PATIENT-REPORTED OUTCOMES IN PEDIATRIC CANCER REGISTRATION TRIALS

A U.S. Food and Drug Administration Perspective

Meena N. Murugappan, PharmD, MPH[1], Bellinda L. King-Kallimanis, PhD[2], Gregory H. Reaman, MD[2], Vishal Bhatnagar, MD[2], Erica G. Horodniceanu, MPH[2], Najat Bouchkouj, MD[2], Paul G. Kluetz, MD[2]

[1]ORISE Fellow, Office of Oncologic Diseases, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (U.S. FDA), [2]Oncology Center of Excellence, U.S. FDA

Introduction

- Collection of Patient-Reported Outcome (PRO) data in adult cancer clinical trials has allowed for more comprehensive documenting of symptomatic Adverse Events (AEs).
- Evidence suggests that using PRO assessments to monitor symptoms during routine care can lead to an improvement in clinical outcomes like survival.[1]
- Despite observed benefits, there is a dearth of work regarding PROs in pediatric oncology drug development.
- Eliciting symptom data directly from the child allows for a more accurate reflection of the safety and tolerability profile of cancer therapeutics and may contribute to FDA's benefit-risk assessment.

Aims

To evaluate use of PROs in pediatric cancer registration trials submitted to FDA for regulatory review and identify opportunities for improvement.

Methods

FDA databases were searched to identify pediatric oncology product applications approved between the years 1997 and 2020.

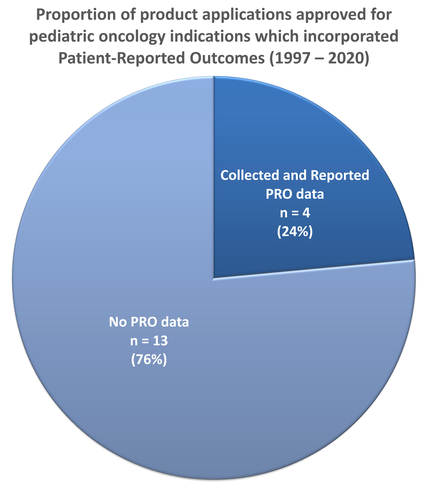
Sponsor-submitted documents (e.g., Clinical Study Reports) were reviewed to extract general information like trial phase, study design, and sample size and to determine whether PRO data were collected.

For trials with PRO data, we recorded the instruments used and evaluated the quality of reported data, through completion rates and use of fit-for-purpose instruments.

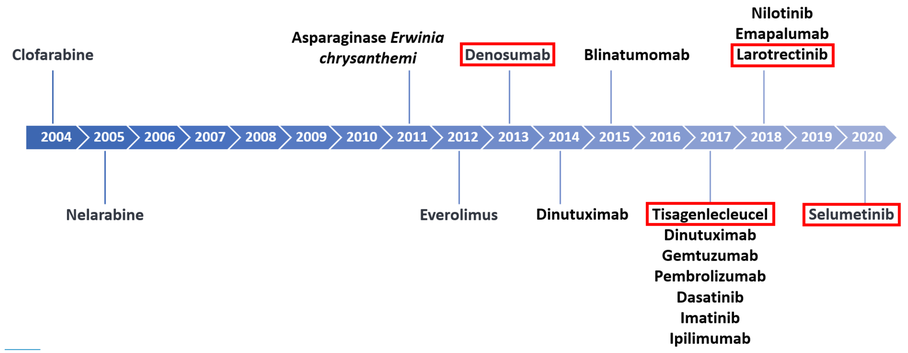
Finally, we recorded whether PRO endpoints were included in product labeling.

Results

- Out of the 17 product applications that met inclusion/ exclusion criteria, four reported PRO data: Denosumab, Tisagenlecleucel, Larotrectinib, and Selumetinib.
- In these four trials, PROs served as exploratory endpoints and were not incorporated in product labeling.
- The most commonly used pediatric PRO instrument was the PedsQL (Pediatric Quality of Life Inventory) generic core scale – the standard version with a 30-day recall period.
- Symptomatic AEs were characterized using clinician-reported Common Terminology Criteria for Adverse Events (CTCAE) **without** additional patient self-report.



Pediatric Product Applications with PROs



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

Discussion

PROs were infrequently utilized in pediatric cancer registration trials. When used, limitations included:

- Lack of a clear research objective and corresponding prospective analysis plan
- Instruments used were often not fit-for-purpose or measured concepts distal from disease symptoms and treatment side effects (e.g., emotional, social, and school functioning).
- Use of proxy report for non-observable domains like pain. While caregiver responses may provide an opportunity to evaluate symptoms and function in even the youngest of children, FDA encourages caregiver responses be limited to *observable* outcomes. Studies have shown that more patient-caregiver agreement in observable domains like mobility as compared to less visible concepts, for example, pain.[2]

Future Directions

- PRO symptom libraries (e.g., National Cancer Institute's Pediatric PRO-CTCAE) may provide an opportunity to better evaluate the occurrence and impact of symptomatic AEs, from the pediatric patient's perspective.
- FDA's newly launched Project Patient Voice (PPV) platform presents a unique opportunity to communicate pediatric PRO data from future trials.
- Improved collection and communication of patient-reported symptom data in pediatric oncology trials can help regulators and ultimately, prescribers, caregivers, patients, and payers make more informed decisions regarding pediatric use of anticancer drugs.

References

1. Basch E, Deal AM, Kris MG, *et al.* Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016;34(6):557-565.
2. Mack JW, McFatrich M, Withycombe JS, *et al.* Agreement Between Child Self-report and Caregiver-Proxy Report for Symptoms and Functioning of Children Undergoing Cancer Treatment. JAMA Pediatrics 2020;174(11):e202861-e202861.