Patient-Reported Outcome (PRO) Tools and CAR T Therapy

Background and Comments on Tools Identified for MEDCAC (Addressing Questions 1 & 2)

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Disclosures

I do not receive funding from manufacturers of pharmaceutical products

I receive research funding from the National Cancer Institute (NCI) and Patient-Centered Outcomes Research Institute (PCORI)

My research group developed the PRO-CTCAE for the NCI under prior government contracts, and that tool is the intellectual property of the NCI

Oncologist Perspective

When I sit with a patient to make a decision about a drug

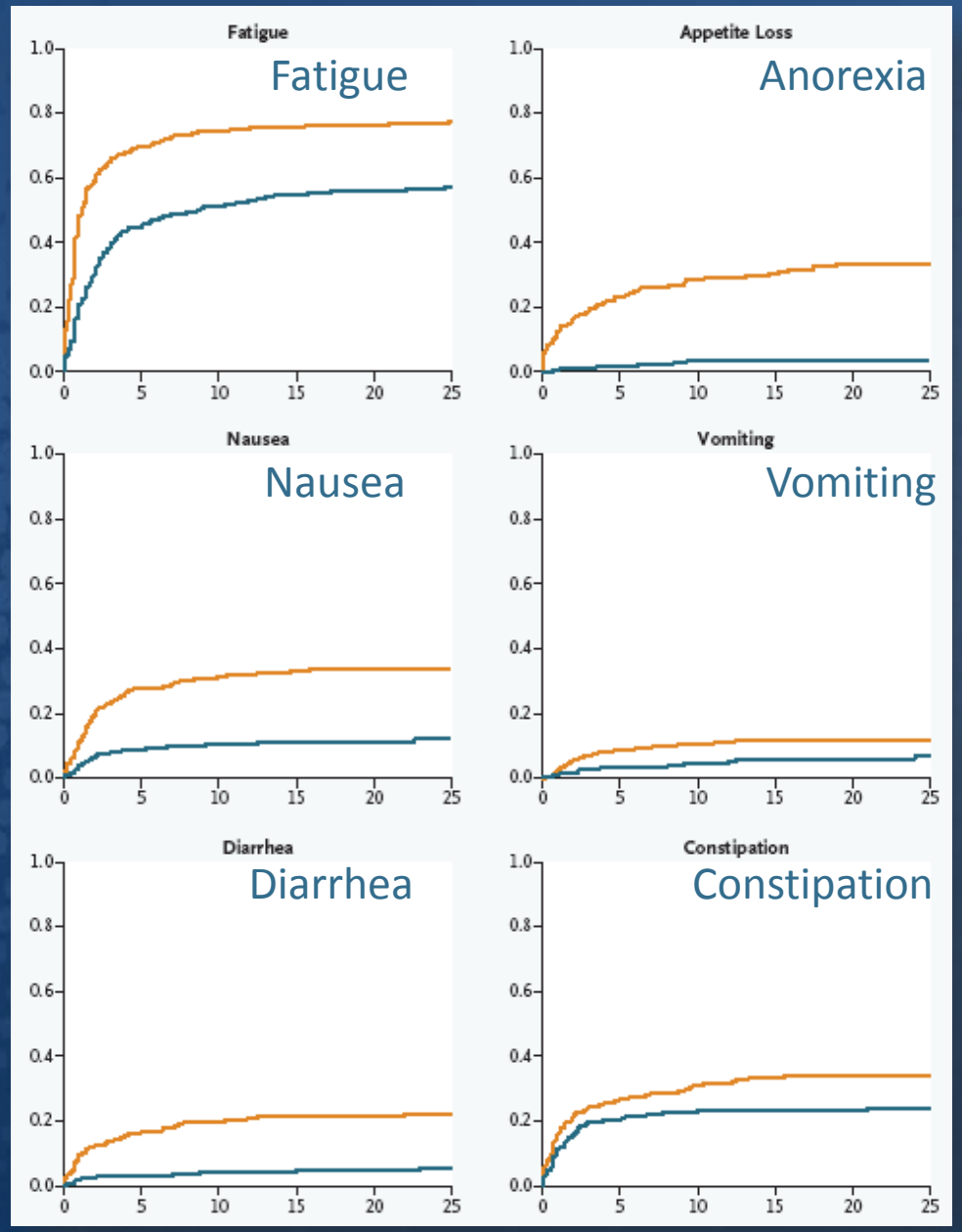
First questions they ask:

- How will I feel with this product? How did patients like me feel previously with it?

Without this information, we have impaired ability to make informed decisions

- Incomplete understanding of product's characteristics
- Limited understanding of longitudinal patent experience

Basch: NEJM 2013;369:397



Can investigators capture this information on behalf of patients? No.

- *Investigators miss more than half of patients' symptoms in documentation*
- *If this information is not collected directly from patients in trials, it will be lost*

Patient-reported

Clinician-reported

Basch: NEJM 2010;369:397

Particularly Important in Assessments of Adverse Events

- Clinician reporting of symptomatic AEs has low inter-rater reliability; introduces noise
- Reporting by clinicians for symptomatic AEs is therefore not adequate for trial grade data
- Well developed PRO tools have highly reliability

Symptom	ICC	95% CI
Constipation	0.48	0.36; 0.58
Diarrhea	0.58	0.49; 0.66
Dyspnea	0.69	0.62; 0.75
Fatigue	0.50	0.39; 0.59
Nausea	0.52	0.41; 0.60
Neuropathy	0.71	0.65; 0.76
Vomiting	0.46	0.34; 0.56

Atkinson/Basch: Qual Life Res 2012;21:1159

	TAXOTERE 75 mg/m2 every 3 weeks	
ADVERSE REACTION	**ANY (%)**	**GRADE 3/4 (%)**
Anemia	67	5
Neutropenia	41	32
Thrombocytopenia	3	1
Infection	32	6
Epistaxis	6	0
Allergic Reactions	8	1
Neuropathy Sensory	30	2
Neuropathy Motor	7	2
Rash/Desquamation	6	0
Alopecia	65	N/A
Nail Changes	30	0
Nausea	41	3
Diarrhea	32	2
Stomatitis/Pharyngitis	20	1
Taste Disturbance	18	0
Vomiting	17	2
Anorexia	17	1
Cough	12	0
Dyspnea	15	3
Cardiac function	10	0
Fatigue	53	5
Myalgia	15	0
Tearing	10	1
Arthralgia	8	1

Table from Taxotere U.S. Drug Label

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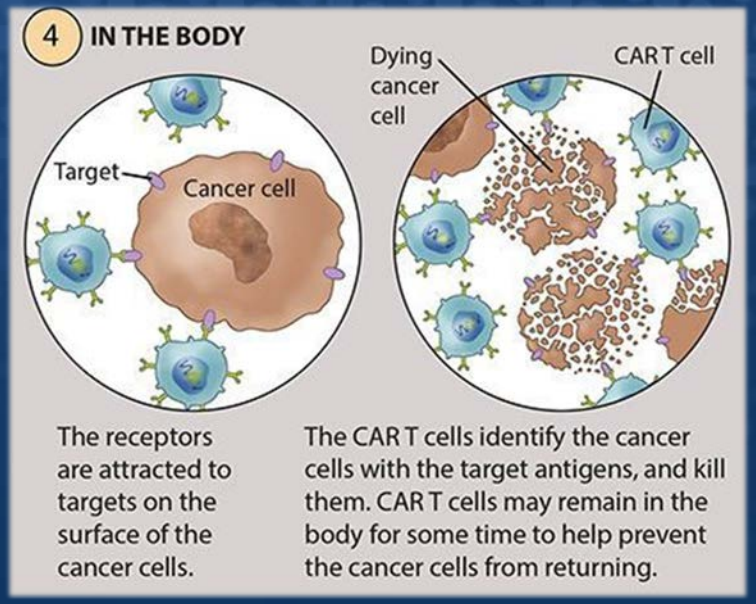
Table from Taxotere U.S. Drug Label

Applicability of PROs to CAR T

Domains of potential interest

- Symptomatic adverse events (AEs)
  - Short-term toxicity profile
  - Long term toxicity profile
  - Early or changing symptoms that might flag impending CRS
- Physical functioning
- Change in disease-related symptoms



PRO Tools Previously Identified by CMS

I have been asked to provide information about each

- Will describe each briefly, comment on measurement properties and issues related to the specific questions being asked of the MEDCAC panel
- Information is supported by reviews of scientific literature and clinical trials conducted by Thomas Atkinson, PhD @ MSKCC

Thomas Atkinson, PhD

PRO Tools Previously Identified by CMS

Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE)
MD Anderson Symptom Inventory (MDASI)
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Core Questionnaire)
University of Washington Quality of Life (UW-QOL)
Patient-Reported Outcome Measurement Information System (PROMIS)
Electronic Self-Report–Cancer (ESRA-C)
Functional Living Index–Cancer (FLIC)

Specified in CMS online materials:
https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=76

PRO Tools Previously Identified by CMS

11 CAR T trials in ClinicalTrials.gov that include PRO endpoints

- 2 using PRO-CTCAE
- 9 using EORTC-QLQ-C30
- 2 using PROMIS

Properties/Characteristics I Will Address for Q1

Q1: “How confident are you that each of the following PRO assessments are valid and generalizable to the Medicare population?” (Assign score 1-5 for level of confidence)

For Q1: Key measurement Properties (“valid”)
Content validity (patient interviews)
Reliability (test-retest)
Construct validity
Clinical responsiveness

For Q1: Prior use in trials (“generalizable”)
Use in CAR T
Use in cancer trials w participants ≥65 (how widely)

Properties/Characteristics I Will Address for Q2

Q2. “Considering all PRO assessments in question 1 with greater than or equal to score 2.5, please vote whether or not those PRO assessments combined have available supporting evidence on each of the following desired characteristics.”

For Q2: Characteristics in CMS’ specific questions to board	*My understanding of each in this presentation*
A) Breadth of measures in emotional, social, and physical well-being	*Includes these QOL domains in the tool*
B) Quick throughput to apply to clinical study	*Can get up and running quickly for a trial*
C) Transferable to community practice settings	*Has been used in community setting*
D) Measures are not sensitive to differences in age	*Age alone does not sway scores*
E) Measures are not sensitive to line of therapy	*Line of therapy alone does not sway scores*
F) Measures are not sensitive to comorbidities	*Comorbidities do not sway scores **(PROBLEM)***
G) Measures are generalizable to study of combinations of therapies	*Has been used with combination therapies*
H) Used in net benefit analysis based on symptom burden and well-being	*Includes metric for overall impact of PROs*

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1.a. Patient version of the CTCAE

PRO item "library" maintained by the NCI

Developed for explicit purpose of patient AE reporting

Incudes 78 distinct AEs

Mapped to CTCAE and MedDRA

No license required, free for use

Adult version in use (pediatric version in development)

http://appliedresearch.cancer.gov/pro-ctcae

1.a. PRO-CTCAE

For Q1: Key measurement Properties	
Content validity (patient interviews)	Yes
Reliability (test-retest)	Yes
Construct validity	Yes
Clinical responsiveness	Yes

For Q1: Use in trials	
Use in CAR T	2 trials
Use in cancer trials w participants ≥65	Yes

1.a. PRO-CTCAE

For Q2: Characteristics in CMS' specific questions to board	
A) Breadth of measures in emotional, social, and physical well-being	N/A (adverse event tool)
B) Quick throughput to apply to clinical study	Yes
C) Transferable to community practice settings	Yes
D) Measures are not sensitive to differences in age	Yes
E) Measures are not sensitive to line of therapy	Yes
F) Measures are not sensitive to comorbidities	Yes (unless symptoms caused by comorbidities, but would presumably be present at baseline)
G) Measures are generalizable to study of combinations of therapies	Yes (has been done)
H) Used in net benefit analysis based on symptom burden and well-being	N/A (measures burden on patients, but one item at a time, not overall)

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1.b. MD Anderson Symptom Inventory

Well established questionnaire with 19 items

- 13 specific symptoms common in patients with cancer (not CAR T specific)
- 6 Qs about symptom interference with: general activity, mood, work, relations w other people, walking, enjoyment of life

Widely used in cancer trials

https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/md-anderson-symptom-inventory.html

1.b. MDASI

For Q1: Key measurement Properties	
Content validity (patient interviews)	Not initially but added subsequently
Reliability (test-retest)	Yes
Construct validity	Yes
Clinical responsiveness	Yes

For Q1: Use in trials	
Use in CAR T	No
Use in cancer trials w participants ≥65	Yes

1.b. MDASI

For Q2: Characteristics in CMS' specific questions to board	
A) Breadth of measures in emotional, social, and physical well-being	Sort of (impact of symptoms on these)
B) Quick throughput to apply to clinical study	Yes
C) Transferable to community practice settings	Yes
D) Measures are not sensitive to differences in age	Yes
E) Measures are not sensitive to line of therapy	Yes
F) Measures are not sensitive to comorbidities	Yes (unless symptoms caused by comorbidities, but would presumably be present at baseline)
G) Measures are generalizable to study of combinations of therapies	Yes (has been done)
H) Used in net benefit analysis based on symptom burden and well-being	Sort of (impact of symptoms on well being)

QLQ-C30

1.c. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC—QLQ-C30 (core questionnaire)

Well established classic QOL questionnaire with 30 items

- 5 items for physical functioning
- 14 symptoms common in patients with cancer (not CAR T specific)
- Multi-item scales for cognitive, emotional, physical role, social

Widely used in cancer trials

http://groups.eortc.be/qol/eortc-qlq-c30

1.c. EORTC QLQ-C30

For Q1: Key measurement Properties	
Content validity (patient interviews)	Not initially but added subsequently
Reliability (test-retest)	Yes
Construct validity	Yes
Clinical responsiveness	Yes

For Q1: Use in trials	
Use in CAR T	Yes (9 trials)
Use in cancer trials w participants ≥65	Yes

1.c. EORTC QLQ-C30

For Q2: Characteristics in CMS' specific questions to board	
A) Breadth of measures in emotional, social, and physical well-being	Yes
B) Quick throughput to apply to clinical study	Yes
C) Transferable to community practice settings	Yes
D) Measures are not sensitive to differences in age	Yes
E) Measures are not sensitive to line of therapy	Yes
F) Measures are not sensitive to comorbidities	Yes (unless symptoms caused by comorbidities, but would presumably be present at baseline)
G) Measures are generalizable to study of combinations of therapies	Yes (has been done)
H) Used in net benefit analysis based on symptom burden and well-being	Sort of (overall QOL items)

UW-QOL

1.d. University of Washington Quality of Life (UW-QOL)

Not well known

- 6 items for physical function
- 6 items for psycho-emotional function

http://www.hancsupport.com/sites/default/files/assets/pages/UW-QOL-update_2012.pdf

1.d. University of Washington Quality of Life (UW-QOL)

For Q1: Key measurement Properties	
Content validity (patient interviews)	No
Reliability (test-retest)	In Spanish and Chinese but unclear if in English
Construct validity	Yes (concurrent with QLQ-C30)
Clinical responsiveness	Yes

For Q1: Use in trials	
Use in CAR T	No
Use in cancer trials w participants ≥65	Limited

1.d. University of Washington Quality of Life (UW-QOL)

For Q2: Characteristics in CMS' specific questions to board	
A) Breadth of measures in emotional, social, and physical well-being	Emotional and physical
B) Quick throughput to apply to clinical study	Probably
C) Transferable to community practice settings	Yes
D) Measures are not sensitive to differences in age	Unclear (likely Yes)
E) Measures are not sensitive to line of therapy	Unclear (likely Yes)
F) Measures are not sensitive to comorbidities	Unclear (likely Yes - unless symptoms caused by comorbidities, but would presumably be present at baseline)
G) Measures are generalizable to study of combinations of therapies	Yes (has been done)
H) Used in net benefit analysis based on symptom burden and well-being	Unclear

National Institutes of Health

PROMIS Patient Reported Outcomes Measurement Information System®

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1.e. Patient Reported Outcomes Measurement Information System (PROMIS)

Brief, precise, fixed or tailored tools

Physical, mental, & social well-being; pain, fatigue, sleep

Meticulously developed

Offers short forms, CAT, single items

Adult & pediatric

https://commonfund.nih.gov/promis/index

1.e. PROMIS

For Q1: Key measurement Properties	
Content validity (patient interviews)	Yes
Reliability (test-retest)	Yes
Construct validity	Yes
Clinical responsiveness	Yes

For Q1: Use in trials	
Use in CAR T	2 trials
Use in cancer trials w participants ≥65	Yes (many)

1.a. PROMIS

For Q2: Characteristics in CMS' specific questions to board	
A) Breadth of measures in emotional, social, and physical well-being	Yes
B) Quick throughput to apply to clinical study	Yes
C) Transferable to community practice settings	Yes
D) Measures are not sensitive to differences in age	Yes
E) Measures are not sensitive to line of therapy	Yes
F) Measures are not sensitive to comorbidities	Yes (unless symptoms caused by comorbidities, but would presumably be present at baseline)
G) Measures are generalizable to study of combinations of therapies	Yes (has been done)
H) Used in net benefit analysis based on symptom burden and well-being	Sort of (overall QOL/heath status items)

ESRA-C

1.f. Electronic Self-Report-Cancer (ESRA-C)

Not well known

This is not a PRO measure, it is an electronic questionnaire system

Currently includes 3 previously developed questionnaires

- EORTC QLQ-C30; PHQ-9; Symptom Distress Scale (SDS)

The ESRA-C itself has not been well tested

Used in very few trials

https://www.ncbi.nlm.nih.gov/pubmed/17102311

FLIC

1.g Functional Living Index – Cancer (FLIC)

Not well known, older measure

22 items (Quick FLIC is 11 items)

Physical, emotional, social function; well-being; pain; nausea

Could only find 1 cancer trial listed using it

https://www.ncbi.nlm.nih.gov/pubmed/6374052

Summary

Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE)	?
MD Anderson Symptom Inventory (MDASI)	?
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Core Questionnaire)	?
University of Washington Quality of Life (UW-QOL)	
Patient-Reported Outcome Measurement Information System (PROMIS)	?
Electronic Self-Report–Cancer (ESRA-C)	
Functional Living Index–Cancer (FLIC)	

https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=76

Additional Questions to MEDCAC

Are there additional PRO assessments to consider?

Yes: FACT GP-5 single item

"I am bothered by side effects of treatment"

As a companion to PRO-CTCAE to assess patient-reported symptomatic adverse events

Rated on a 5-point Likert scale

Well developed, broad interest in using with PRO-CTCAE

https://www.ncbi.nlm.nih.gov/pubmed/29131323

Additional Questions to MEDCAC

Are there additional desired characteristics besides in Q2?

Measurement properties (content validity, construct validity, reliability, responsiveness)

Prior testing and use in populations with cancer

Availability of language translations

Includes items for key outcomes salient to CAR T trials

- What are those outcomes? – need qualitative work to be done

https://www.ncbi.nlm.nih.gov/pubmed/29131323

Conclusion

PROs provide valuable information about the patient experience, and about characteristics of products that cannot be well captured otherwise

There are well developed, available PRO tools that can be used in CAR T trials

Assessment of physical function, symptomatic adverse events, and disease-related symptoms should be considered in any given trial

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