FDA Perspective:
Patient Self-Reporting in the Evaluation of Cancer Drug Tolerability

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Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)

Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC)
May 11, 2021
Outline

• Definitions & Background

• How Patient Reported Outcomes (PROs) inform understanding of tolerability

• Key elements of PRO selection for symptomatic adverse events in clinical trials

• Unique considerations in pediatrics
Types of Clinical Outcome Assessments

Clinical Outcome Assessments (COA)

- Patient Reported Outcome (PRO)
  - Report directly from patient without interpretation by others
- Observer Reported Outcome (ObsRO)
- Clinician Reported Outcome (ClinRO)
- Performance Outcome (PerfO)
Importance of Patient Reported Outcomes

• Drug development is about and for **patients**

• Gives a formal avenue for the patient voice

• Symptoms in a given clinic visit ≠ the whole story

• Patients with same disease & same treatment can have vastly different experiences

• Cultural differences in how symptoms are perceived and expressed
History of Patient Reported Outcomes in Drug Development

- **2001**: PRO Harmonization Group Meeting at FDA
- **2013**: pedsODAC meeting on PROs
- **2014**: 21st Century Cures Act
- **2016**: 21st Century Cures Act
- **2017**: PRO-CTCAE* published
- **2020**: Pediatric PRO-CTCAE* published
- **2017**: OCE & Patient Focused Drug Development program established
- **2020**: Project Patient Voice

*PRO-CTCAE: Patient Reported Outcomes-Common Terminology Criteria for Adverse Events*
PROs in Labels of FDA Hematology and Oncology Products

- **PRO Objective**
  - Efficacy
  - Safety/Tolerability
  - Preference

- **Samarium** (1997)
- **Topotecan** (2003)
- **Gemcitabine** (2009)
- **Crizotinib** (2012)
- **Ceritinib** (2015)
- **Rituxan** (2017)
- **Hycela** (2019)
- **Phesgo** (2020)

- **Strontium**
- **Imatinib** (2009)
- **Abiraterone** (2012)
- **Eculizumab** (2015)
- **Ibrutinib** (2017)
- **Emicizumab** (2019)
- **Fedratinib** (2020)
- **Darolutamide**
- **Ravulizumab-cwvz**
Use of PROs to Evaluate Tolerability

• Safety vs. Tolerability

• Adjunct to clinician-reported safety data

• Friends of Cancer Research White Paper:
  “...degree to which symptomatic and non-symptomatic adverse events associated with the product’s administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy. A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment.” — Basch et al, 2020
Core Clinical Outcomes

Overall Survival
Progression Free Survival
Overall Response Rate
Serum Biomarkers

CTCAE* Safety Data
Dose Modifications

Hospitalizations
ED* Visits
Morbid Procedures
Supportive Care Use

Clinician Reported and Biomarker Data

*CTCAE: Common Terminology Criteria for Adverse Events; ED: Emergency Department
Core Clinical Outcomes

- Overall Survival
- Progression Free Survival
- Overall Response Rate
- Serum Biomarkers

CTCAE* Safety Data
- Dose Modifications

Hospitalizations
- ED Visits
- Morbid Procedures
- Supportive Care Use

Disease Symptoms
- Symptomatic Adverse Events
- Overall Side Effect Impact

Physical Function:
- Ability to Carry Out Activities that Require Physical Effort

Role Function:
- Ability to Work and Perform Leisure Activities

Clinician Reported and Biomarker Data
- Patient Generated Data

*CTCAE: Common Terminology Criteria for Adverse Events
Example: PRO data as complement to traditional safety data in adults

CTCAE:

<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL</td>
<td>Increase of &gt;=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements.

PRO-CTCAE:

16. PRO-CTCAE™ Symptom Term: Diarrhea

a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?

<table>
<thead>
<tr>
<th>O Never</th>
<th>O Rarely</th>
<th>O Occasionally</th>
<th>O Frequently</th>
<th>O Almost constantly</th>
</tr>
</thead>
</table>

Considerations when Collecting PRO Data to Characterize Tolerability

• Careful selection of specific items
  – Consider relationship to drug mechanism of action & expected toxicities

• High completion rate

• Assessment frequency
### Considerations for PRO Assessment Frequency in Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Standard 6-month treatment period</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 2</td>
</tr>
<tr>
<td>Symptomatic Adverse Events</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Global Single Item Side Effect</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical Function</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Role Function</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Disease Symptoms</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other Health-Related Quality of Life measures</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Assessments at further timepoints would be context dependent*
Effective Collection of PROs in Pediatric Populations

- Age-appropriate vocabulary and language comprehension
- Understanding of health concept being measured
- Duration of recall
- May need alternative approaches for younger children (e.g., observer report)
Conclusions

• Increasing use of PROs in oncology clinical trials

• PROs add complementary tolerability data

• Importance of pre-defined measures, study design & analyses

• Inclusion of the pediatric patient’s voice
Acknowledgments

- Paul Kluetz
- Vishal Bhatnagar
- Martha Donoghue
- Harpreet Singh
- Greg Reaman
- Rick Pazdur
Resources

- Oncology Center of Excellence Project Patient Voice ([https://www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice](https://www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice))
- NIH Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE; [https://healthcaredelivery.cancer.gov/pro-ctcae/](https://healthcaredelivery.cancer.gov/pro-ctcae/))
Patient-Reported Outcomes (PROs) in Pediatric Cancer Registration Trials

An FDA Perspective

Meena N. Murugappan, PharmD, MPH
Research Fellow, Oncology Center of Excellence
Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory (pedsODAC)
May 11, 2021
MOTIVATION
Utility of PROs in Cancer Drug Development in Adults

- Enhances reporting of symptomatic adverse events
- Informs benefit-risk assessment
- Facilitates shared decision making
- Improves clinical outcomes\(^1\)
The case for PROs in Pediatric Oncology

- The child’s voice is currently missing among the chorus of voices essential to pediatric oncology drug development.

- Clinicians and caregivers frequently under or overestimate symptoms and function when compared to children’s self-report, especially for less observable domains.²

- Pediatric PRO data can complement traditional safety data by quantifying symptoms from the patient’s perspective.
Research Questions

1. What % of pediatric oncology registration trials incorporated PROs?

2. Which Pediatric PRO instruments were most commonly used?

3. Were PRO endpoints approved for product labeling?

4. What are some opportunities to improve use of PROs in future trials?
Methods

- Identified pediatric oncology product applications approved between 1997 and 2020
- Reviewed sponsor submitted documents (e.g., Clinical Study Reports and Study Protocols)
- Extracted general information (e.g., approval year, trial phase, study design, and sample size)
- When PRO data available, we recorded: instruments used, endpoint hierarchy, approval for product labeling, and other quality indicators
RESULTS
PROs in pediatric oncology registration trials included in this review

- Clofarabine
- Asparaginase *Erwinia chrysanthemi*
- Everolimus
- Blinatumomab
- Denosumab
- Nilotinib
- Emapalumab
- Larotrectinib
- Dinutuximab
- Tisagenlecleucel
- Selumetinib

Years:
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
- 2019
- 2020
## PROs in FDA-approved Pediatric Oncology Product Applications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Approval Year</th>
<th>Trial Phase/Study Design</th>
<th>Sample Size</th>
<th>Age Median (range)</th>
<th>PRO/COA instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>Giant cell tumor of the bone</td>
<td>2013</td>
<td>Phase II, Open label, single arm</td>
<td>28</td>
<td>16 years (13 – 17)</td>
<td>Brief Pain Inventory – Short Form (BPI-SF)</td>
</tr>
<tr>
<td>Tisangenlecleucel</td>
<td>Relapsed/Refractory B-ALL</td>
<td>2017</td>
<td>Phase II, Open label, single arm</td>
<td>88</td>
<td>12 years (3 – 27)</td>
<td>PedsQL 4.0 Generic Core, EQ-5D-Y</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Advanced solid/primary CNS tumors</td>
<td>2018</td>
<td>Phase I/II, Open label, single arm</td>
<td>31</td>
<td>5 years (0.1 – 20)</td>
<td>PedsQL Infant Scale, PedsQL 4.0 Generic Core, Wong-Baker Faces Scale</td>
</tr>
<tr>
<td>Selumetinib</td>
<td>Neurofibromatosis Type 1, Inoperable plexiform neurofibromas</td>
<td>2020</td>
<td>Phase I/II, Open label, single arm</td>
<td>50</td>
<td>10 years (3.5 – 17)</td>
<td>NRS-11, PII, Pain Medication Survey, PedsQL 4.0 Generic Core, DVQ, PROMIS – Mobility and Upper Extremity, 6-minute walk test</td>
</tr>
</tbody>
</table>

**Abbreviations:** B-ALL: B-cell Acute Lymphoblastic Leukemia, CNS: Central Nervous System, PedsQL: Pediatric Quality of Life Inventory™, EQ-5D-Y: EuroQoL 5-Dimension (Youth), NRS: Numeric Rating Scale, PII: Pain Interference Index, DVQ: bowel and bladder Dysfunctional Voiding Questionnaire, PROMIS: Patient-Reported Outcomes Measurement Information System

PROs were treated as exploratory endpoints in all four trials and were not included in product labeling.
Common reasons for non-inclusion of PRO endpoints in Product Labeling Claims

⊙ Absence of a **clear research objective** and prospective analysis plan

⊙ Use of instruments that were **not fit-for-purpose or well defined**

⊙ Use of **proxy report** for non-observable domains like pain
DISCUSSION
Observers-Reporter Outcomes > Proxy Report

Child old enough/able to self-report?

Yes

Patient self-report preferred over caregiver report

No

Limit caregiver responses to observable domains

Studies have shown that more patient-caregiver agreement is seen in observable domains like mobility as compared to less visible concepts like pain.\textsuperscript{2-5}
Future Opportunities
Acknowledgements

Richard Pazdur
Paul Kluetz
Vishal Bhatnagar
Gregory Reaman
Erica Horodniceanu
Najat Bouchkouj
Elizabeth Duke
Martha Donoghue
Bellinda King-Kallimanis


FDA’s Project Patient Voice: Let the children be heard

Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
May 11, 2021

Vishal Bhatnagar, MD
Associate Director for Patient Outcomes
Oncology Center of Excellence (OCE)
Communicating Patient Experience Data

21st Century Cures Act encourages FDA to review and communicate patient experience data submitted in product applications

• Key Challenges:
  • Patient-reported outcomes (PRO) data are frequently submitted, but heterogeneity exists in collection, analysis, and presentation of data
  • United States Prescribing Information (USPI) offers limited space to communicate patient experience data adequately
Project Patient Voice

- Pilot website that provides a description of patient-reported, longitudinal, symptomatic adverse event data collected in registrational cancer clinical trials for approved drugs

FDA’s Project Patient Voice
Project Patient Voice is an online platform for patients and caregivers along with their healthcare providers to look at patient-reported symptom data collected from cancer clinical trials.

- **What is the purpose of Project Patient Voice?**
- **Why is this needed?**
- **What is the source of this patient-reported symptom information?**
- **What is the difference between patient-reported symptom information and the safety information in the drug label?**
- **What is the Pilot Phase of Project Patient Voice?**
- **How to use Project Patient Voice**
- **Limitations of Project Patient Voice**
- **Can my experience with symptoms be added to this information?**
- **Where can I send comments or questions about Project Patient Voice?**

### AURA3

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Disease Type</th>
<th>Drug</th>
<th>Study Design</th>
<th>Masking</th>
<th>Comparator Arm</th>
<th>Patient Questionnaire Used to Collect Symptom Data</th>
<th>FDA Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>AURA3</td>
<td>Advanced non-small cell lung cancer with EGFR mutation</td>
<td>TAGRESSO</td>
<td>Randomized</td>
<td>Open label</td>
<td>Platinum-based doublet chemotherapy</td>
<td>PRO-CTCAE</td>
<td>Here</td>
</tr>
</tbody>
</table>
How Was the AURA3 Study Conducted?

AURA3 is a Phase III, open label, randomized study comparing TAGRISSO™ with platinum-based doublet chemotherapy. To be included in AURA3, patients had an abnormal epidermal growth factor receptor (EGFRm+/T790M+) lung cancer that had spread to other parts of the lungs or body (locally advanced or metastatic non-small cell lung cancer - NSCLC) and had previously been treated with an approved EGFR-TKI medicine that had stopped working or did not work. Patients were allocated by a ratio of 2:1 Tagrisso: chemotherapy. For more information on how this study was conducted, refer to the product label.

Which Questionnaire Was Used to Collect Patient-Reported Symptoms?

Patients reported their symptom experiences via the Patient Reported Outcomes – Common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaire. PRO-CTCAE was developed by the National Cancer Institute (NCI) to evaluate symptomatic toxicity in patients in oncology clinical trials. The PRO-CTCAE questionnaire was designed to provide additional information that is complementary to existing safety and tolerability assessments reported by clinicians.
<table>
<thead>
<tr>
<th>Symptom (Attribute)</th>
<th>Column A</th>
<th>Column B</th>
<th>Column C</th>
<th>Column D</th>
<th>Column E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of Patients</td>
<td>Any symptom before treatment (%)</td>
<td>Any Worsening on treatment (%)</td>
<td>Worsening to Score 3 or 4 (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tagrisso</td>
<td>Chemo</td>
<td>Tagrisso</td>
<td>Chemo</td>
</tr>
<tr>
<td>Nausea (F)</td>
<td>30</td>
<td>44</td>
<td>25%</td>
<td>32%</td>
<td>41%</td>
</tr>
<tr>
<td>Blurry Vision (S)</td>
<td>30</td>
<td>44</td>
<td>29%</td>
<td>32%</td>
<td>39%</td>
</tr>
<tr>
<td>Decreased Appetite (S)</td>
<td>30</td>
<td>44</td>
<td>54%</td>
<td>52%</td>
<td>39%</td>
</tr>
<tr>
<td>Constipation (S)</td>
<td>30</td>
<td>44</td>
<td>43%</td>
<td>45%</td>
<td>38%</td>
</tr>
<tr>
<td>Ridge or Bumps on your Fingernails or Toenails (O)</td>
<td>30</td>
<td>44</td>
<td>30%</td>
<td>34%</td>
<td>38%</td>
</tr>
<tr>
<td>Problems Tasting Food or Drink (S)</td>
<td>30</td>
<td>44</td>
<td>24%</td>
<td>30%</td>
<td>36%</td>
</tr>
<tr>
<td>Change in Color of your Fingernails or Toenails (O)</td>
<td>30</td>
<td>44</td>
<td>6%</td>
<td>7%</td>
<td>36%</td>
</tr>
<tr>
<td>Skin Cracking at Corners of your Mouth (S)</td>
<td>30</td>
<td>44</td>
<td>14%</td>
<td>2%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Attributes: A – Amount; F – Frequency; O – Occurrence; S – Severity/Intensity
Chemo = Chemotherapy; N/A = Not Applicable (For symptoms with Occurrence attribute, worsening to score 3 or 4 is not applicable, as responses are either Yes or No)

1. **No. of Patients**: The number of patients who provided a score before treatment and at least one on-treatment score (between weeks 1-24).
2. **Any Symptom Before Treatment (%)**: The percentage of patients whose symptom score before treatment was 1-4.
3. **Any Worsening (%)**: The percentage of patients whose symptom score increased during treatment, with respect to their score before treatment.
4. **Worsening to Score 3 or 4 (%)**: The percentage of patients whose symptom score increased to 3 or 4 during treatment, with respect to their score before treatment.
Figure 1. Patient-Reported Nausea During the First 24 Weeks on Treatment

<table>
<thead>
<tr>
<th>Tagrisso 80 mg</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Patients Without Symptoms (%)</td>
</tr>
<tr>
<td>81</td>
<td>75%</td>
</tr>
<tr>
<td>86</td>
<td>78%</td>
</tr>
<tr>
<td>89</td>
<td>80%</td>
</tr>
<tr>
<td>92</td>
<td>83%</td>
</tr>
<tr>
<td>88</td>
<td>85%</td>
</tr>
<tr>
<td>81</td>
<td>88%</td>
</tr>
<tr>
<td>91</td>
<td>81%</td>
</tr>
<tr>
<td>84</td>
<td>83%</td>
</tr>
<tr>
<td>83</td>
<td>82%</td>
</tr>
<tr>
<td>90</td>
<td>80%</td>
</tr>
<tr>
<td>73</td>
<td>85%</td>
</tr>
<tr>
<td>76</td>
<td>78%</td>
</tr>
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<td>80</td>
<td>85%</td>
</tr>
<tr>
<td>73</td>
<td>78%</td>
</tr>
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<td>76</td>
<td>71%</td>
</tr>
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<td>85</td>
<td>75%</td>
</tr>
<tr>
<td>69</td>
<td>77%</td>
</tr>
<tr>
<td>70</td>
<td>81%</td>
</tr>
<tr>
<td>73</td>
<td>79%</td>
</tr>
<tr>
<td>75</td>
<td>77%</td>
</tr>
<tr>
<td>82</td>
<td>82%</td>
</tr>
</tbody>
</table>

Percentage of Patients (%)

Frequency:
- Never
- Rarely
- Occasionally
- Frequently
- Almost Constantly

Legend:
- N = Number of Patients
Worst Response Option for Nausea That Patients Reported During the First 24 Weeks on Treatment, for Patients Who Did Not Have Nausea Before Treatment:

Figure 4. Worst Patient-Reported Nausea During the First 24 Weeks on Treatment: Patients Without Nausea Before Treatment

<table>
<thead>
<tr>
<th>Tagrisso 80 mg</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>55%</td>
<td>27%</td>
</tr>
</tbody>
</table>

**Frequency:**
- Never
- Rarely
- Occasionally
- Frequently
- Almost Constantly

Patients who had no Nausea before treatment and at least one on-treatment Nausea score were included in the analysis. Tagrisso (N=60), Chemotherapy (N=30).
Key Technical Challenges

• Providing adequate warning to users on limitations of the data presented
• Website content considerations (e.g., text reading level)
• Access for individuals with disabilities (508 compliance)
• Agreement with commercial sponsor on tables and figures
Trials Appropriate for Project Patient Voice

• Registrational trial for an approved indication
  • Adult or pediatric populations

• Should contain rigorously collected patient-reported symptomatic adverse event data:
  • Appropriate symptoms selected
  • Focus on treatment-related/tolerability data
  • Appropriate assessment frequency
  • High completion rate
  • Single-arm trials could be included

• Current focus is symptomatic adverse events – considering how to include physical function data

• Inclusion for Project Patient Voice is at OCE’s discretion
Conclusions

• PRO data should be collected and analyzed in a way that is meaningful and interpretable for patients and healthcare providers.

• FDA’s Project Patient Voice is a way to disseminate high-quality PRO.

• Better collection of patient-reported tolerability data from children enrolled in registrational clinical trials can lead to inclusion on Project Patient Voice.

• This data can be informative to children, caregivers, and healthcare providers as descriptive, complementary information before and during treatment.
Acknowledgements

FDA Project Patient Voice Development Team

OCE
Rick Pazdur
Paul Kluetz
Vishal Bhatnagar
Bellinda King-Kallimanis
Kirsten Goldberg
Erica Horodniceanu

Office of Oncologic Diseases
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Office of Biostatistics
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Mallorie Fiero
Laura Lee Johnson
Scott Komo