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LITERATURE REVIEW:

Chronic Myeloid Leukemia

Trying to Calculate the Economic Value of Dasatinib or Nilotinib for Imatinib-Resistant CML

Although it is now standard practice to utilize the second-generation tyrosine-kinase inhibitors dasatinib or nilotinib in patients whose chronic myeloid leukemia has recurred while taking imatinib treatment, published support for the economic value of this approach is lacking. Investigators from the University of Exeter, United Kingdom, conducted a review of the literature and produced an economic model to help fill this information gap.

They evaluated contributions to key databases (MEDLINE [including MEDLINE In-Process and Other Non-Indexed Citations], EMBASE [ISI Web of Science], Conference Proceedings Citation Index, as well as 4 other sites). Their research led to 15 relevant studies, the most recent from June 2009.

Two separate decision-analysis economic models for chronic myeloid leukemia (CML) were utilized, in which patients in chronic-phase CML either showed the potential to become or did become resistant to a normal dose of imatinib (imatinib resistant), or due to adverse events had to cease imatinib treatment (imatinib intolerant). Another was used to evaluate patients with CML that had progressed to blast crisis.

Although the number of studies regarding the effectiveness of dasatinib and nilotinib for treating chronic-phase CML patients (who were either imatinib resistant or imatinib intolerant) was limited, the investigators found ample evidence for the clinical effectiveness of these agents, based on positive cytogenetic and hematological responses.

However, it was very difficult, they stated, to come to any conclusions regarding cost-effectiveness with either dasatinib or nilotinib treatment of patients in those with imatinib-resistant CML. Serious data flaws were noted, in one way or another, for all the economic models produced.

All available data regarding accelerated and blast crisis came from observational single-arm trials. Unfortunately, meaningful comparisons between the treatments was greatly undercut because of various and possible baseline characteristic variations.

Accelerated phase and blast crisis de novo models could not be expanded because the available clinical data were deficient. In addition, there was sparse evidence regarding the effectiveness of second-generation tyrosine-kinase inhibitors (TKIs) compared with high-dose treatment with imatinib, which severely weakened the economic evaluations done by the manufacturers.

Interestingly, a separate review of the studies on the value of high-dose imatinib in patients with chronic-phase CML resistant to standard-dose imatinib revealed that up to one-third experienced a

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complete cytogenetic response (up to four-fifths experienced a complete hematologic response), with grade 3 or 4 adverse events occurring in 40% of patients (up to one-fifth discontinued because of these adverse effects). In an economic analysis, nilotinib appeared to have greater cost-effectiveness than high-dose imatinib, followed by dasatinib, in these resistant patients. However, they caution that the study was not based on direct comparisons with identical outcomes measures.

Although the second-generation TKIs appear to add clinical value to the armamentarium against CML, the clinicians acknowledge that a meaningful cost-effectiveness conclusion is not possible. Until a randomized, 3-way, double-blind clinical study involving dasatinib, nilotinib, and high-dose imatinib is conducted, they added, the true economic value of the second-generation TKIs cannot be revealed.

Sources: Rogers G, Hoyle M, Thompson Coon J, et al. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. *Health Technol Assess*. 2012;16(22):1-410.

Loveman E, Cooper K, Bryant J, et al. Dasatinib, high-dose imatinib, and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. *Health Technol Assess*. 2012;16(23): iii-xiii, 1-137.

Chronic Myeloid Leukemia Treatment Practices in the United States

The multinational, prospective WORLD CML registry was established in order to measure how patients with CML are managed by evaluating global clinical practice patterns. This registry, with sites around the world, recently examined results for patients with CML at locations in the United States and assessed how practice patterns correspond with National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines.

The care of 377 patients (median age, 53 years; range, 18-91 years) with a confirmed CML diagnosis enrolled in the United States from February 2008 to December 31, 2010, was analyzed by American researchers. Of these participants, 363 (96%) received a chronic phase diagnosis.

First-line therapy of imatinib was prescribed for 73% of patients with chronic phase CML, compared with hydroxyurea (6%), nilotinib (3%), and dasatinib (1%). (The clinicians noted that patients may have received more than 1 medication.) The median treatment period lasted 7.6 months (range, 0.1-33.5 months).

The dose of imatinib treatment was increased in 29 of the 363 patients with chronic phase CML (8%) primarily as a result of physician request and lack of efficacy. In 32 patients (9%), the imatinib dose was reduced, primarily because of adverse events and physician request. Lack of efficacy and adverse events led to the treatment regimen being changed from imatinib to nilotinib in 21 patients (6%) and to dasatinib in 20 patients (6%).

Clinicians most commonly used hematology assessments to evaluate CML treatment progress (**Table 1**). After 3 months of imatinib treatment, a molecular assessment was sought for only 16% of patients, although up to 64% of patients underwent molecular disease testing by 2 years of therapy. The least common assessment, cytogenetics, was performed in only 13% of patients after 3 months and up to 34% after 6 months of treatment.

The investigators concluded that many patients being treated with first-line imatinib for chronic phase CML did not routinely undergo cytogenetic or molecular assessments. According to NCCN guidelines, such testing should be conducted more frequently (**Table 2**). They indicate that access to molecular testing may have been an issue during the study period, and that these findings therefore should be updated to reflect more current availability of cytogenetic and molecular testing.

Source: Hermann R, Miller CB, Catchatorian R, et al. Understanding US treatment practices for the management of chronic myeloid leukemia (CML) in clinical practice: a US subgroup analysis of the WORLD CML Registry. Presented at the 54th annual meeting of the American Society of Hematology, Atlanta, December 8-11, 2012.

Table 1. Type of Disease Assessments in Patients With Chronic-Phase CML Treated With First-Line Imatinib

	Time Since Start of Imatinib[a,b]					
	3 mo	6 mo	12 mo	18 mo	2 y	3 y
	(N = 265)	(N = 233)	(N = 193)	(N = 135)	(N = 92)	(N = 18)
Patients with assessment	49%	74%	85%	79%	89%	78%
Hematologic	45%	68%	76%	67%	82%	72%
Cytogenetic[c]	13%	34%	32%	25%	28%	33%
Molecular	16%	43%	51%	47%	64%	50%

[a]N values correspond to the number of patients still in the registry at each time point.
[b]Includes assessments within the following ranges: 3 mo, start of first-line therapy to 4.5 mo; 6 mo, >4.5-9 mo; 12 mo, >9-15 mo; 18 mo, >15-21 mo; 2 y, >21-30 mo; 3 y, >30-42 mo.
[c]Includes fluorescence in situ hybridization.

Table 2. Monitoring Guidelines From the National Comprehensive Cancer Network

Test	Recommendation
Bone marrow cytogenetics	At diagnosis to establish the disease phase, if collection of bone marrow is not feasible. FISH on a peripheral blood specimen using dual probes for the *BCR* and *ABL* genes is an acceptable method of confirming the diagnosis of CML. At 3 months from initiation of therapy, if QPCR using International Scale (IS) is not available. At 12 months from initiation of therapy, if there is not CCyR or MMR. At 18 months from initiation of therapy, if not in MMR and lack of CCyR at 12 months. Rising levels of *BCR-ABL* transcript (1-log increase) without an MMR.
Quantitative RT-PCR (QPCR)	At diagnosis to establish baseline BCR-ABL transcript level. Every 3 months when a patient is responding to treatment. After CCyR has been achieved, every 3 months for 3 years and every 3-6 months thereafter. If there is a rising level of *BCR-ABL* transcript (1-log increase) with an MMR, QPCR analysis should be repeated in 1-3 months.

BCR-ABL kinase domain mutation analysis	• Chronic phase
	  • For patients with inadequate initial response (failure to achieve PCyR or *BCR-ABL/ABL* ≤10% (IS) at 3 months or CCyR at 12 and 18 months.
	  • Any sign of loss of response (defined as hematologic or cytogenetic relapse or 1-log increase in *BCR-ABL* transcript levels and loss of MMR).
	• Disease progression to accelerated or blast phase.

Source: Reprinted with permission from Hughes T, Deininger M, Hochhaus A. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood*. 2006;108(1):28-37.

PAYER PERSPECTIVE

Will Cytogenetic Testing Improve Value in CML Care?

Maria Lopes, MD, MS

As demonstrated in the presentation by Hermann and colleagues at the December 2012 American Society of Hematology meeting,[1] it is clear that in practice, cytogenetic testing in patients with CML is not performed according to the latest NCCN guidelines, which now call for an evaluation at 3, 12, and 18 months to assess cytogenetic response. This affords the opportunity to assess whether the choice of therapy is effective, and if not, to evaluate patient compliance, drug-drug interactions, or mutations that may render current treatment ineffective. Given the guidelines, it would seem appropriate for testing to be a standard of care, and yet variability in testing still exists. At least 2 major issues may help explain why cytogenetic testing is not following NCCN recommendations.

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One reason may be that although the NCCN guidelines call for cytogenetic testing at certain milestones, they do not sufficiently inform the decision-making process and recommend assessment and choice in second-line TKIs. For instance, once cytogenetic testing is done and resistance is apparent (in the form of mutations like T315I), it is unclear how to incorporate this information into a treatment decision and whether current therapy should be discontinued simply based on lab test results. It is also unclear whether a change in treatment ultimately affects overall survival and health outcomes. Furthermore, how does this influence what payers do to minimize waste and at what point should a payer require prescribers to change treatments that may be ineffective? How will testing impact shared decision making for patients of a specified age range, with comorbidities, specific mutations, and other considerations? As new therapies emerge that may induce fewer mutations or are the only agents that work in specific mutations, including T315I, this may become a more important consideration that minimizes waste and brings clinical utility to testing.

Second, NCCN guidelines do not factor cost into the treatment consideration. In other words, the guidelines are suggestive but are not sufficiently prescriptive for providers or payers to take action based on the results of cytogenetic testing. The updated guidelines offer a step in possibly identifying drug resistance and ineffective therapy, but new therapy options need to be incorporated for a more personalized approach to second-line therapy, defining which mutation is causing the resistance and which second-line treatment is appropriate to reduce waste and improve survival.

On a more practical level, the actual cytogenetic testing report may not always be easy to interpret, which leads to further ambiguity on how it should be incorporated into decision making. Payers, providers, and members need decision support tools to assist with patient assessment, compliance and adherence, and education on the clinical utility of cytogenetic testing, its implications for treatment considerations, and a framework for addressing the test results.

Given this level of ambiguity, it may be challenging for managed care organizations alone to take action at this time to promote or encourage the use of cytogenetic testing. Clear guidance is needed from NCCN on the implications of the results for treatment decisions and selection of therapy, and the approach to treatment.

The opportunity now exists, based on NCCN's focus on cytogenetic testing, to discuss with providers ways to optimize value from the available TKIs. Payers worry about the cost of these agents and invite discussions on ways to mitigate waste and inappropriate use associated with ineffective treatment to ensure that these represent adequate value for the dollars being spent. This will become even more critical should the use of combination TKIs be incorporated into the CML guidelines. The increased costs will affect not only health plans and insurers, but patients and those bearing risk for total cost of care, such as accountable care organizations.

The concept of value in cancer care is gaining momentum among providers. In October 2012, executives from Memorial Sloan-Kettering Cancer Center wrote in the *New York Times* that they would not utilize an expensive colon cancer therapy because they did not believe it represented good value.[2] This is a highly significant statement from a cancer center of excellence. In the past, providers did not generally consider cost of treatment a priority issue. With the trend toward accountable care organizations and using global or bundled forms of payment, this view may now be more common from the provider side.

As with many diseases, we often find significant variation in treatment and in the approach to patient management. Often, variability adds to cost, poor patient outcomes, and inefficient use of medical and financial resources. Evidence-based guidelines can help reduce this variation, but are often broad and too complex to implement. In a recent article in *BMJ*, the authors noted "unnecessary treatment in America accounts for 10% to 30% of health care spending, or up to $800 billion per year."[3] The US system can no longer sustain or afford such waste.

CML represents another example of where more can now be done to improve the dialogue between health plans, key opinion leaders, and community oncologists to formalize pathways, reduce unnecessary treatment variability, and maximize the value of treatments, particularly when it comes to combining TKIs. This is a cost benefit discussion that will be increasingly common among unusual partners.

Dr Lopes is chief medical officer at CDMI in Newport, RI.

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2. Bach PB, Saltz LB, Wittes RE. In cancer care, cost matters (editorial). *New York Times*, October 14, 2012. www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html. Accessed December 11, 2012.

3. Lenzer J. Unnecessary care: are doctors in denial and is profit driven healthcare to blame? *BMJ*. 2012;345:e6230.

Unfavorable Results of Imatinib Treatment in Patients With High BCR-ABL Levels

With several TKIs available today to treat patients whose CML has recurred despite standard imatinib therapy, it may be beneficial to predetermine in some way those patients who may be optimally treated with alternative agents. This points to the need for a better understanding of the relevant biomarkers to predict who will not respond sufficiently to imatinib treatment.

Recent reports have suggested that after 3 months of treatment with imatinib, patients with CML may experience inferior outcomes (in terms of both progression-free survival and overall survival [OS]) when they experience *BCR-ABL/ABL*^{IS} levels above 10%, or more than 1% after 6 months of imatinib therapy. Italian and German researchers have attempted to extend this finding by 1 step: to determine whether high levels of *BCR-ABL* transcripts found at the time of diagnosis would also be connected with an inadequate reaction to imatinib treatment.

The researchers analyzed *BCR-ABL* levels of 230 patients with newly diagnosed CML who were to receive imatinib 400 mg/day. Either *ABL* or glucuronidase-beta (*GUS*) was used as reference genes for all molecular verifications.

The median follow-up time in the study population was 42 months. Cumulative incidences estimated at 5 years for complete hematologic responses, complete cytogenetic response (CCyR), and major molecular response were 98%, 89%, and 65%, respectively. Overall survival rate using 5-year probabilities was 93.8%, while a transformation-free survival rate, defined as survival without disease transformation to the accelerated phase or blast crisis, and failure-free survival (sur-

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vival without imatinib failure as indicated in the 2009 European Leukemia Net recommendations) were 98% and 76%, respectively.

When *GUS* was used instead of *ABL* as a reference gene at diagnosis, connections between high *BCR-ABL* transcripts and the differential in inadequate IM responses were much greater. Both elevated *BCR-ABL/GUS*^{IS} (P <.0001) and elevated *BCR-ABL/ABL*^{IS} (P <.0001) levels were associated with a lower probability of optimal response. The investigators also indicated that after 12 months of imatinib therapy, a link existed between lower rates of cytogenetic response and higher *BCR-ABL/GUS*^{IS} measurements (P <.0001) but not higher *BCR-ABL/ABL*^{IS} values (P = .18).

They noted that overall survival could not be predicted by levels of *BCR-ABL/GUS*^{IS} or *BCR-ABL/ABL*^{IS} at diagnosis. However, a more accurate connection between high levels of *BCR-ABL/GUS*^{IS} and lower probabilities of failure-free survival (P <.0001) and transformation-free survival (P = .01) was found when compared with high levels of *BCR-ABL/ABL*^{IS} (P = .02 and P = .36, respectively).

After subdividing the patient cohort into optimal responders, suboptimal responders, and subjects failing first-line therapy, based on the 2009 European Leukemia Net criteria, the authors discovered that elevated *BCR-ABL/GUS*^{IS} (P <.0001) was a better determinant of patient outcome than elevated *BCR-ABL/ABL*^{IS} (P <.004). In addition, at diagnosis, the number of *BCR-ABL/GUS*^{IS} transcripts was significantly different between the 3 patient groups (optimal vs suboptimal responses, P = .0002; optimal vs resistant responses, P <.0001; suboptimal vs resistant responses, P <.0001). At the time of diagnosis, *BCR-ABL/ABL*^{IS} levels only discriminated optimal from resistant responders (P = .005). The researchers determined the threshold distinguishing those at low risk from patients at high risk as 16% *BCR-ABL/GUS*^{IS} at diagnosis.

Patients with CML who would probably not benefit from imatinib treatment can be identified by high *BCR-ABL* transcripts when diagnosed, using *GUS* as a reference gene, the researchers concluded, and therefore should be given other TKIs as first-line treatment.

Source: Vigneri PG, Stagno F, Stella AS, et al. High BCR-ABL levels at diagnosis are associated with unfavorable responses to imatinib mesylate. Presented at the 54th annual meeting of the American Society of Hematology, Atlanta, December 8-11, 2012.

Emerging Type 2 Diabetes Treatment Strategies: Practical Solutions for a Complex Environment

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James T. Kenney, Jr, RPh, MBA

Diabetes is a chronic disease that affects nearly 27 million adults in America.[1] Type 2 diabetes mellitus (T2DM) is the most common form of the disease in the United States, and it accounts for more than 95% of all diagnosed adult cases of the disease.[1] Since the 1980s, the prevalence of T2DM has tripled. Contributing factors include an aging population, increasing rates of obesity, and a longer lifespan among people with diabetes. Healthcare costs attributable to the disease are expected to grow from approximately $194 billion in 2010 (7% of overall healthcare spending) to almost $500 billion in 2020 (10% of healthcare spending).[2]

The cornerstones of diabetes management include dietary modification, diabetes self-management, and regular physical activity. Lifestyle modifications are often augmented with pharmacologic therapy, and there are now 11 classes of antihyperglycemic agents available, including the recently introduced incretin-based therapies. Despite the overwhelming evidence that improved glycemic control reduces diabetic complications, and the growing array of effective therapies, achieving recommended treatment targets remains a challenge.

Managed care decision makers must not only consider the efficacy and safety of specific antihyperglycemic drugs, but also take into account the overall value provided by the class of agent. For example, consideration must be given to the effects the drug class may have on body weight or the occurrence of hypoglycemia; these unintended consequences of treatment may adversely affect patient adherence or require utilization of additional healthcare resources to manage the side effects. In addition, policy makers must also consider how to optimally structure the pharmacy benefit to ensure delivery of high-quality healthcare while simultaneously minimizing barriers to care and managing utilization and costs. Making decisions about formulary inclusion and benefit design requires robust data. Unfortunately, data of sufficient quality and quantity to guide these decisions are not often available. Consequently, data must be acquired through the use of sophisticated decision support tools, including comparative effectiveness research and pharmacoeconomic modeling.

This supplement to the *American Journal of Managed Care* summarizes 3 presentations given at a satellite symposium held in conjunction with the Academy of Managed Care Pharmacy's 24th Annual Meeting and Expo in San Francisco, California, on April 18 to 20, 2012. The overall objectives for the symposium are provided in the **Table**.

In the first paper, Dr Lawrence Blonde, director of the Diabetes Clinical Research Unit at the Ochsner Medical Center in New Orleans, compares and contrasts the clinical trial data of current and emerging incretin-based therapies, such as glucagon-like peptide-1 agonists, with other T2DM treatment options. In the second paper, Dr John Cruickshank, chief medical officer at the Lovelace Health Plan in Albuquerque, explains how diabetes treatment guidelines published by professional societies such as the American Diabetes Association and the American Association of Clinical Endocrinologists can be effectively integrated into the managed care algorithm. Dr Cruickshank also discusses emerging pharmacy benefit management methods, including value-based designs that can be implemented to improve the overall value of diabetes care. In the third paper, James Kenney, pharmacy operations manager at Harvard Pilgrim Health Care in Wellesley, Massachusetts, reviews the use of decision support tools, such as comparative effectiveness research and pharmacoeconomic models, to make fully informed and weighted decisions that appropriately invest resources for T2DM therapies within a health plan setting.

Recent advances in the understanding of the pathophysiology of T2DM have led to the development of novel classes of drugs such as the incretin-based therapies. The positioning of incretin therapies in the national treatment guidelines as potential second-line agents underscores a need for managed care plans and payers to understand how these agents compare with historically available therapies to provide optimal clinical care. This supplement provides an overview of recent therapeutic advances as well as innovative benefit management strategies to improve treatment success while managing complexities brought about by advancements in the treatment of T2DM.

Table. Learning Objectives

- Compare and contrast the safety and efficacy of current and emerging incretin-based therapies, such as GLP-1 agonists, with other type 2 diabetes treatment options on glucose management and other aspects of diabetes pathology.
- Explain how evolving type 2 diabetes treatment guidelines can be integrated with a managed care algorithm to achieve optimal therapeutic value.
- Recommend emerging pharmacy benefit management methods, including value-based designs that managed care organizations can implement to improve the overall value of antidiabetic treatments.
- Apply the use of decision support tools such as comparative effectiveness research and pharmacoeconomic modeling to make fully informed and weighted decisions to appropriately invest resources on type 2 diabetes therapies within a health plan setting

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