Dynamic Assessment of Value During High-Cost Cancer Treatment: A Response to American Society of Clinical Oncology and European Society of Medical Oncology

Charles W. Given, PhD, Barbara A. Given, PhD, RN, Cathy J. Bradley, PhD, John C. Krauss, MD, Alla Sikorskii, PhD, and Eric Vachon, RN

Michigan State University, East Lansing, MI; University of Colorado, Denver, Denver, CO; and University of Michigan, Ann Arbor, MI

The rise in the numbers of high-cost targeted oral molecular agents approved and entering the market for cancer treatment has prompted interest in how to explain value to patients with late-stage diseases and limited life expectancies. Although these treatments are a form of hope, they vary in the survival they produce, the adverse effects and symptoms patients experience, and the out-of-pocket costs they generate. Without a framework to explain how value changes as treatment unfolds, patients may continue on a course of treatment that has marginal survival benefit, places them at considerable financial risk, and provides a poor quality of life during their final months of life.

Recently, ASCO¹ and the European Society of Medical Oncology (ESMO)² developed a conceptual framework to assess the value of high cost-targeted oral molecular agents. ASCO published a follow-up article that explained the calculation of the net health benefit (NHB) in detail.³ The NHB is seen as the resolution of cost and clinical toxicities against benefits that include overall survival, time to progression, symptom management, and quality of life. In addition, the National Comprehensive Cancer Network expanded their definition of value to include efficacy, safety, quality, and affordability.^{4,5} Work continues on the

development of algorithms to guide how payers and practitioners associate costs with benefits of oral agents.^{6,7}

In this editorial, we argue that, for oral molecular agents, the NHB should be viewed distinctly for each patient as the treatment progresses. The balance among the benefits of treatment, the symptoms and adverse effects, and how the costs of medications threaten the finances of patients and families will vary for each patient over time. There is a large and robust body of literature on cost-effectiveness models.⁸⁻¹³ However, the models are not well suited to capture and summarize patient interpretations of changes in symptoms and adverse effects, increases in out-of-pocket costs, and the combination of those data with oncologists' summaries of changes in clinical benefit.¹⁴ We argue in this editorial why a dynamic approach to value is critical.

Oral molecular agents are likely to be second- or third-line treatments of advanced cancers offered to patients who have limited life⁶ expectancies. The value of treatment may hang on modest reductions in progression, tolerable adverse effects, and out-of-pocket costs that are not ruinous. Each dimension can change quickly as treatment progresses. Therefore, we suggest, at each encounter, that patients summarize the financial burdens

ASSOCIATED CONTENT

See accompanying editorial on page 1211

DOI: 10.1200/JOP.2016.012401; published online ahead of print at jop.ascopubs.org on August 16, 2016.

of payment for treatment and the severity of their symptoms and that oncologists summarize the benefits of treatment and observed adverse effects that may require a change in treatment. As changes occur, each discussion becomes an opportunity to revise treatment plans and determine when to shift toward palliative and supportive care. Our rationale for this approach is discussed in this editorial.

Limited Evidence of Value at Outset of Treatment

Interpolation of data from clinical trials of oral molecular agents to the benefit of these agents for individual patients is uncertain at best. The ASCO¹ and ESMO reports² draw on evidence from clinical trials to establish value. The evidence from these trials may not translate well to individual patients. Prior courses of treatment, stages of disease, comorbid conditions,^{1,2} or the presence of certain mutations that may increase treatment efficacy all bear upon responses to treatment, including the toxicities and symptoms a patient may experience.^{1,15-17} After treatment is initiated, timely assessments of treatment benefits and patient reports about out-of-pocket costs and adverse effects should be focal points and part of the discussions between oncologists and patients at each visit.¹⁴ For example, when a dosage is altered because of toxicities or adverse effects, patients must be informed and must discuss the implications of the dosage changes on the effectiveness of treatment. Such conversations open discussions about value and suggest how integration of supportive care options into treatment may enhance the quality of life for the patient. Throughout treatment, the focus remains on value for the patient, and discussions focus on how this value is best achieved.

Adverse Effects and Symptoms

When oral agents are prescribed, oncologists must encourage patients to report treatment adverse effects and symptoms as they occur. Although oncologists rely on well-established taxonomies, such as the National Cancer Institute Common Terminology Criteria for Adverse Events,¹⁸ to report adverse effects, newly refined patient-reported indicators have been beneficial. Recent work by Basch et al^{19,20} moved these patient reports into clinical practice. Recent findings indicate that patients can use multiple approaches, including e-health reports that may be forwarded to their electronic medical record. By using these approaches, an increase or a change in symptom severity could initiate a follow-up visit and an opportunity to reconsider the dose of treatment and, eventually,

the value of continued treatment. Symptom reporting and management may in fact improve health-related quality of life for patients and extend their times on treatment.²⁰

Costs and Value

Patients with cancer are more likely than those with other chronic diseases to experience financial burdens of increased copays and bankruptcy.²¹⁻²⁵ Debates about cancer treatment costs continue; pharmaceutical manufacturers focus on the costs of drug development,²⁶ and oncologists question the sustainability of treatment with oral agents that have such high costs.²⁷ For patients, receipt of approval from their insurance companies or the arrival of their initial prescription may be the first time they realize the amount of their out-of-pocket contributions for oral agents.²⁸ Some patients may initially report small out-of-pocket costs but are shocked by the sharp increases in their costs when they exceed their pharmacy benefits or no longer are eligible for their medication assistance programs. Only recently have patients been offered a tool to calculate costs and benefits for oral agents.^{29,30}

The complicated nature of reconciliation of benefits, costs, and adverse effects are highlighted by two examples at different ends of the cost–adverse effect–benefit spectrum. On one end of the spectrum, there are the effective, but expensive, therapies of the oral breakpoint cluster region (BCR)/tyrosine kinase inhibitors imatinib, nilotinib, and dasatinib, which are nearly universally effective. They markedly reduce cancer burden, drastically reduce progression to blast crisis, and restore survival to near normal estimates. However, they are expensive (\$100,000 to \$180,000 per year); the value is expressed in months of progression-free survival with few symptoms or adverse effects. One analysis has demonstrated that nilotinib is the most cost-effective medication.³¹

On the other end of the spectrum, regorafenib, a third-line therapy for incurable and metastatic colon cancer, is expensive, often not tolerated at its full dose, only rarely controls symptoms, and only offers a small survival benefit compared with placebo.³² The value of this medication, from the perspective of most oncologists and patients, is much lower. However, the will to live longer at any toxicity level is powerful for some patients; thus, they are willing to endure the adverse effects. However, over time, as out-of-pocket costs increase, adverse effects intensify, and the effect of treatment declines, the patient needs to understand that value will come more from supportive care to preserve a better quality of life.

These scenarios exemplify the dilemmas that oncologists and their patients face. In some cases, treatment is effective but expensive; alternatively, regorafenib may be prescribed because oncologists prefer to offer patients some hope and, although the probability of success overall may be low, each patient may respond differently. Thus, given all of these uncertainties, we propose conversations in which patients report their adverse effects and affordability of the medications, oncologists summarize current benefits, they outline together a short-term plan, and they evaluate the success of the plan at their next encounter. Together, the oncologist and patient can arrive at decisions about when to introduce supportive care and when to stop treatment to preserve quality of life during the remaining months of life.

In conclusion, the approach taken by ASCO¹ and ESMO² is a significant step in the formulation of treatment value. We have offered a number of reasons why value should be treated as dynamic and a result of regular assessments discussed by oncologists and patients as a basis for adjusting the treatment plan. We argue for ongoing exchanges at each encounter concerning the current valuation of treatment and discussions about when to reformulate treatment as benefits, symptoms, and adverse effects change. The weight of each dimension will form the basis for making value explicit and open to change as treatment progresses. This approach is individualized; recognizes the uncertainties of the treatment; and, through patient and oncologist discussions, shapes the transition to supportive and end of life care. This approach can be introduced when oral agents are prescribed and oncologists make their responsibilities clear to patients. An algorithm, such as the NHB presented by ASCO,³ could be modified and used to document changes in benefits of treatment and patient reports of symptoms, adverse effects, and changes in out-of-pocket costs. Used as such, the algorithm focuses the conversation and does not add time to or slow the pace of care. Reviews of these summaries across visits would reveal the changes in the NHB of treatment and would open discussions about the transition toward supportive care.

The research and clinical community know remarkably little about how patients formulate value. A recent review of literature on the withdrawal of treatment toward the end of life suggests a range of approaches.^{33,34} Given the costs of oral targeted molecular agents, the rates at which their doses are altered or stopped, and the adverse effects they produce, we argue that oncologists can better serve patients by informing them and helping them define and possibly alter their views

of the value of future treatment as the care trajectory evolves and by helping patients determine how they wish to experience their last months of life. **JOP**

Acknowledgment

This work was supported by grant No. 1R01CA162401-01A1 (2013-2017) from the National Cancer Institute.

Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

Author Contributions

Conception and design: All authors

Collection and assembly of data: John C. Krauss, Alla Sikorskii, Eric Vachon

Data analysis and interpretation: Alla Sikorskii

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

Corresponding author: Charles W. Given, PhD, Michigan State University, College of Human Medicine, 135 E Fee Hall, 965 Fee Rd, East Lansing, MI 48824; e-mail: bill.given@hc.msu.edu.

References

1. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. *J Clin Oncol* 33:2563-2577, 2015
2. Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology magnitude of clinical benefit scale (ESMO-MCBS). *Ann Oncol* 26:1547-1573, 2015
3. Schnipper L, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. *J Clin Oncol* doi:10.1200/JCO.2016.68.2518 [epub ahead of print on May 31, 2016]
4. National Comprehensive Cancer Network: Chronic myelogenous leukemia guidelines (version 1.2016). http://www.nccn.org/professionals/physician_gls/f_guidelines_nojava.asp
5. Bach PB, Edge SB, House L, et al: NCCN roundtable: Value-based decision making at the bedside. *J Natl Compr Canc Netw* 13:659-661, 2015
6. Bach PB: Walking the tightrope between treatment efficacy and price. *J Clin Oncol* 34:889-890, 2015
7. Durkee BY, Qian Y, Pollom EL, et al: Cost-effectiveness of pertuzumab in human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 34:902-909, 2015
8. Weinstein MC, Stason WB: Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med* 296:716-721, 1977
9. Siegel JE, Weinstein MC, Russell LB, et al: Recommendations for reporting cost-effectiveness analyses. *JAMA* 276:1339-1341, 1996
10. Snedecor SJ: Understanding and use of dynamic models in health economic analyses. *ISPOR Connections* 18:5-8, 2012
11. Diaby V, Tawk R, Sanogo V, et al: A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer. *Breast Cancer Res Treat* 151:27-40, 2015
12. Bach PB, Pearson SD: Payer and policy maker steps to support value-based pricing for drugs. *JAMA* 314:2503-2504, 2015
13. Ramsey SD, Lyman GH, Bangs R: Addressing skyrocketing cancer drug prices comes with tradeoffs: Pick your poison. *JAMA Oncol* 2:425-426, 2016
14. Mack JW, Cronin A, Taback N, et al: End-of-life care discussions among patients with advanced cancer: A cohort study. *Ann Intern Med* 156:204-210, 2012
15. Thanarajasingam G, Hubbard JM, Sloan JA, et al: The imperative for a new approach to toxicity analysis in oncology clinical trials. *J Natl Cancer Inst* 107:djv216, 2015

16. Scagliotti GV, Parikh P, von Pawel J, et al: Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 26:3543-3551, 2008
17. Jardim DL, Schwaederle M, Wei C, et al: Impact of a biomarker-based strategy on oncology drug development: A meta-analysis of clinical trials leading to FDA approval. *J Natl Cancer Inst* 107:djv 253, 2015
18. Xiaobo Zhong X, Lim EA, Hershman DL, et al: ReCAP: Identifying severe adverse event clusters using the National Cancer Institute's common terminology criteria for adverse events. *J Oncol Pract* 12:245-246, 2016
19. Basch E, Abernethy AP, Mullins CD, et al: Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. *J Clin Oncol* 30:4249-4255, 2012
20. Basch E, Deal AM, Kris MG, et al: Symptom monitoring with patient-reported outcomes during routine cancer treatment: A randomized controlled trial. *J Clin Oncol* 34:557-565, 2015
21. Ramsey S, Blough D, Kirchhoff A, et al: Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. *Health Aff (Millwood)* 32:1143-1152, 2013
22. Chino F, Peppercorn J, Taylor DH Jr, et al: Self-reported financial burden and satisfaction with care among patients with cancer. *Oncologist* 19:414-420, 2014
23. Ubel PA, Abernethy AP, Zafar SY: Full disclosure: Out-of-pocket costs as side effects. *N Engl J Med* 369:1484-1486, 2013
24. Zafar SY, Peppercorn JM, Schrag D, et al: The financial toxicity of cancer treatment: A pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *Oncologist* 18:381-390, 2013
25. Bestvina CM, Zullig LL, Rushing C, et al: Patient-oncologist cost communication, financial distress, and medication adherence. *J Oncol Pract* 10:162-167, 2014
26. Walker J: For prescription drug makers, price increases drive revenue. *The Wall Street Journal*, October 6, 2015. <http://www.wsj.com/articles/for-prescription-drug-makers-price-increases-drive-revenue-1444096750>
27. Tefferi A, Kantarjian H, Rajkumar SV, et al: In support of a patient-driven initiative and petition to lower the high price of cancer drugs. *Mayo Clin Proc* 90:996-1000, 2015
28. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *J Oncol Pract* 7:46s-51s, 2011
29. DrugAbacus Interface: Evidence-driven drug pricing project tool. <http://www.drugabacus.org/drug-abacus/tool/>
30. Loftus P: How much should cancer drugs cost? *The Wall Street Journal*. June 18, 2015. <http://www.wsj.com/articles/how-much-should-cancer-drugs-cost-1434640914>
31. Romero M, Chávez D, De Los Ríos M, et al: Cost-effectiveness of nilotinib, dasatinib and imatinib as first-line treatment for chronic myeloid leukemia in Colombia, 2012. *Biomedica* 34:48-59, 2013
32. Goldstein DA, Ahmad BB, Chen Q, et al: Cost-effectiveness analysis of regorafenib for metastatic colorectal cancer. *J Clin Oncol* 33:3727-3732, 2015
33. Gogineni K, Shuman KL, Chinn D, et al: Patient demands and requests for cancer tests and treatments. *JAMA Oncol* 1:33-39, 2015
34. Clarke G, Johnston S, Corrie P, et al: Withdrawal of anticancer therapy in advanced disease: A systematic literature review. *BMC Cancer* 15:892, 2015

Coming Soon! *JCO Precision Oncology*

Editor-in-Chief: James M. Ford, MD

JCO Precision Oncology will publish original research, reports, opinions, and reviews that will advance the science and practice of precision oncology and define genomics-driven clinical care of patients with cancer.

Innovative and timely scientific and educational content will provide a deeper understanding of actionable cancer genomics, personalized translational and clinical oncology research, and recent treatment advances based on tumor molecular profiling.

The first articles for this new online-only journal from ASCO are scheduled to be published in late 2016 or early 2017. Learn more at po.jco.org.

ASCO
American Society of Clinical Oncology

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Dynamic Assessment of Value During High-Cost Cancer Treatment: A Response to American Society of Clinical Oncology and European Society of Medical Oncology**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jop.ascopubs.org/site/misc/ifc.xhtml.

Charles W. Given

Leadership: Sparrow Health System (I)

Barbara A. Given

Leadership: Sparrow Health System

Cathy J. Bradley

No relationship to disclose

John C. Krauss

Research Funding: Abbvie (Inst), Pfizer (Inst), Taiho Pharmaceutical (Inst), X-Biotech (Inst), Ignyta (Inst)

Alla Sikorskii

No relationship to disclose

Eric Vachon

No relationship to disclose