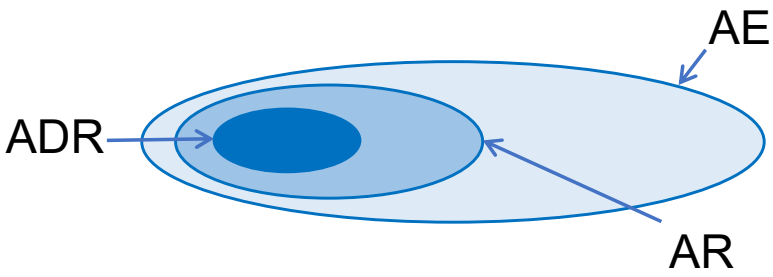
- Includes all the following factors
  - Side effect
  - Complication
  - Toxicity
  - Morbidity
- Definition of “adverse events” by NCI
  - Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

What is an adverse event?

- Adverse Event (AE)
  - Any adverse medical event that has occurred to the patient
  - Regardless of the attribution to treatment
- Adverse Reaction (AR)
  - AEs whose attribution to any drug as well as other treatments and concomitant therapy, such as radiation therapy or surgery, cannot be ruled out

    *Not clearly defined in ICH guidelines
- Adverse Drug Reaction (ADR)
  - Adverse and unintended reaction to medication at any dose
  - Adverse events (AR) whose attribution to a drug cannot be ruled out

    ＝also called “side effect”



- The requirement of recording / reporting adverse events is not determined by the presence or absence of attribution to treatment
- Determining attribution is a secondary step and not used to examine whether to record / report adverse events

Relevance: attribution

- Attribution in five stages (NCI definition)

	Judgment	Conceptualization of judgment
Attributable	Definite	The AE is clearly related to the intervention Judged that the AE was clearly being caused by or aggravated by protocol treatment and that there was almost no possibility of the AE being caused by the progression of the original disease or other factors (such as comorbidities, other drugs / treatments, accidental symptoms)
	Probable	The AE is likely related to the intervention Judged that the AE being caused by the progression of the original disease or other factors (comorbidities, other drugs / treatments, accidental symptoms) was unlikely and that the possibility of it being caused by or aggravated by protocol treatment was high
	Possible	The AE may be related to the intervention Judged that it is more plausible to think that the AE was caused by or aggravated by protocol treatment and that the possibility of it being caused by progression of the original disease or other factors (comorbidities, other drugs / treatments, accidental symptoms) was low
Not attributable	Unlikely	The AE is doubtfully related to the intervention Judged that it is more plausible to think that the AE was caused by the progression of the original disease or other factors (comorbidities, other drugs / treatments, accidental symptoms) rather than thinking that it was caused by or aggravated by protocol treatment
	Unrelated	The AE is clearly NOT related to the intervention It is clear that the AE was caused / aggravated by the progression of original disease or other factors (comorbidities, other drugs / treatments, accidental symptoms), and it is judged that there is little possibility of it being due to protocol treatment

https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

History of CTCAE

- 1983：ver. 1 (formerly known as NCI-CTC）
  - Former JCOG side effect judgment criteria / JSCO side effect criteria…conform to these criteria
  - Many groups subsequently added their own items→no longer common criteria
  - Establishment of working groups by NCI
  - U.S. / European / Canadian clinical trial groups and regulatory agencies
- 1998：NCI-CTC ver. 2.0 -β version
- 1999：Revision of NCI-CTC ver. 2.0
- 2004：CTCAE ver. 3.0
- 2009：CTCAE ver. 4.0
  - Conforms to MedDRA terminology
- 2017：CTCAE ver. 5.0
  - Return of Navigational Note
  - Existence of terms with different grade definitions depending on whether test values are recorded before the start of treatment (baseline), are within reference range (normal), or are abnormal.

Structure of CTCAE

- SOC：System Organ Class
  - 26 classifications
  - Alphabetical order

    Examples: Blood and lymphatic system disorders, Cardiac disorders, Ear and labyrinth disorders, Endocrine disorders…
- AE term：Adverse Event
  - 837 terms
  - All adverse event names correspond to MedDRA terminology
  - All adverse events belong to some SOC
  - Each adverse event has a simple definition
- Grade
  - Adverse event severity / seriousness classification: defined terms do not correspond with MedDRA
  - 1: Mild–5: Death
- Definition
  - Brief definition provided to clarify the meaning of each AE term
- Navigational Note

Principles of grade definition

- Classification of seriousness
  - Evaluate the extent of life-threatening or permanent disability
  - Not just for intensity of symptoms
  - Grade 1
    - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2
    - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3
    - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
  - Grade 4
    - Life-threatening consequences; urgent intervention indicated.
  - Grade 5
    - Death related to AE.

How CTCAE is used in clinical trials

- Reporting safety results
  - Phase I / II trials: comparisons with safety levels reported in previous trials
  - Phase III trial: comparison of safety between treatment arms (e.g., adverse event rate)
- Eligibility criteria
  - Example: Grade 2 or higher leukopenia (white blood cell count ≤ 3,000 / mm^3) is ineligible
- Treatment change / discontinuation criteria
  - Example: Discontinuation of protocol treatment with grade 3 pneumonitis
  - Example: Postponement of start of course due to grade 2 diarrhea
- Definition of dose-limiting toxicity (DLT) and maximum tolerated dose (MTD)
  - Determination of recommended dose in Phase II trials
- Reporting criteria for serious adverse events (SAEs)

Let's use CTCAE! (1)

TRY

Q: A patient undergoing radiation therapy for external ear cancer was examined.
At the time of examination, the doctor explained, “the inflammation is getting stronger.”
The skin was turning red and seemed to bleed when it rubbed against the shirt collar.
What is the name and grade of the adverse event?

CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v5.0 AE Term Definition	Navigation Note
Otitis externa	Localized; local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage.	Changes associated with radiation to external ear (pinnae) are graded under injury, poisoning, and procedural complications: Dermatitis radiation
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death	A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.	Synonym: Radiation induced skin toxicities (CTCAE v3.0)

A. Grade 3 dermatitis radiation

Let's use CTCAE! (2)

TRY

Q: A patient says, “I have recently been having bowel movements about five times a day, and I am passing stools. I am worried that I’ll want to go to the toilet again even after I’ve had a bowel movement.”
What is the grade of diarrhea?

CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v5.0 AE Term Definition
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with the baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with the baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an increase in frequency and/or loose or watery bowel movements.

A. Cannot determine from this information alone
(baseline information needed)

Let's use CTCAE! (3)

TRY

* ULN：Upper limit of normal (at the institution)

CTCAE v4.0

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase level increased	>ULN* - 3.0 x ULN ＞30-90	>3.0 - 5.0 x ULN ＞90-150	>5.0 - 20.0 x ULN ＞150-600	>20.0 x ULN ＞-600	-

CTCAE v5.0

CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase level increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal ＞60-120	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal ＞120-200	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal ＞200-800	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal ＞800	-

Q. When the institutional reference range is 13–30 (ULN=30), the baseline value (before treatment) is 40 U/L, and treatment value is 110 U/L, then what is the:

- Grade in ver. 4.0? Grade 2
- Grade in ver. 5.0? Grade 1

Precautions while using CTCAE

- Principles of the “nearest match” (ver. 2.0 manual)
  - Grade to classification with the closest content
  - May not fit perfectly
  - Not the case where if even part of it is applicable, then classified to higher grade

December 2019: Confirmed by the NCI

- Grade to classification with the closest content
- If definition of multiple grades is equally applicable and it is difficult to decide which grade, then evaluate as higher grade (record the highest grade)

Example:

CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
○○	A1; B1	A2; B2	A3; B3	A4; B4	Death

The concept is as follows: for condition A, when unsure between A2 and A3 but then going with A2 according to the nearest match, and for condition B, when similarly unsure between B2 and B3 but then going with B3 according to the nearest match, when both A2 and B3 are satisfied, then the grade is judged as grade 3.

Precautions while using CTCAE

- “What should be done” principle
  - Medical judgment of “what should be done” rather than “what was actually done”
  - Based on the medical opinion of what should be done, not what was actually done
- “No modification at baseline” principle
  - Do not adjust grade according to status before treatment (baseline)

    Q: “There was grade 2 nausea before treatment, and it continued to be grade 2 after starting treatment”
    Should this be set as an adverse event or not?

    A: Nausea: set as grade 2 adverse event
    However, attribution to treatment is set as “unlikely” or lower

Let's use CTCAE! (4)

TRY

Q: A patient undergoing outpatient treatment with oral anticancer drugs was examined without an appointment. After seeing the test results, the doctor explained to the patient that, “you are dehydrated, so please increase fluid intake.” The patient then responded, “I’m worried, so I’d like to have an intravenous drip.” The patient was then given a drip and sent home.
What is the grade of dehydration in this case?

CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v5.0 AE Term Definition
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated	Hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.

✓ Increase fluid intake : what should be done
✓ Drip given : what actually done

A. Grade 1

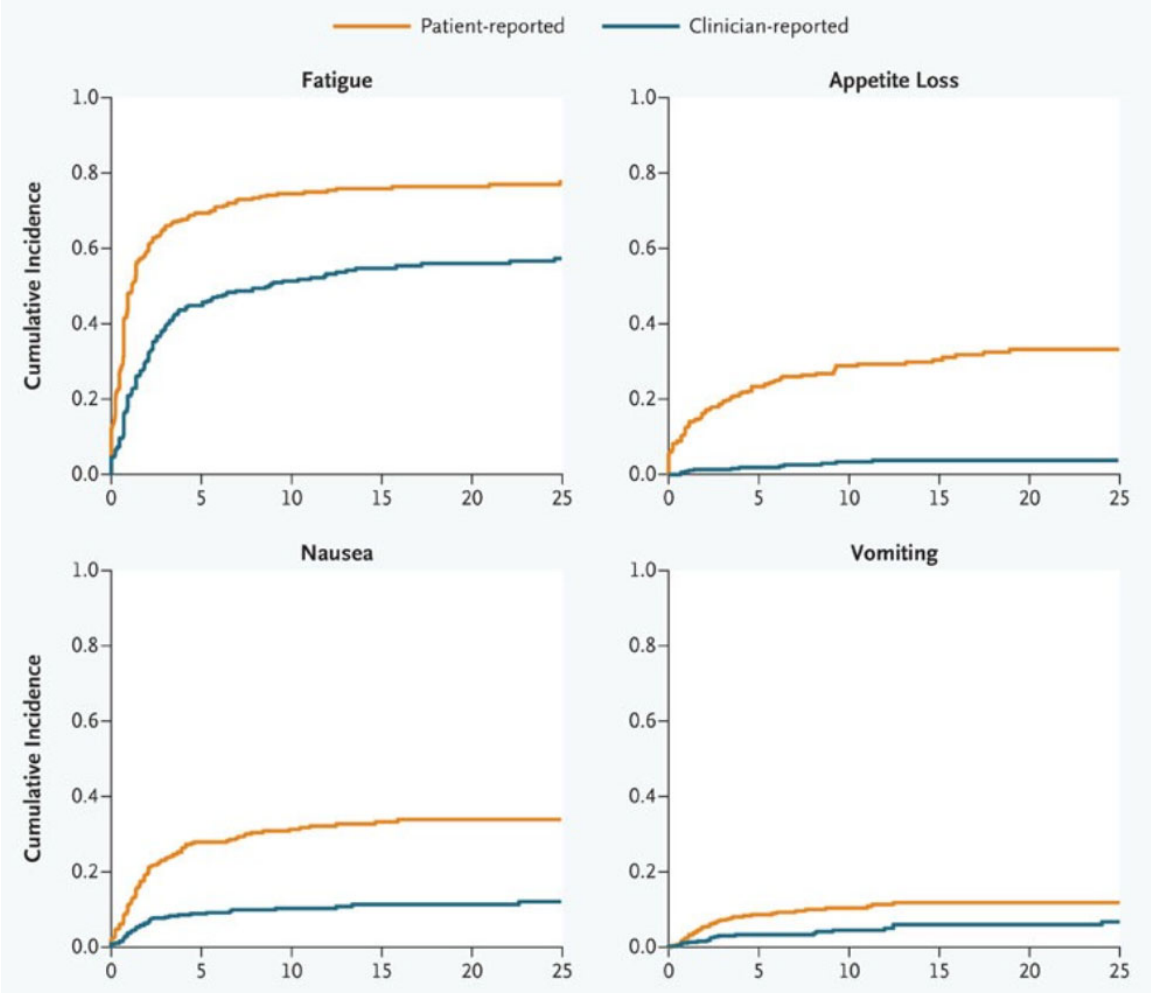
PRO-CTCAE

- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
- PRO-CTCAE™ ver. 1.0

  Downloadable from the NCI website

  https://healthcaredelivery.cancer.gov/pro-ctcae/overview.html
- Reports of patients' health status obtained directly from patients without interpretation by clinicians or anybody else (FDA Guidance for Industry [2009])
- Measurement of symptoms, signs, and functions related to disease states from patient's perspective
- Importance of subjective evaluations by the patients themselves (patient-reported outcomes [PRO]), in addition to outcome evaluations by healthcare professionals in clinical trials, has been recognized in recent years

Differences in perception of symptoms between doctors and patients



Basch E et al. NEJM 2010

PRO-CTCAE ver.1.0

- Concept of PRO applied to the evaluation of adverse events in clinical trials and developed with the aim of constructing an evaluation system that allows more accurate and precise grading [research team at the U.S. NCI (principal investigator: Ethan Basch)]
- A tool that can evaluate adverse events based on patients' self-evaluation by introducing PRO elements while using the existing CTCAE

https://healthcaredelivery.cancer.gov/pro-ctcae/instrument-pro.html

PRO-CTCAE questionnaire

National Cancer Center Japan

NCI- PRO-CTCAE® ITEMS-ENGLISH

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1. PRO-CTCAE® Symptom Term: Dry mouth				
a. In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

2. PRO-CTCAE® Symptom Term: Difficulty swallowing				
a. In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3. PRO-CTCAE® Symptom Term: Mouth/throat sores				
a. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES				
O None	O Mild	O Moderate	O Severe	
b. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

124 questions about 80 events
Other symptoms
(18 pages total)

PRO-CTCAE ver.1.0

National Cancer Center Japan

- Are all entries needed?
  - Partially available for each trial, depending on the purpose
- Recommended time
  - Evaluation before the start of treatment: < 20 minutes
  - Evaluation after the start of treatment: <10–15 minutes
- Target period
  - Period for patients to reflect on symptoms (recall period) is 7 days
- Simultaneous evaluation and reporting of CTCAE items that correspond to PRO-CTCAE endpoints is recommended

Summary of CTCAE

- What is an adverse event?
  - Adverse Event (AE)
  - Adverse Reaction (AR)
  - Adverse Drug Reaction (ADR)
- CTCAE are international common criteria for adverse events
  - Purpose is to enable comparison of clinical trial data from around the world
  - Prioritize “comparability (precision)” rather than “accuracy”
  - CTCAE are the adverse event evaluation criteria themselves
- CTCAE principles
  - “nearest match, highest grade”
  - “what should be done”
  - “no modification at baseline”

Take-Home Message

- RECIST and CTCAE are common international criteria for cancer clinical trials
  - Purpose is to enable comparison of clinical trial data worldwide
  - Prioritize “comparability (precision)” over “accuracy”
- RECIST
  - Common international guideline for response evaluations
  - Not response evaluation criteria themselves (need to describe details in protocol)
  - Not an index to decide treatment continuation / discontinuation
- CTCAE
  - Common international criteria for adverse events
  - Can be used as-is, unlike with RECIST
  - Principles：“nearest match” “what should be done”
    “no modification at baseline”
- PRO-CTCAE