The Importance of Endpoints in Oncology Clinical Trials

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Innovative clinical trials identify appropriate endpoints when seeking to evaluate potential new cancer treatments, better ways of using existing medications, or enhanced supportive care techniques. A recent X (formerly Twitter) post highlighted a workshop held in July 2023 sponsored by the FDA, American Association for Cancer Research (AACR), and the American Statistical Association (ASA). The workshop convened experts who discussed how to improve the collection and assessment of endpoints in oncology clinical trials (AACR, 2023).

As an advanced practitioner (AP) who treats individuals with various cancers and blood disorders, it is important to me to evaluate each clinical trial and its study methodology, design, and overall quality. As a grant and study protocol reviewer, the study design and endpoints of each clinical trial are important when assessing whether the clinical trial has proven the benefit of an intervention or drug; whether it has improved the overall survival (OS) or progression-free survival (PFS), or provided clinical benefit to the patient. With the influx of drugs in development, it is more important than ever to understand these statistical measures.

OVERALL SURVIVAL

The gold standard for an endpoint in interventional cancer clinical research, such as phase II or III randomized trials, has been OS. A statistically significant OS advantage of one group when compared with another is calculated from when a patient is randomized to a clinical trial arm until death from any cause (Delgado & Guddati, 2021).

PFS

Demonstrating an OS advantage of one treatment compared with another is logistically difficult in diseases with favorable survival such as chronic lymphocytic leukemia (CLL) and early-stage multiple myeloma. As a result, PFS, defined as the time when a patient is treated to the first documentation of objective disease recurrence or death by any cause, has become an accepted surrogate endpoint so patients with these and other rare conditions can access the drug earlier through the FDA Accelerated Approval program. Although it may take an extended period of time to measure a drug's clinical benefit to the patient, the PFS endpoint considerably shortens the time required to study the drug prior to receiving approval by the FDA for use in a particular population.

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CLINICAL BENEFIT RATE

Finally, clinical benefit rate, defined as the percentage of patients who achieve a response as a result of therapy, can be argued for use to seek early approval, especially in patients with advanced cancer. However, if the primary endpoint is not met with ongoing studies, FDA regulatory procedures can remove the drug from the market (FDA, 2023).

WITHDRAWN APPROVALS

In the past 2 years, several drugs were withdrawn from the market, including the one discussed in an article by Popat and colleagues in this issue of *JADPRO* (2023). In August 2020, the myeloma community was thrilled that belantamab mafodotin, an antibody-drug conjugate, was granted accelerated approval by the FDA for relapsed/refractory multiple myeloma (RRMM) after the DREAMM-2 trial released data on the overall response rate. This represented a new treatment option for patients. Unfortunately, with ongoing evaluation, the drug failed to confer a statistically significant improvement in PFS when compared with the pomalidomide and dexamethasone arm. As a result, belantamab mafodotin was removed from the market.

In the study, secondary endpoints included overall response rate, duration of response (DOR), as well as OS. Other study endpoints such as health-related quality of life and other patient-reported outcomes continue to be evaluated in studies, which may bring a change to approval status, especially when it is given in combination with other drugs. Although patients cannot start this drug in the US, patients remain on belantamab mafodotin and in remission in the US, Europe, and other parts of the world. I am optimistic that with ongoing studies with belantamab mafodotin in combination with other drugs, and in studies where patient-reported outcomes are an outcome measure, the drug will be approved for future indications.

Belantamab mafodotin was not the only drug withdrawn from the market this year. Indications that have failed to meet statistical endpoints include pralsetinib for the treatment of adult and pediatric patients with advanced or metastatic medullary thyroid cancer (withdrawn July 20, 2023) and ibrutinib for patients with relapsed or refractory marginal zone and follicular lymphomas (withdrawn May 18, 2023). The FDA site (2023) has a list of drugs whose accelerated approvals have been withdrawn since 2011.

What does this all mean to APs? Well-designed clinical trials are critical to evaluate new therapies with potential benefit to patients. Understanding outcome measures prepares APs as consumers of research and for future roles in research protocol development. I look forward to downloading the slides and watching videos from the FDA-AACR-ASA workshop to sharpen my skills (AACR, 2023). In addition, a *JADPRO* article by Kurtin and Taher (2020) discusses the clinical trial process for oncology drug development and approval in the US.

IN THIS ISSUE

The article by Popat and colleagues provides insights into ocular symptoms reported by patients while taking belantamab mafodotin. I hope you find the patient handouts included in the Guest Editorial by Mary Heery to be helpful. Read about an NP/PA-based model for increasing the number of patients receiving palliative care and advance care planning. The article by Kachur and colleagues provides practical guidance for the use of post-transplant cyclophosphamide. The article by Lowe and colleagues addresses tools to screen individuals at risk for familial pancreatic cancer. Read a case study illustrating the diagnosis and treatment of a patient with gastrointestinal stromal tumor. Finally, learn from a case of infection in a patient receiving daratumumab for the treatment of multiple myeloma.

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