Outcomes that matter to patients with cancer: living longer and living better

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Summary

Oncologists and cancer patients generally agree that the primary goals of advanced cancer treatment are to lengthen and/or improve patient survival. Yet over the last two decades, clinical trials of new cancer treatments have moved away from measuring outcomes that matter to patients. Increasingly, new drugs for advanced cancer treatment reach the market by demonstrating improvements in surrogate endpoints such as progression-free survival (PFS), which is not a measure of how a patient feels, functions, or survives. Research has shown that when patients are fully informed about the meaning of PFS, about half would not choose additional treatment for any magnitude of gain in PFS in the absence of an overall survival improvement. It's time to get back to designing trials that answer clinically meaningful questions and measure the outcomes that truly matter to patients. Engaging educated patient advocates in meaningful ways in clinical trial design and reporting would be a step in this direction.

Keywords: Oncology clinical trial endpoints; Patient centered outcomes research; Patient preferences; Progression-free survival

Introduction

Oncologists and cancer patients generally agree that the primary goals of cancer treatment are to lengthen survival and, especially in the advanced disease setting, to improve quality of life.[1,2] Yet over the last two decades, clinical trials of new cancer treatments have moved away from measuring outcomes that matter to patients.

Until the early 2000s, overall survival was the predominant endpoint in clinical trials of new cancer drugs. Today, however, most cancer drugs and biologics come to market based on clinical trials that use surrogate endpoints such as progression-free survival (PFS) to demonstrate benefit.[3,4] Patients and the public must understand what actual benefit if any these surrogate endpoints mean for their lives. To help ensure this, we need public education on this issue, and educated patient advocates who represent a constituency need to play meaningful roles in the design, conduct, and reporting of clinical trials.

Defining progression-free survival, its advantages, and limitations

Despite what the term implies, PFS is not a measure of clinical benefit: how a patient feels or functions, or how long they survive.[5] PFS is one of a number of tumor response metrics adopted to help standardize measures of anticancer activity in clinical research among varying investigators and institutions.[6,7] Moertel and Hanley were among the first to investigate oncologists' ability to detect tumor progression and shrinkage using simulated tumors (marbles of varying size) placed under simulated skin (mattress covered in rubber foam).[8] They reported that erroneous measures of tumor progression and regression were minimized when simulated tumors increased in diameter by at least 25 percent or shrunk by at least 75 percent.

Today, PFS is defined according to the Response Evaluation Criteria in Solid Tumors first published in 2000 and updated in 2009. It represents the time from randomization or the initiation of treatment to measurable disease progression (typically by radiographic assessment in solid tumors) or death, with progression being defined as a relative increase in the sum of maximum tumor diameters of at least 20 percent (absolute increase of at least 5 mm), the development of any new lesions, or an unequivocal increase in non-measurable malignant disease (e.g., bone metastases).[9]

PFS was developed to support the advancement of drugs in Phase 2 clinical trials to Phase 3 testing, not to serve as a measure of clinical benefit to patients.[6,7] Indeed, patients may not even perceive a deterioration in their health status when their tumor has progressed based on the definition above.

There are multiple arguments for the growing use of PFS as the primary endpoint in Phase 3 advanced/metastatic cancer clinical trials.[10] PFS can be measured more quickly and with smaller patient sample sizes than overall survival, thereby speeding the delivery of new

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anti-cancer agents to patients and theoretically lowering the cost of development. Additionally, unlike overall survival, PFS is not confounded by subsequent lines of treatment following disease progression. Moreover, PFS or "stable disease" can also have intrinsic value to some patients.

While PFS improvements sometimes translate into improvements in overall survival and/or quality of life, often, this is not the case. PFS has routinely failed to demonstrate a strong correlation with overall survival[11,12] or quality of life[13] in systematic reviews and validation studies across many different cancer types. In some instances, increases in PFS have been accompanied by shortened survival.[14,15] In addition to not providing a measure of clinical benefit, PFS is also subject to various forms of bias (e.g., measurement error, assessment bias, informative censoring, and intermittent assessment of progression bias) that either do not exist or are less likely to occur (in the case of informative censoring) when measuring overall survival.[16–19] And while the 20 percent increase in the sum of diameters of target lesions is widely accepted as the definition of disease progression, there is still the potential for terminating a drug early based on a false identification of disease progression (because of measurement error), especially when tumor burden is low.[20] Despite this, the use of PFS as an endpoint for regulatory approval of cancer drugs is now widespread.

Patient perspectives on the value of progression-free survival

While there is much debate among the oncology community about the increasing use of PFS as a primary endpoint in clinical trials,[21,22] it is critically important to consider how patients interpret and understand this endpoint, and once fully informed of its meaning, the value they place on PFS compared with other endpoints.

Studies have demonstrated that patients with cancer (and the general public for that matter) are unfamiliar with many of the endpoints utilized in cancer trials,[23–25] often confusing PFS and objective response rates with improvements in overall survival. Studies have also demonstrated that patients and the general public alike have difficulty accurately interpreting results described in drug labels and/or direct-to-consumer marketing.[26,27] This poses a challenge for studies that aim to assess how patients value different endpoints such as PFS. However, when patients are queried specifically about their goals for treatment in the advanced cancer setting, it's clear that patients place the most value on living longer and maintaining a reasonable quality of life, if not a cure.[28]

A robust assessment of patients' valuation of PFS requires that patients have an unambiguous understanding of the distinction between PFS and clinically meaningful endpoints such as overall survival and quality of life. Unfortunately, a 2019 systematic review[29] of available literature on the topic demonstrated that this has generally not been the case. To address this limitation in available research on this question, a 2023 study[30] attempted to measure the value that patients place on PFS, particularly in the absence of overall survival gains, after being fully briefed on the meaning of PFS. Using both quantitative and qualitative methods, the investigators demonstrated that when confronted with unambiguous discrete choice scenarios, approximately half of patients would not choose additional treatment for any magnitude of gain in PFS in the absence of an overall survival improvement. However, a smaller subset of patients in this study (~17%) indicated they would accept additional treatment with mild or moderate toxicity even in the absence of a PFS benefit, showcasing the complexity of patients' views on this endpoint and during treatment decision-making in the context of a terminal illness.

Additionally, most studies exploring patients' evaluations of PFS and other endpoints query patients at a single time point, and patients' preferences, values, and expectations are likely to change over the course of their treatment experience, and with increased exposure to clinical, financial, and time toxicity.[31]

Indeed, a 2018 longitudinal study (Assessing the 'VALue' to patients of PROgression Free Survival; AVALPROFS)[32] queried advanced-stage patients at multiple time points and demonstrated that patients were significantly less likely to value cancer control strategies with increasing exposure to toxic treatments that reduce their quality of life.

Involving educated patient advocates in the clinical research continuum

Educated patient advocate voices must be included in clinical research to ensure new treatments address patients' goals and values, particularly for terminal illnesses and unmet needs, and numerous initiatives to this end have emerged. For example, driven in part by mandates outlined in the 21st Century Cures Act, the U.S. Food and Drug Administration has formed a number of patient engagement initiatives[33] and released guidance for industry on patient engagement in clinical trials.[34] The Patient Protection and Affordable Care Act of 2010 mandated the development of a quasi-governmental agency, the Patient-Centered Outcomes Research Institute, which emphasizes the engagement of patients and other stakeholders in the research process. The National Cancer Institute (NCI) supports patient advocate involvement in research through its Office of Advocacy Relations and the federally funded National Clinical Trials Network engages patient advocates in a variety of capacities in clinical trials research at the network level and individual participating academic sites. Patient advocates also have increasing involvement in the peer review

process for both Federally funded (e.g., Department of Defense Congressionally Directed Medical Research Programs and to a lesser degree, the NCI) and non-profit funding cancer research sectors, thereby helping shape the research that is conducted.

Patient participation has been a tenet of the National Breast Cancer Coalition (NBCC) since its inception in 1991. But NBCC has also long recognized that patient participation alone is not sufficient. Patient advocates must be thoroughly educated and informed if they are to be involved in influencing systems-level decision making. NBCC continues to work to ensure that educated patient advocates who represent a constituency have a meaningful "seat at the table" in all levels of healthcare decision-making that affects their lives. Educated patient advocates with lived experience provide a unique perspective that others cannot offer. They are the ones who ultimately receive and pay for healthcare services and, along with their families, are required to navigate the complexities of the health insurance and healthcare delivery systems.

Along with a right to meaningful participation in clinical trials comes a responsibility to be educated. Advocates must be knowledgeable and confident to participate in the decision-making process of science and healthcare. They must understand how to critically appraise information, and how to evaluate evidence, especially in the context of clinical trials, drug approval, and other public health issues that impact society. NBCC was a pioneer in designing training programs to prepare lay patient advocates for this role. First developed in 1995, NBCC's Project LEAD®[35] is an intensive science course that teaches breast cancer advocates the basic language and concepts critical to understanding scientific research including clinical trials research. A host of other advocacy training initiatives have since formed with the intent of bringing educated patient advocate voices to the clinical research continuum (e.g., Fight Colorectal Cancer's Research Advocacy and Training Supports [RATS] program, the International Association for the Study of Lung Cancer's Supportive Training for Advocates on Research and Science program [STARS], the American Association for Cancer Research's Scientist ↔ Survivor Program, and the Cancer Research UK VOICE Vision On Information, Confidence and Engagement [VOICE] Science for Patient Advocates training program, among others).

The key objectives of educated patient engagement in all levels of clinical research are ultimately to inform the research agenda, set research priorities, and ensure patient-centered clinical trial design, all while keeping the healthcare and research communities laser focused on the urgency that patients face. At present, the impact of patient engagement in clinical research remains unclear and is difficult to measure, but engaging patients is increasingly viewed as central to delivering patient centered health care.[36–38]

Conclusion

Clinical trial research over the past two decades has moved away from measuring what really matters to patients, resulting in a system that increasingly delivers more drugs with little evidence of clinical benefit. It's time to get back to designing trials that answer clinically meaningful questions and measure the outcomes that truly matter for patients' lives. Engaging educated patient advocates in meaningful ways in clinical trial design and reporting would be a step in this direction. We are all desperate to find interventions that will save or significantly prolong lives without reducing the quality of life. We should not redefine progress to include what can be measured in the short term, rather than what is ultimately the most meaningful for patients.

Contributors

MT and FV developed and contributed to this manuscript. MT prepared the first draft in consultation with FV. FV read successive drafts, made suggestions to improve, and contributed references. Both authors read and approved the final draft.

Declaration of interests

Neither author has any conflicts of interests to report.

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