Moving from Evaluation to Value in Cancer Care

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Running Title: Creating Value in Cancer Care

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Summary

Defining clinically meaningful outcomes for clinical trials provides a foundation for assessing and improving the value of cancer care by conducting multi-disciplinary research in clinical trial design, comparative effectiveness, patient preferences, health outcomes and economics captured through analysis of data generated in clinical trials and real world clinical practice.

Main Text

In this issue of Clinical Cancer Research, Sobrero and colleagues (1) propose an approach to defining a minimum clinically meaningful outcome (mCMO) for cancer clinical trials. Their method relies on overall survival, assessed using four different metrics, as the primary efficacy endpoint and sets the threshold for a mCMO at one of three levels determined by prognosis of the study population as well as expected toxicity and cost of the new therapy. Their thesis is that to produce a clinically meaningful outcome a high level of efficacy should be demonstrated for treatments that are expected to be more toxic or costly than prevailing alternatives but that lower levels of efficacy might be acceptable for less toxic or less expensive treatments. They applied their methodology to 43 completed phase III clinical trials of drugs recently approved by the Food and Drug Administration that had mature survival information. Remarkably, only 2 studies met their criteria for high benefit using the metrics of hazard ratio (HR) (0.6-0.7) for overall survival (OS) and improvement in median OS (3-6 months) and none of the studies satisfied their criteria for demonstrating a large benefit using an increase in both absolute (15% increase) and proportional (100% increase) survival at 2-3 years as the outcome measures of interest. Nevertheless, all of the drugs studied met regulatory approval standards for marketing in the United States and all are now used in clinical practice. Some are among the most
expensive cancer drugs in use today. Did Sobrero and colleagues set the bar for mCMO too high? Are regulatory standards for drug approval too low? Should drugs of modest efficacy come with high price tags in our cost-constrained healthcare system?

The criteria developed by Sobrero et al. comport well with the goals advanced by Ellis and colleagues (2) to establish clinically meaningful outcomes for clinical trials in patients with cancers of the breast, colon, pancreas and lung. Groups of experts convened by the American Society of Clinical Oncology Cancer Research Committee identified an HR < 0.8, corresponding to an improvement in median OS of 2.5 to 6 months depending on the clinical context, as the minimum incremental improvement over standard therapy that would define a clinically meaningful outcome. Like Sobrero et al., these authors felt that new regimens that are substantially more toxic than current standards of care should also produce the greatest increments in OS to be considered as having achieved a clinically meaningful outcome for patients. Both groups acknowledged shortcomings in their approaches, including reliance on mature survival data that complicates assessment of new treatments that enter the marketplace before such data becomes available, the failure to consider more patient-centric measures in the definition of a clinically meaningful outcome, and the limited availability, thus far, of predictive biomarkers to identify patients most likely to benefit from treatment. Both groups recognize the need for further research to better define and accurately measure outcomes that are meaningful to patients.

Defining clinically meaningful outcomes for clinical trials also provides a foundation for assessing and improving the value of cancer care at a time when healthcare costs in general, and drug prices in particular, are rapidly climbing. Recently, the venerable CBS news program...
60 Minutes aired a story about the high cost of cancer drugs (3). When coupled with high insurance co-payments, these costs are placing a significant financial burden on many cancer patients resulting in personal bankruptcy, lack of adherence to treatment and poor quality of life that is directly attributable to financial stress (4, 5). However, focusing on drug costs alone greatly oversimplifies the issue of most concern to cancer patients, i.e., optimizing the value of the care they receive. As defined by Porter, value is health outcomes achieved per dollar spent (6). To be sure, cancer drugs take years to develop and billions of dollars invested in research and for every success, there are dozens of failures. Yet oftentimes even successful drugs, judged by achieving regulatory approval for marketing, produce only modest incremental improvements in clinically important endpoints like overall survival and then enter the market with extraordinarily high prices. How do we define the value of new cancer treatments?

The work of Sobrero and colleagues represents an important starting point in a translational research cycle that aims to create value in cancer care as illustrated in Fig. 1. Medical needs identified through clinical practice and patient experience spur innovation leading to new drug products and/or molecular diagnostic tests that are evaluated through clinical trials to determine their safety and efficacy. Products that meet regulatory standards for marketing approval advance into clinical practice once pricing decisions are made by the product sponsor and reimbursement rates are established by the insurance industry. Effectiveness research, often conducted by publically-funded research groups, is essential to determine how well the new product performs compared to available alternatives and in more diverse populations that those typically included in the clinical trials used to establish efficacy (7). Patient goals, preferences and choices shape the real world experience with new products
and the direct and indirect costs of treatment to patients and their families impact their widespread adoption. New information developed throughout this cycle about how to best use the product and its impact on a patient and their illness contribute to and refine the assessment of the product’s value in the context of the medical need it was developed to address.

Research opportunities abound to improve the assessment of the value of new cancer treatments. New clinical efficacy endpoints, both provider- and patient-reported, that accurately assess how a patient feels and functions must be developed and may reflect outcomes of greater value to patients than survival, particularly in non-curative settings (8). Better predictive biomarkers can transform a drug of modest efficacy in an unselected population to high efficacy in a biomarker-defined subgroup and thereby contribute to improving the value of a treatment in a segment of the patient population. Studies of factors that impact patient decision-making, and that determine adherence to treatment and the economic burden of cancer care are necessary to truly understand how each person values the available treatment alternatives and communication tools to facilitate discussion with patients about the value of their treatment options are ripe for development. Regulatory and policy initiatives such as adaptive licensing (9), value-based insurance (10) and indication-specific pricing (11) all deserve careful consideration and further research to determine their impact on value generation while insuring patient access to life-prolonging therapies and continuing to support innovation in product development. The work of Sobrero et al. sets a high bar for cancer clinical trials but, more importantly, it fuels a necessary discussion and provides a platform for multi-dimensional research that is vital to improve the value of cancer care.
References


Figure 1. Generating value through research: Medical needs defined through clinical practice and patient experience spur innovation leading to new drug products and/or molecular diagnostic tests that are evaluated through clinical trials to determine their safety and efficacy. Products that meet regulatory standards for marketing approval advance into clinical practice once pricing decisions are made by the product sponsor and reimbursement rates are established by the insurance industry. Effectiveness research determines how well the new product performs compared to available alternatives and in more diverse populations that those typically included in the clinical trials used to establish efficacy. Patient goals, preferences and choices shape the real world experience with the product and the direct and indirect costs of treatment to patients and their families impact its widespread adoption. New information developed throughout this cycle enable the assessment of the product’s value in the context of the medical need it was developed to address.
Figure 1:
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