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Introduction

Since 2012, the FDA has approved 88 new oncologic therapies or indications, including 28 drugs for hematologic malignancies (centerwatch.com/drug-information/fda-approved). Correspondingly, the Surveillance, Epidemiology, and End Results (SEER) program reported a 20% decline in the overall cancer-attributable death rate over the past three decades.1 However, improvements in cancer therapy has been accompanied by a boom in health care expenditures from 125 billion in 2010, to a projected 173 billion by the year 20202. New drugs carry a wide range of expected therapeutic efficacy at the expense of increased cost for patients and payers. The shifting dynamics of novel therapies and increasing cost, have brought the concept of “value” to center stage. The meaning of value in reference to cancer treatment differs substantially from the patient, physician, and payer point of view, with different weights added to improvements survival, convenience, side effects, and cost.

Some of the largest gains in survival have occurred in lymphoid and hematologic malignancies, reflecting improved treatment protocols and novel targeted therapies.1 For example, chronic myeloid leukemia (CML), which was uniformly lethal if untreated and best managed with stem cell transplantation before the discovery of imatinib in 2001, is now considered largely a chronic disease, with survival gains in elderly patients from a historic 20% at 5 years to 84% in the modern era.3 Similarly, survival in multiple myeloma (MM) continues to improve from an estimated 5-year survival of only 34% in 2000, to approximately 50% at the last update in 2012.4

The availability of targeted agents has greatly altered the practice patterns of chemotherapy administration. For example, in MM, traditional chemotherapy-based regimens have largely been replaced by novel immunomodulatory agents (IMiDs), owing to data demonstrating

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improved survival with novel therapy. Although novel therapy combinations can cost approximately $145,000 per year compared to $48,000 for chemotherapy, such approaches are associated with increased survival. In addition to altering the sequence of therapy, novel agents are often given for a longer duration. Emerging data seem to support the continuous use of these expensive new drugs in many hematologic malignancies. Continuous therapy in myeloma increased from less than 10% 15 years ago to greater than 60% by 2014.5

An analogous scenario can be observed for chronic lymphocytic leukemia (CLL), which was traditionally treated with chemoimmunotherapy in the frontline setting. Therapy in this context was fixed and led to long term remissions. The approval of ibrutinib for CLL in 2012, and subsequent indications for frontline use have altered this sequence.6 Alterations in drug sequence can have real consequences on cost. A recent analysis on the economic burden of novel targeted therapies for CLL found that with increased use of novel oral agents in earlier lines of therapy, the annual cost of CLL management would increase nearly six-fold from $0.74 billion in 2014 to a projected $5.13 billion by 2025.7 As the majority of patients with CLL are over 65 and on Medicare, the corresponding total out-of-pocket cost would increase from $9,200 to $57,000. One of the contributors to the increased economic burden to patients and society was the use of frontline ibrutinib, associated with increased cost and increased disease prevalence due to prolonged survival. Rising drug costs and decreased insurance coverage coupled with rising premiums and out of pocket expenses, may lead drug cost to play a larger role in patient’s perceived value. Physicians and other health care providers serve as key intermediaries, guiding the appropriate usage and timing of novel therapies to strike the optimal balance between efficacy and cost-effectiveness.

Defining Value and Cost

The science of cost-effectiveness attempts to quantify the increment benefit associated with a new drug compared to an existing intervention in concert with the differences in cost. Assigning numeric values to life years (LYs), quality of life, and the cost of drugs allows payers and society to enumerate the cost-effectiveness of treatment strategies. Cost-utility analyses use a specific variable, QALY (quality life-adjusted years), to measure the benefits of an intervention. A QALY quantifies the quality and quantity of life; so that 1 equals one year in perfect health, and 0 equals death. The incremental cost effectiveness ratio (ICER) defines how much additional money is spent for 1 year of perfect quality life and allows comparisons across healthcare interventions. The major determinants of value in these models are the cost of therapy and number of life years or QALY’s gained.

Value from a System Perspective

Rises in cancer drug prices have increased the visibility of studies of cost effectiveness and attention to value. In one review evaluating global studies of cost effectiveness of therapies for hematologic malignancies, researchers examined 29 studies from 1996–2012 within the Tufts Center CEA registry.8 Nine of the studies included in the analysis were based in the U.S. The remainder were based in European countries, and 76% were funded by pharmaceutical companies. The authors noted that 73% of the analysis demonstrated cost effectiveness, with a benchmark of less than $50,000 per QALY, and 86% were cost
effective with a cutoff of less than $100,000/QALY. The authors’ controversial conclusion was that the improvements in cancer survival justified the cost of drug development. A critical appraisal and reanalysis of this article defined some significant flaws in the study design: 1) the analysis utilized outdated drug prices which were substantially lower than modern prices, 2) prices from other countries that were not consistent with US pricing were used, and 3) definitions of “cost-effective” therapy differed significantly from standard literature.

Nevertheless, several novel therapies seem to be cost effective owing to reduced therapy related monitoring, complications, and prolonged survival. MM has experienced more new drug approvals than many other cancers in the past 5 years. A European study demonstrated the cost effectiveness of novel therapies including frontline lenalidomide and second line carfilzomib, lenalidomide, and dexamethasone (KRd) over bortezomib and thalidomide due to reduction in therapy related hospitalizations. However, the projected yearly total cost of lenalidomide therapy was €40,692 in the UK, whereas a U.S. based study evaluated the total cost of lenalidomide therapy at >$150,000/per year. Data between countries are difficult to compare due to different methodologies in analyzing total cost, drug prices, as well as differences in outpatient and hospital-based utilization. While the latter study utilized real-world health Medicare claims, the U.K. study developed a cost-impact model that may ignore some costs relevant in the US healthcare system. The inputs and metrics used by these studies must be noted when assessing these conclusions. Indeed, another study demonstrated that in spite of improved survival, novel myeloma therapies could only be considered cost-effective when willingness to pay thresholds were increased to $230,000. This threshold is far beyond the $50,000-$100,000 levels that are usually consider cost-effective in studies in the United States.

Value from a Patient’s Perspective

Drug value from a patient perspective often weighs efficacy and quality of life above cost, provided the cost is sufficiently covered by a third party. However, the financial responsibility of drug cost has shifted more toward patients. Studies demonstrate that approximately 25% of cancer patients stop taking or inappropriately take medications due to inability to afford them. Among Medicare beneficiaries with CML, there also was decreased initiation of therapy, with approximately 30% of newly diagnosed patients not initiating treatment within 6 months of diagnosis, and 40% of those initiating therapy were non-adherent within the first 180 days. Nevertheless, physicians may impact compliance by initiating open discussions regarding the financial impact of cancer therapies.

Drug value can be further ascertained by defining clinically meaningful benefits. While overall survival is the gold standard for measuring therapeutic efficacy, progression-free survival (PFS) is often treated as a surrogate in clinical trials. This substitution provides easier and earlier attainment of the outcome, allowing for more rapid transit of novel drugs through the regulatory process to approval. One critical role for physicians is to distinguish clinical scenarios where PFS is not an applicable surrogate and interpret the clinical benefits of novel drugs appropriately.
Indolent lymphomas, such as follicular lymphoma, are generally considered incurable, yet some patients have an expected survival of 20 years or more following diagnosis. Several novel expensive therapies have recently been approved for indolent lymphoma that improve PFS. Clinicians and patients should carefully discuss the potential benefits and financial and nonfinancial costs associated with novel therapies that produce PFS benefits only. Moreover, since outcomes for patients with follicular lymphoma remain variable, cost effective approaches may involve targeting novel therapies toward the patients with the greatest unmet needs.

CML has likewise experienced a surge of novel agent approvals. New tyrosine kinase inhibitors (TKIs) such as dasatinib and nilotinib demonstrate increased efficacy in terms of the rate and depth of response, however, these newer TKIs increase cost substantially, and it remains unclear whether survival is improved by utilizing them in the frontline setting, or after imatinib, which has a generic formulation recently available.\textsuperscript{15} Cost effectiveness models demonstrated that two major strategies could be cost effective: imatinib→nilotinib→chemotherapy/SCT and nilotinib→dasatinib→chemotherapy/SCT, depending on willingness-to-pay. The ICERs for each strategy were $253,500 and 445,100/QALY respectively.\textsuperscript{16} The multitude therapies available in the physician’s vital role in determining the appropriate sequence of therapy to maximize Tacit and minimize cost.

Novel therapies may add value in other ways such as minimizing therapy related adverse effects and increasing convenience. Oral formulations may reduce the need for frequent monitoring, visits, infusions, and associated co-pays. In some circumstances, this may allow patients can thus positions of employment and minimize time away from work. Physicians can thus serve as the gatekeepers in choosing the therapies that optimally balance disease-specific outcomes, health, convenience, and physical function with cost.

**Expert Commentary**

The surge in innovation has made numerous new drugs available for clinical practice from monoclonal antibodies and small molecule inhibitors to immune- and cellular therapies. However, the trajectory of drug prices is unsustainable to the current health care system. Increased emphasis on value in cancer therapy, would aim to increase the availability of affordable drugs administered to the right patients to minimize unnecessary cost while improving patient outcomes and quality of life. This could be accomplished by decreasing drug price and increasing selectivity through consistent quality care and the use of biomarkers and pharmacogenomics for personalized therapy.

In 2014, The American Society of Clinical Oncology (ASCO) released an action brief on the value in cancer care, which highlighted that the increased cost of cancer care does not necessarily translate into improved quality.\textsuperscript{17} To systematically address the issue, the Quality in Oncology Practice Initiative (QOPI) was launched in 2006, and continues to refine methods to improve cancer value. The initiatives have included, the “Choosing Wisely” campaign—which outlines a responsibility to “provide health care that is based on wise and cost-effective management of limited clinical resources.”\textsuperscript{18} QOPI further notes
that providing high quality care, itself, helps to contain cost by reducing ineffective and unnecessary medical expenses.

Improvements in drug selectivity have been one of the hallmark accomplishments of modern therapy, yet the goal of personalized medicine is far from complete. Pharmacogenomics may be utilized to improve patient selectivity and cost effectiveness. Several examples already exist such as the use of all trans retinoic acid for PML/RAR translocations in leukemia, TKIs for Philadelphia chromosome translocations in acute lymphoblastic lymphoma and CML, and the use of PD-ligand expression for checkpoint inhibitors across multiple malignancies. While testing carries its own costs, cost-effectiveness analyses can be used to guide which tests are appropriate and cost-saving for clinical use. 19

Drug prices are the other major obstacle to enhanced value. A thorough discussion of the barriers to affordable drug prices is beyond the scope of this article. However, novel pricing strategies tying efficacy to cost have been advocated. In the current model, highly effective therapies, expected to result in long term remissions are priced similarly to drugs that improve survival by only 1–3 months. One innovative approach to drug pricing was proposed by Goldstein and colleagues. 20 A “value based” price for a novel agent was determined by calculating the ICER across a range of prices and evaluating thresholds for cost effectiveness. While global changes to the policies and practices that have led to markedly increased drug costs may ultimately be necessary, physicians can contribute to immediate changes capable of balancing patient value and payer cost by providing high quality, evidence-based care and utilizing available biomarkers appropriately.

5-Year View

The surge of novel therapies in oncology has been accompanied by an improved understanding of the mechanisms of action and resistance patterns in various malignancies, as well as genetic and clinical biomarkers of response. Maturing data detailing drug mechanisms may foster improved patient selectivity. Genomics testing is expensive, however, by offsetting pharmaceutical prices, this is one maneuver that may save money in the long run. 19 Using a conceptual framework such as the ASCO, European Society for Medical Oncology, or National Comprehensive Cancer Network value framework whereby future oncologic therapies could be given a value “score” that incorporates key elements addressing clinical benefit, toxicity, and cost may guide clinical practices consistent with patients’, payers’, and societal values. 21 Clinical benefit can be re-defined in this framework to encompass improvements to a patient’s quality or quantity of life, whether that be through overall survival benefits, lengthening a disease-free interval in symptomatic disease, or decreasing disease associated symptoms. Toxicity, especially where treatment results in a detriment to quality of life, would be negatively valued in this model. Cost would include expenses distributed to any involved in the payment structure—patients, insurers, and society.

Physicians will continue to play a major role in selecting the appropriate timing, sequence, and duration of therapy, as well as utilizing pharmacogenomics and biomarkers to improve patient selectivity. Future drug pricing methods should be based on a combination of value
and cost of innovation. Increasing awareness and implementation of value based practices could ultimately lead improved quality of care for patients, reduced waste, and overall improvements in value to patients, payers, and society.

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