

Application of Decision-Analytic Models in Personalized Medicine for CML Treatment Decisions Made by Payers, Providers, and Patients

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As personalized medicine gains momentum, patients' perspectives and their individual responses to treatment, including their particular disposition to side effects of therapy, will play increasingly important roles in guiding treatment decisions for physicians and their patients, as well as those involved in making reimbursement decisions in oncology. Under this emerging paradigm, undertaking analyses that strive to explain, quantify, and predict variation in treatment response by individuals is essential for informing treatment decisions, designing clinical practice guidelines, and making reimbursement decisions that are aligned with a patient-centered approach to optimize outcomes and the benefit-harm balance for each individual patient. Decision-analytic models provide an opportunity to evaluate expected outcomes of treatments and/or biomarker-guided strategies in the management of cancer. The models can be applied to existing technologies across large populations or used to predict the impact on outcomes of technologies in development.

Decision analysis is a systematic and quantitative method of deciding between 2 or more alternatives under uncertainty.¹ According to Weinstein et al. (2003), the purpose of decision-analytic modeling is "to structure evidence on clinical and economic outcomes in a form that can help to inform decisions about clinical practices and health-care resource allocations."² A variety of data sources can be used to construct these mathematical models, including data from registries, clinical trials, surveys, and administrative claims databases.² Models that are designed to assist decision makers with the allocation of scarce health care resources by considering both costs and consequences of the decision, commonly referred to as cost-effectiveness, cost-utility, or cost-benefit models, have become commonplace in the medical literature, especially in therapeutic areas associated with costly treatment options, such as oncology. For example, a systematic review of the literature published through January 2011 (presented as a poster [Rochau et al., 2011]) identified 15 published decision-analytic models for chronic myeloid leukemia (CML).³ Fourteen (93%) of the studies were cost-effectiveness studies. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society of Medical Decision Making (SMDM) Joint Modeling Good Research Practices Task Force recommend consultation with subject matter experts and stakeholders, which may include payers, providers, and patients, during the construc-

tion of a model to "assure that the model represents the disease processes appropriately and adequately addresses the decision problem."⁴

Despite the potential benefits of using decision-analytic models in health care decision making, it is unclear how and to what extent these types of tools are being used to inform oncology-related coverage and treatment decisions by payers, providers, and patients. In a disease such as CML, for example, where the advent of tyrosine kinase inhibitors (TKIs) has dramatically improved outcomes,⁵⁻⁸ to what extent are payers using outcomes research and decision-analytic models to inform their coverage decisions? From the perspective of the provider and patient, are decision-analytic models being used to inform treatment decisions in CML and if so, how? The intent of this commentary is to consider the current and potential future use of decision-analytic models in treatment decisions for CML from the perspectives of payers, providers, and patients.

Payers' Perspectives

There has been an increase in the use of decision-analytic models to inform payer decisions, corresponding with an increasing demand for evidence regarding efficacy, effectiveness, safety, and the trade-offs between clinical benefit and harm of treatment alternatives. Decision-analytic models provide a process to synthesize various types of evidence-based data, including short-term efficacy data, long-term epidemiologic data, quality-of-life (QOL) data, charges/costs, and resource use.^{9,10}

The increasingly high price of oncology products in the United States would warrant such a cost-effectiveness evaluation. However, regulatory mandates can limit the ability of payers to consider these results in coverage decisions for these products. For example, Medicare Part D formularies are required to include "substantially all" medications in 6 protected drug classes, including antineoplastics.¹¹ In the treatment of CML, the TKIs are oral chemotherapy medications eligible for reimbursement under Medicare Part D. This Medicare Part D formulary coverage policy, in effect, limits the ability of Part D plans to negotiate lower prices with manufacturers of these products. The current trend of many Part D prescription drug plans is to place expensive oncology products on a "specialty tier" with coinsurance rates of 25%-33%.¹² Pharmacy benefit management companies (PBMs) of private health plans

are also using this specialty tier strategy in the formulary, often with coinsurance cost share for beneficiaries.¹² Alternative approaches include an out-of-pocket maximum or restricted use policies based on U.S. Food and Drug Administration (FDA)-approved indications.

According to the systematic review of decision-analytic models in CML by Rochau et al., only 1 published decision-analytic model evaluated a treatment strategy that included 1 of the newer second-generation TKIs.³ Another systematic review by Rogers et al. (2012), which focused on the use of dasatinib or nilotinib in patients intolerant or resistant to imatinib, also failed to identify any published full cost-effectiveness models meeting the authors' inclusion criteria.¹³ Rogers et al. pointed out that evidence on the efficacy of the second-line TKI agents is generally limited and often includes no comparisons with the most common alternative, which is to increase imatinib dose. There are several randomized controlled trials (RCTs) under way, mostly open label, which will take several years to complete.¹³

Unfortunately, the development of models, which attempt to reflect real-world practice, can lag behind current practice. Real-world data on these agents have been difficult to obtain due to a relatively slow uptake in a small market. The policies outlined here indicate, however, that even if there were numerous decision-analytic models in CML that reflected currently available treatments and practice patterns, for some plans in the United States, the incentives for using decision-analytic models in their formulary management processes for CML would not be fully maximized. In addition, concerns remain regarding the uncertainty of using a clinical trial outcome, complete cytogenetic response (CCyR), to predict long-term real-world effectiveness and regarding the limited value of QOL utility in U.S. health plan formulary decisions.

Unlike the U.S. health care system, which lacks national coverage decisions made in part on the basis of evaluation of cost-effectiveness, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom evaluates the clinical and cost-effectiveness of cancer therapies and interventions. In technology appraisals, NICE specifically evaluates the cost per quality-adjusted life-year (QALY) gained and advises the National Health Service (NHS) regarding which treatments should be covered.^{14,15} The incremental cost-effectiveness ratio (ICER) threshold used in evaluations by NICE is usually between £20,000 and £30,000 per QALY gained.¹⁶ However, NICE's chair Michael Rawlins said in 2008 that "NICE has long recognized that society places great value on extending the life of people with life-threatening diseases"¹⁷ and issued in 2009 a special guidance on life-extending end-of-life treatments that include cancer therapies. Under certain criteria, the cost-effectiveness threshold may then be exceeded.¹⁸ One of the highest thresholds that NICE has accepted has been for the management of CML patients in the blast-cell phase; NICE

accepted an ICER of £49,000 (\$84,000) per QALY gained for imatinib in these circumstances.¹⁹ If a new technology is evaluated positively by NICE, NHS organizations have to ensure that the technology is available within 3 months.²⁰

Payers have a vested interest in developing further evidence to reduce uncertainty, but often there are trade-offs associated with gathering additional information to inform the decision-making process. Additional studies may, for example, result in additional costs, contribute to a delay in the decision (and thus potentially affect patients' health), or present additional risks for those patients involved in further studies. Despite remaining uncertainty, coverage decisions about new technologies must be made.²¹ In such situations, value-of-information analyses based on decision-analytic models provide a formal approach to answer the question whether additional evidence is needed to support or reject adoption of a technology and can be used to guide further research prioritization.²² Another approach to solving this dilemma is the concept of "coverage with evidence development (CED)." This approach involves payer coverage of a product that the payer believes to be associated with significant uncertainty in exchange for the accumulation of additional population-level evidence to reduce this uncertainty.²³ A review of reimbursement schemes between 1998 to 2009 revealed that 34 CED schemes had been initiated across a total of 5 countries, one of which involved the NHS and imatinib, a TKI, for the treatment of CML.²³

Medical Providers and Treatment Decisions

Medical providers make hundreds of decisions daily. Paramount to physicians' prescribing decisions is evidence of efficacy, safety, side effects, cost, and the impact these factors have on the patient.²⁴ Treatment decisions need to combine clinical evidence with the individual needs of the patient. Both components are critical to ensure patient response and compliance with the chosen intervention.

In CML, the most common first-line treatment is a TKI. These compounds have dramatically improved outcomes in CML, and survival is no longer a major concern for the majority of patients.⁵⁻⁸ Imatinib (STI571 or Gleevec) was the first TKI to market in 2001²⁵ and became the standard of care based on results from the International Randomized Study of Interferon and STI571 (IRIS; O'Brien et al., 2003), comparing imatinib with interferon- α plus low-dose cytarabine.⁶ At 18 months, a CCyR (elimination of Philadelphia chromosome-positive [Ph+] cells from bone marrow) was demonstrated in 76% of patients randomized to imatinib compared with 14.5% of patients receiving interferon- α .⁶ At a median follow-up of 19 months, 85.7% of patients remained on imatinib compared with only 10.8% of patients treated with interferon- α plus cytarabine.⁶ Crossover was allowed in the IRIS trial, and because of the superiority of imatinib, 57.5% of patients initially treated with interferon- α plus cytarabine crossed over to the imatinib arm

compared with 2% of patients initially randomized to imatinib; thus, no comparison of survival rates was made.⁶ A follow-up analysis of the imatinib-treated IRIS patients, reported by Deininger et al. (2009) in a poster, found that at 8 years, the estimated overall survival was 85% (93%, considering only CML-related deaths); the event-free survival was 81%; and the estimated rate of freedom from progression to accelerated or blast phase was 92%.²⁶ In comparison, the historical 9- or 10-year overall survival rates for interferon- α used alone or with cytarabine range from 27% to 35%.²⁷⁻³¹

Despite these impressive results, 10%-20% of patients exhibit primary or secondary resistance to imatinib, and another 20% fail due to intolerance.³² The predominate reason for resistance to imatinib stems from point mutations in the kinase domain of BCR-ABL1. Mutations resulting in high insensitivity to imatinib include Y253H, Y253F, E255K, E255V, and T315I.³³ A multitude of other mutations result in intermediate or high sensitivity to imatinib. The effect of these mutations has not been addressed in any decision-analytic models published to date.

To overcome resistance and provide options for patients with imatinib intolerance, second-generation TKIs with enhanced BCR-ABL inhibition were developed, including dasatinib (Sprycel) and nilotinib (Tasigna). To date, the only mutation-conferring resistance to both first- and second-generation TKIs is the T315I mutation, which portends poor outcomes.^{33,34} However, third-generation agents that are active against this mutation are in development.^{34,35} The FDA initially approved dasatinib in 2006 for adults with Ph+ CML in chronic, accelerated, or myeloid or lymphoid blast phase with resistance or intolerance to prior therapy, including imatinib.³⁶ Nilotinib followed in 2007 for the treatment of adults with Ph+ CML in chronic or accelerated phase who are resistant to or intolerant to prior therapy, including imatinib.³⁷ Subsequently, the FDA approved both dasatinib and nilotinib for first-line treatment of chronic phase CML in 2010 after demonstration of superiority over imatinib in obtainment of a major molecular response (MMR=less than or equal to 0.1% BCR-ABL1 transcripts from serum on International Scale) and a CCyR.^{36,37}

Therefore, the optimal first-line treatment of patients with chronic phase CML is a subject of debate in light of these differences in efficacy, sensitivity against BCR-ABL1 mutations, and, as will be discussed, side-effect profile. Other areas of clinical controversy that could be addressed with decision-analytic modeling include TKI switching patterns and outcomes, especially in light of data demonstrating that BCR-ABL transcript levels at 3 months predict patients' likelihood of experiencing a clinical failure and thus allowing for early intervention by dose modification or switching TKIs.³⁸

The human factor, encompassing patient attitudes and behaviors in the real-world setting, is often poorly reflected in RCTs but can be a significant determinant of health outcomes.

Therefore, it is not surprising that providers consider the individual issues of patients, including the financial burden of treatment options and patients' QOL, in their decision making. QOL analyses are used to assess how diseases and treatments affect an individual's ability to function in normal daily activities. Two large meta-analyses have shown that self-assessed QOL is associated with overall survival and may have prognostic value in patients with cancer; patients reporting a good QOL were found to have an improved overall survival, often by several months.^{39,40} However, one of these meta-analyses did not include patients with CML, and the other meta-analysis report did not indicate whether any patients with CML were included.

Health-related QOL and patient preferences are particularly relevant when considering the treatment options available for patients with CML. All of the TKIs approved by the FDA for the treatment of CML are associated with significant costs. The TKIs are oral medications, which need to be taken for life or until disease progression. The TKIs are not without side effects, and as such, many patients will need to manage these side effects throughout their lifetimes.⁴¹ Myelosuppression can be seen with all TKIs and is the most likely side effect to alter treatment course. Side effects, such as the gastrointestinal toxicity of TKIs, can be adequately managed with supportive care, while others including myelosuppression, hepatotoxicity, and cardiotoxicity are dose limiting and alter response to treatment. Additional side effects of TKIs, such as nausea and fluid retention, may be perceived as intolerable by the patient, thus affecting compliance and treatment response.^{41,42} Side effects and tolerability may well provide rationale for treatment with one TKI over another, since side effects are a major factor in patient nonadherence to TKIs.⁴³ Lastly, since these medications are taken orally at home, instead of an intravenous infusion at a clinic, patients are responsible for both therapy administration and adherence. Adherence can be a challenging commitment for many patients as documented in analyses of therapies for CML⁴⁴ and for other life-threatening, chronic conditions.⁴⁵ Patient preferences for particular outcomes and a QOL standard, balanced against their tolerance for side effects and ability to accept cost, need to be considered by the provider.

Decision-analytic models assessing prognosis, therapeutic impact, and cost-effectiveness of available therapies can aid in the provider decision-making process. A survey of U.S. oncologists (Neumann et al., 2010) revealed that a majority of oncologists favor an increased use of these cost-effectiveness data for coverage and reimbursement decisions relating to cancer therapies.⁴⁶ However, current use of cost-effectiveness data by oncology providers may be limited, in part, by a lack of experience or confidence in interpreting these studies. The survey reported by Neumann et al. revealed that less than one-half of those surveyed felt "well prepared to interpret and use cost-effectiveness information" in their decision making.⁴⁶ Furthermore, in the United States, results of cost-effectiveness

studies, including cost-utility studies, may have little or no correlation with out-of-pocket drug costs for patients, a cost parameter many oncologists consider when making treatment decisions.⁴⁶

Because cost-effectiveness models are often undertaken from the perspective of the payer or society, their immediate relevance to providers and individual patients may be limited. The systematic review of CML decision-analytic models by Rochau et al. found that of the 11 models with a clearly stated perspective, 6 (55%) had a health care system perspective, 3 (27%) had a societal perspective, and 2 (18%) had a third-party payer perspective.³

Other types of decision-analytic models have gained wide acceptance by oncology providers. For example, some decision-analytic models can provide clinicians with patient-tailored treatment recommendations in conditions of uncertainty or when faced with a variety of treatment options. Adjuvant! Online is an evaluation tool developed for oncologists and patients with early breast cancer that utilizes patient- and tumor-specific information to estimate prognosis and therapeutic efficacy of adjuvant therapy.⁴⁷ This model is widely utilized⁴⁸ and advocated for use in the United States⁴⁹ and Europe⁵⁰ to aid in shared decision making between the patient and clinician regarding the benefits, side effects, and costs of adjuvant therapy. A decision-analytic model assisting in the determination of the most appropriate TKI treatment for CML taking into account disease severity, efficacy, BCR-ABL1 mutations, side effects, health-related QOL, and costs would also assist in shared decision making of CML treatment. Adaptations of such models to other cancers and disease states are also warranted.

Consideration of the Patient Perspective

Medical decision making has changed significantly over the last century, from the paternalistic model in which physicians were trusted to make decisions on the behalf of patients,^{51,52} to an increasingly popular patient-centered model in which individual goals and preferences direct therapy decisions in collaboration with the expertise of the health care team. This model is based on studies suggesting that patient involvement in treatment decisions leads to greater QOL and satisfaction in treatment outcomes, independent of the treatment received.⁵³⁻⁵⁷ The Institute of Medicine, recognizing the importance of patient centeredness, recommends that all patients should be provided the pertinent information necessary to make informed treatment decisions along with the opportunity to direct these decisions.⁵⁸

A methodology to increase patient involvement in medical decision making is patient-oriented decision aids. Decision aids are instruments designed for patients to help communicate the various treatment or screening options available, including their benefits and harms, and to assist patients with decision making when faced with uncertainty.⁵⁹ Many of the RCTs involving decision aids have been conducted in the field

of oncology.⁶⁰ Evidence about the use of decision aids in oncology indicates that these tools can improve patient involvement in decision making and improve the quality of treatment decisions.⁵⁹ Decision aids help patients decide which factors are the most important and relevant to them when choosing between options.

As patients become more involved in their own treatment decisions, it becomes increasingly important to gather QOL and other patient-reported outcomes data to improve the clinical decision-making process. Evidence of the movement towards patient-focused treatment decisions can be found in the Patient Protection and Affordable Care Act of 2010, which created the Patient-Centered Outcomes Research Institute (PCORI) aimed at promoting comparative clinical effectiveness research (CER) that can “assist patients, clinicians, purchasers, and policy-makers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed through research and evidence synthesis.”⁶¹ The varying efficacy and side-effect profiles of TKIs for the treatment of CML, coupled with the need for data on the long-term tolerability and adherence of these medications, underscores the importance of incorporating patient-specific factors in clinical decision making. These factors may include medication side effects, disease-related symptom burden, and financial cost to the patient. More research on how these factors affect health-related QOL is needed in the area of CML. Currently, there has been a limited amount of research on the QOL of CML patients since the first TKI, imatinib, was introduced in the marketplace in 2001.^{25,62,63}

Nothing beats asking patients what is important to them. Congruent with the shift to personalized medicine and a patient-centered approach to care, the use of decision aids for patient decision making is likely to increase in the future. Decision aids constructed from decision-analytic models that are developed transparently and with assumptions that are comprehensible by patients and their health care providers have the potential to facilitate a more tailored approach to shared decision making between the provider and patient as the individual characteristics (e.g., genetic/demographic features, preferences) of the patient are taken into consideration. A patient-centered approach in construction of a decision-analytic model has the potential to inform treatment decisions of physicians and their patients.

Future Initiatives and Limitations of Decision-Analytic Models

In an attempt to elucidate the current role of decision-analytic models to inform treatment decisions of payers, providers, and patients, CML was chosen, in part, because some may believe that there is no role for these models in a disease with 2 or more generally well-tolerated and efficacious

treatment options. Decision-analytic models have a role in these situations because there is great uncertainty surrounding the effects of various treatment options, including their long-term safety and effectiveness; optimal treatment sequence; and how any given patient will respond, tolerate, and value the costs and consequences of one therapy versus another. In the United States, worthwhile endeavors would address the value of a decision-analytic model in facilitating more informed formulary decisions on the TKIs and would perhaps establish thresholds of evidence that would be required in order to use such a model in decision making.

The strength of any decision-analytic model lies partially in the quality of estimates used to populate the model. However, even the best available data may be limited and may not provide enough information to support a comprehensive and useful decision model for end users. RCTs are the gold standard for comparative trials of efficacy, but head-to-head RCTs between therapeutic competitors often do not occur for many reasons (e.g., cost, time, lack of requirement by FDA, and lack of incentive by manufacturer). In the absence of such data, observational data can provide valuable information on the relative effectiveness of therapies. Sometimes, observational data may be preferred over clinical trial data because observational data can provide information on real-world effectiveness and costs that may not be captured in an RCT, a perspective often requested by payers and government agencies.

A lack of clinical evidence for populating an economic model that evaluated dasatinib and nilotinib as second-line therapy for chronic phase CML led Rogers et al. to conclude that “our cost-effectiveness model should be viewed as an exploratory analysis of uncertainty in the available evidence, rather than a robust evaluation of cost-utility.”¹³ The limitations of the use of a particular data source for populating a decision-analytic model should be explicitly delineated in the modeling report. Furthermore, one of the primary limitations of decision-analytic models is that even with the use of the best available data, these models ultimately do not determine true outcomes. Therefore, when using a decision-analytic model, one should validate the outcomes against real-world data as they become available. This is an important step that is still not done often by those who use these models.^{64,65}

Conclusions

The construction of pharmacoeconomic decision-analytic models for CML therapies requires assumptions and complex scenarios that are not easily comprehensible to patients. Under the personalized medicine framework, decision-analytic models are likely to play an increasing role in shared decision making among payers, providers, and patients. Such models should be transparent and describe the assumptions in terms that are comprehensible for patients and their providers regarding treatment benefits, harms, and costs.

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