Supportive Care in Cancer (2023) 31:602
https://doi.org/10.1007/s00520-023-08068-9

COMMENT

Use of patient-reported outcome measures for oncology drugs receiving accelerated approval

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Received: 30 May 2023 / Accepted: 22 September 2023 / Published online: 29 September 2023

Abstract

Patient-reported outcomes (PROs) represent an important evaluation of health-related quality of life that has become more commonly incorporated into oncology drug clinical trials. The frequency of PRO inclusion as an endpoint in oncology drug clinical trials leading to the initial accelerated approval of a new therapy is not yet known. We conducted a cross-sectional study evaluating all new drug applications submitted to the FDA over the past 10 years (2013–2022) that led to the initial approval of an oncology drug through the accelerated approval process. The objective was to assess whether the trials leading to such an approval included PROs. Between 2013 and 2022, the FDA approved 59 unique drugs for an oncology indication via the accelerated approval pathway, and 35 (59%) included a PRO assessment in the clinical trial. A median of 1 PRO measurement was used in each trial, with 23 different types of PRO assessment tools were used across the 59 new drug applications. In summary, we found that PRO measurements are inconsistently utilized in trials leading to initial accelerated approval of oncology drugs, and there seems to be a lack of harmonization of different PRO measurement tools used across trials.

Keywords Patient-reported outcomes · Health-related quality of life · Oncology-related drugs

The United States Food and Drug Administration's (FDA) Accelerated Approval (AA) pathway has become a common means of new oncology-related drugs to achieve initial approval and market availability [1]. Through this pathway, drugs receive initial regulatory approval based on a surrogate endpoint that may confer clinical benefit, such as overall response rate. Confirming clinical benefit of a drug must occur for full approval, which is often subject to the ability of the drug to improve survival or quality of life.

To assess health-related quality of life (HRQoL) and patient perceptions of their disease and treatment(s), patient-reported outcomes (PROs) assessments have been recently more commonly incorporated into cancer clinical trials [2]. In 2021, the FDA issues an updated draft guidance and acknowledgement on the importance of PROs and symptom assessment in the oncology drug approval process [3]. While clinical endpoint measurements of disease response, survival outcomes, and safety events are standardized, there is no standard for PRO measurement in cancer clinical trials. The objective of our analysis was to evaluate the utilization of PRO measures in clinical trials leading to the initial AA of oncology-related drugs.

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Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies [4]. Drugs that were initially approved through the AA pathway as their first initial regulatory approval were identified by searching the FDA notifications for oncology drugs systematically in chronological order from 2013 through 2022. All initial FDA new drug applications (NDAs) for oncology-related drugs that received an initial FDA approval through the AA pathway were reviewed. NDA files were searched for each identified drug and obtained via the Drugs@FDA website [5]. Only the initial indication that led to market availability was included in our analysis. Data extraction from each NDA was performed independently by two reviewers (D.M. and J.E.), and a third reviewer (J.P.) resolved conflicts. Data collected included whether PRO measurements were included in the clinical trial leading to approval, PRO characteristics, and other relevant information. Descriptive statistics using measures of central tendency were used to describe our findings. Ethics committee approval was not required for this study as FDA NDA files are publicly available documents.

Results

Between 2013 and 2022, the FDA approved 59 unique drugs for an oncology-related indication via the AA pathway. There were 51 drugs (86%) that received AA based on the results of single-arm/non-comparative clinical trials and 8 drugs (14%) that received AA based on a randomized trial that compared the approved drug to a control. Thirty-five trials (59%) leading to an AA included PRO assessments. Thirty single-arm/non-comparative trials (59%) and 5 randomized/comparative (63%) trials included PRO assessments. A median of 1 PRO measurements (range 0–4) was used in each trial. Eighteen trials (30%) used ≥2 PRO measurement tools. Three trials did not specify the PRO test assessed, and one did not include PRO results in the NDA. Among the 59 NDAs, there were 23 different types of PRO assessment tools used. The most common PROs used are described in Table 1. Between solid tumor and malignant hematology approvals, there were no significant differences between the frequency of PRO utilization (57% vs. 64%). A higher frequency of PRO utilization in trials leading to AA were observed between 2018 and 2022 ($n = 25$; 69%) compared to 2013–2017 ($n = 10$; 44%).

Table 1. Use of patient-reported outcomes in clinical trials leading to accelerated approvals for oncology drugs, 2013–2022

	***n* = 59**
Approval indication	
• Hematologic malignancy	22 (37%)
• Solid tumor	37 (63%)
Trials with PRO measurements used	35 (59%)
Trials with ≥2 PRO measurements used	18 (30%)
PRO use by year of approval	
• 2013–2017	10 (44%)
• 2018–2022	25 (69%)
PRO use by approval indication	
• Hematologic malignancy	14 (64%)
• Solid tumor	21 (57%)
PRO assessments used in trials	
• EORTC-QLQ-C30	19 (32%)
• EQ-5D	12 (20%)
• EORTC-QLQ-LC13	5 (8%)
• FACT-Lym	4 (7%)
• EORTC-QLQ-MY20	2 (3%)
• Other*	18 (30.5%)

PRO, patient-reported outcome

*Each of the following PRO assessments $n = 1$: EORTC-QLQ-BIL21, EORTC-QLQ-CLL16, EORTC-QLQ-CX24, FACIT-Fatigue, FACT-GOG/Ntx, FACT-MM, FACT-O, mBFI-sf, MDASI, MDASI-CML, NEI-VQF, OSDI, PGIC, PGIS, PRO-CTCAE, SMF, TINAS, WPAI-CML

Discussion

These findings suggest that there has been inconsistent PRO utilization in clinical trials leading to the initial AA for oncology-related drugs over the past decade. With 23 different PRO measurement tools utilized across 59 AAs, there also appears to be inconsistency and a lack of harmonization among PRO assessments when they are used in oncology drug approval trials. There are several disease-specific-PRO measurement tools; however, there appears to be a lack of consistent utilization even within the context of specific cancer types. Previous analyses have observed similar findings. An analysis comparing PRO labeling for approved oncology drugs between the FDA and European Medicines Agency (EMA) observed a lack of consistency in PRO use, labeling, and language used to describe PROs both within and between each regulatory agency [6]. An analysis of PRO application and regulatory considerations for novel oncology drugs approved by the FDA found that PROs do not currently play a significant role in drug marketing review and how they can be incorporated into regulatory decision-making is still exploratory in nature [7].

The inconsistency in PRO utilization among clinical trials leading to AA of new cancer drugs is likely multifactorial. Firstly, there are no set universal consensus standards on PRO incorporation, instrument selection, collection, and reporting [8]. In light of this, the FDA has recently provided draft guidance recommendations for how to consider selection of PRO instruments, frequency of assessments, and how PROs can be incorporated into drug labeling [3]. Although there are no current international standards for PRO use and assessment, efforts to establish this are currently underway [8]. Secondly, most clinical trials in the past 10 years that have led to the AA of new cancer therapies have primarily been single-arm or non-comparative clinical trials. As PROs are inherently subjective assessments, there is a concern for bias with patients knowing their trial assignments in single-arm or open-label trials, and how this may impact their perception of symptoms, functional status, and experience [9]. Due to the non-comparative nature of these trials, PRO objectives may be descriptive or exploratory; standards have yet to be established on how to describe PRO data without drawing confirmatory conclusions.

A recent analysis demonstrated that PROs are more often assessed in phase III clinical trials and randomized controlled trials compared to phase I, II, and open-label trials [10]. Additionally, a systematic review showed a wide variability in the use of PROs within specifically single-arm studies evaluating oncology drugs, with only 22% of such studies including PROs among 60 studies evaluated between 2018 and 2021 [11]. Being that most oncology drugs that are initially approved through the AA pathway via a single-arm, open-label, phase II trial, there exists significant opportunity to better improve how PROs can be incorporated into such study designs.

PRO data in single-arm trials can still be useful as they can help to explore the direct impact of new cancer therapies on HRQoL and how tolerability can affect the patient's experience. Single-arm trials leading to AA often are the first large-scale evaluation of the efficacy and safety of a new drug entity at a recommended phase II dose, thus PROs can enhance clinical trial results by adding the patient's experience to the exploratory nature of the trial results. Additionally, having PROs integrated into early phase, single-arm clinical trials that may lead to AA of new oncology drugs can also potentially assist in determining more precise dosing that balances biologic activity with tolerability [12]. Although such data may only be descriptive in nature, it may help to inform future hypothesis testing when comparing a new drug to a standard of care in a randomized clinical trial.

PROs represent important endpoints in evaluating the impact new therapies can have on HRQoL. Given the general cancer population is often exposed to drugs initially approved under AA but subsequently withdrawn [13], it is paramount in the drug development process to ensure the introduction of novel therapies do not significantly worsen HRQoL [14]. More guidance is needed on standardization and harmonization of PRO measurements in clinical trials leading to initial AA of oncology-related drugs.

A potential limitation of our analysis is that we did not assess the quality of PRO measurement data realized from these registration trials. The present analysis is also not a systematic review to determine if PROs from registration trials leading to AA were reported in follow-up publications or abstracts. Only PROs measured and reported as part of the initial registration trial were included.

Conclusion

More guidance is needed on standardization and harmonization of PRO measurements in clinical trials leading to initial AA of oncology drugs.

Author contributions All authors were involved with the conceptualization of the manuscript. D.C.M. and J.B.E. collected and analyzed the data. D.C.M. wrote the main manuscript text and prepared Table 1. All authors reviewed the manuscript.

Declarations

Competing interests The authors declare no competing interests.

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