Mock Clinical Pathways: A Method for Exploring the Oncology Clinical Pathway Development Process

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ABSTRACT: Clinical pathways are a critical structural element in the effort to reduce variation in health care as well as to make costs and outcomes more predictable, measurable, and accountable. A mock clinical pathway development simulation was conducted to make transparent the process of developing consensus-driven, evidence-based clinical pathways in oncology. A total of 15 medical oncologists/hematologists served on a steering committee to create pathways for the treatment of chronic-phase chronic myeloid leukemia. Consensus for patient stratification and treatment selection for low/intermediate- and high-risk patients was achieved for first-, second- and third-line therapies. A compliance threshold was set at 80%. The simulation provided an opportunity for interested stakeholders to observe the processes by which oncologists determine initial and subsequent diagnostic tests critical to treatment selection, timing and extent of such testing, the most appropriate treatment for each line of therapy, definition of treatment failure, and criteria for subsequent treatment selection.

KEY WORDS: clinical pathways, value-based care, outcomes research, oncology programs, chronic myeloid leukemia, tyrosine kinase inhibitor


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The first report of consensus-driven oncology clinical pathways was published in 1998. One decade later, the first payer-sponsored oncology provider network clinical pathway collaborations were launched. These programs proved that aligned stakeholder incentives can drive high levels of provider participation and compliance in clinical pathways. A pathways program that is appropriately incentivized and instituted as a collaboration among a payer, the majority of community providers, and other network providers can modify physician prescribing behavior and improve patient outcomes. In the ensuing years, a host of oncology clinical pathway pilot programs were reported that demonstrated improved clinical and financial outcomes. The results of these programs affirmed that cancer care cost savings and reductions in cancer-related emergency room visits and inpatient admissions can be achieved with provider participation in payer-supported oncology pathways programs. These analyses also affirmed that savings on aggregated breast cancer, colon cancer, and lung cancer spending as high as 15% can be achieved in the first year of a pathways program concurrent with as much as a 7% reduction in hospital admissions.

In 2015, Anthem, the country’s second largest health insurer, introduced its AIM Oncology Pathways across its 14-state Blue Cross and Blue Shield programs. In 2016, the American Society of Clinical Oncology published...
a policy statement on oncology clinical pathways recommending that, in order for collaboration and consensus to occur, transparency is an absolute requirement.8 It seems increasingly more apparent that consensus-driven clinical pathways in oncology will become a foundational platform in the transformation to value-based cancer care. Whether that care is delivered through an Accountable Care Organization or an Oncology Medical Home, reimbursed via episode of care or bundled payment, or configured as an Oncology Care Model, clinical pathways are a critical architectural element that reduce variance as well as make costs and outcomes predictable, measurable, and accountable.

Consensus-driven, evidence-based clinical pathways represent the natural evolution of guidelines such as those developed by the National Comprehensive Cancer Network (NCCN). Disease management was the initial impetus for creating care paths or treatment algorithms. Guidelines were then necessary to categorize the universe of care options that might be included within those care paths or algorithms. Value-based care requires comparisons of various care options to establish consensus standards; one might conclude that clinical pathways are the end products of those consensus standards.

The result of this trend has heightened interest in the process of clinical pathway development. Cardinal Health, an innovator in the pathway movement, has developed a mock clinical pathway simulation to allow health care stakeholders to witness first-hand the process by which physicians determine rules, review evidence, and reach consensus in the creation of disease-specific oncology pathways. This article introduces one such mock pathway initiative for chronic-phase chronic myeloid leukemia (CP-CML).

CLINICAL PATHWAYS STEERING COMMITTEE
In February 2016, Cardinal Health Specialty Solutions conducted a market research initiative involving 15 medical oncologists/hematologists that focused on the development of clinical pathways for CP-CML.

Clinicians for this initiative were selected from the master recruitment list using a pre-defined screener. Clinicians were screened to identify medical oncologists who: (1) are currently practicing and have been in active full-time practice for more than 3 years and less than 30 years; (2) spend more than 50% of their professional time treating patients and spend more than 20% of their time treating liquid tumors; (3) have treated or managed at least 5 chronic myeloid leukemia (CML) patients in the past 12 months; (4) actively treat and are involved in the treatment decisions for CML patients; and (5) actively participate in the development of clinical pathways in their practice. A total of 15 medical oncologists/hematologists from 13 states who met the screener criteria accepted the invitation to serve on the steering committee for this initiative. The steering committee represented both academic-based and community-based practices (Figure 1).

Although the committee members were experienced in pathway development, it was predominantly for high-frequency solid tumors like breast, colon, lung, and prostate cancers. The steering committee members’ survey of their disease management activity revealed a minimum of 12 active CML patients under treatment (range, 12–30). This level of experience in treating CML was somewhat remarkable, given that all the physicians described themselves as generalists in hematology and oncology. Some expressed strong interest in hematologic malignancies and, as a result, garnered disproportionate referrals within their practice. All indicated experience with each of the approved tyrosine kinase inhibitor (TKI) agents at the time of the meeting. None of the steering committee members’ practices had formal clinical pathways for CML, although all had participated in practice- or payer-sponsored clinical pathways in common solid tumors. A discussion of current practice patterns revealed a high degree of variability in regard to patient selection process, timing of mutational testing, treatment preferences in the first and second lines of therapy as well as perceptions/observations regarding efficacy and toxicity of the second generation TKI drug alternatives.

CLINICAL PATHWAYS DEVELOPMENT PROCESS
The steering committee was brought together at a market research facility in Atlanta, GA, to reach consensus and jointly develop clinical pathways for CP-CML. The event was double-blinded such that the industry sponsor did not know the identities of the participating physicians and the physicians did not know the identity of the industry sponsor.

The live event was moderated by the chief medical officer of Cardinal Health Specialty Solutions, a certified medical oncologist. The moderator was responsible for guiding the discussion of the committee to reach a consensus decision. The participants were presented the following guideline for the ensuing process:

1. The exercise we are about to do is to simulate a pathway development process in CML.
2. The simulation is for a national payer who desires to launch a collaborative pathway with its provider network.
3. You have been selected to represent that network and serve on the steering committee that creates the pathway.
4. The payer is not only interested in the academic process of pathway development but also in your consultation regarding barriers and incentives for network provider pathway adoption.
5. A clinical trial is always compliant and the preferred therapy when available.
6. Palliative care and hospice are reasonable at any time for the appropriate patient.
7. The pathway should never conflict with good clinical judgment; therefore, the pathway compliance threshold will be 80%.
8. The payer agrees to provide financial support to mitigate costs of pathway management and compliance.

The NCCN Clinical Practice Guidelines in Oncology for Chronic Myelogenous Leukemia with Evidence Blocks (version 1; 2016) and package insert prescribing information on all FDA-approved drugs for CML were reviewed by the steering committee members before the live event in preparation for clinical pathways development. The committee members were asked to define: (1) the initial and subsequent diagnostic tests critical to treatment selection; (2) the timing and extent of such testing; (3) the most appropriate treatment for each line of therapy; (4) the characterization of treatment failure; and (5) the criteria for subsequent treatment selection. The objective was to reach mutual consensus on the best treatment for each line of therapy. In addition, the committee made further recommendations for scenarios in which a patient could not receive the recommended therapy (ie, in the event of comorbidity, contraindication, or mutation) and for determining whether such scenarios were within the 20% non-compliance allowance or required pathway incorporation. Mutational analysis and monitoring measures were incorporated into the selection of treatment for each line of therapy.

The clinical pathways for CP-CML were developed considering efficacy, toxicity, and cost—in that order of priority—when selecting TKI agents (Figure 1). The goal for this exercise was to reduce variability in treatment, attain meaningful clinical outcomes, and deliver the right treatment to the right patient at the right time for >80% of the patients with CP-CML who were managed using this clinical pathway.

**CONSSENSUS-DRIVEN PATHWAYS FOR CP-CML**

**Diagnosis and Patient Selection**

There was near uniformity of opinion regarding patient selection and stratification. All committee members agreed that all diagnoses be confirmed by a hemato-pathologist and that all newly diagnosed patients with CML should undergo bone marrow aspiration and/or bone marrow biopsy to characterize the staging of CML. Once the disease is identified as CP-CML, Sokal scoring was recommended to stratify the risk of the patient with CP-CML to optimize treatment for the minority found to be high risk (Figure 2). There was little to no support for mutational testing as part of the initial evaluation.

Although a minority of newly diagnosed patients would be scored high risk, it was agreed upon that, based on Sokal scoring, the treatment selection algorithm should fork such that low/intermediate-risk patients would be managed differently from high-risk patients.
Figure 2. Clinical Pathways for CP-CML

Abbreviations: AP-CML, accelerated-phase chronic myeloid leukemia; BMA, bone marrow aspiration; BMB, bone marrow biopsy; BP-CML, blastic phase chronic myeloid leukemia; CML, chronic myeloid leukemia; CP-CML, chronic-phase chronic myeloid leukemia; TKI, tyrosine kinase inhibitor
Treatment of Low/Intermediate-Risk CP-CML

Lengthy debate ensued over selection of first-line treatment for low/intermediate risk CP-CML, because half of the participants were currently prescribing second-generation TKIs as first-line therapy for their patients with low/intermediate risk CP-CML. Cost entered this debate, especially as it related to market entrance of generic imatinib. Literature review specific to predictive value of 3-month response assessment seemed to assuage concerns and, in conjunction with a compelling cost argument, resulted in the eventual unanimous consent for imatinib as first-line treatment in low/intermediate risk CP-CML.

There was consensus that all patients should undergo response analysis 3 months after imatinib initiation based upon published reports that early responses predict better outcomes in patients with newly diagnosed CML. If cytogenetic testing (fluorescent in situ hybridization [FISH] or polymerase chain reaction [PCR]) reveals >1 log reduction in BCR-ABL level, the patient should continue treatment with imatinib. If, on the other hand, testing reveals <1 log reduction in BCR-ABL level, there was unanimity that a mutational analysis should be performed as the initial response in order to guide mutation-based treatment selection.

In the event of BCR-ABL mutations, it was agreed that the TKI agent specific to that mutation should be administered (Figure 2). However, robust dialogue surrounded the treatment selection process for patients without mutations. Individual participants expressed preferences for dasatinib, nilotinib, and bosutinib, respectively. None of the participants had used ponatinib in this setting since its transient withdrawal from the market. As the group debated restricting the pathway to a single agent for second-line treatment of CP-CML without secondary mutations, it was requested that the group review together the primary literature for responses and adverse events. It was at this time that the highly variable patient experiences with second-generation TKIs became apparent. The most remarkable experiences involved the use of bosutinib. Some expressed observations of relatively early and profound diarrhea, while others had found that initial dosing of 400 mg rather than 500 mg resulted in a well-tolerated and highly effective therapy.

After continued lengthy debate, it was decided that, if no mutations are identified, treatment selection should be based on comorbid conditions. There was unanimity that, if there are no comorbidities, the default TKI selection should be dasatinib. In the event of comorbid conditions, contraindication should be avoided. Comorbidities were clustered into four categories: cardiac conduction diseases, myocardial insufficiency/fluid retention, vascular occlusive disease, and gastrointestinal issues. Recommendations were to avoid dasatinib in the event of congestive heart failure; avoid ponatinib in those with vascular occlusion, heart failure, and hepatotoxicity; avoid nilotinib in those with QT prolongation, diabetes, and hyperglycemia; and avoid bosutinib in those with gastrointestinal issues due to diarrhea risk. In case of intolerance to imatinib, the default treatment should be dasatinib if there are no comorbid conditions. In the event of comorbid conditions, contraindication should be avoided as described in the algorithm (Figure 2).

Treatment of High-Risk CP-CML

The committee agreed that dasatinib should be the first-line therapy for high-risk CP-CML, and all patients should undergo response analysis 3 months after dasatinib initiation. If cytogenetic testing (FISH or PCR) reveals >1 log reduction in BCR-ABL level, the patient should continue treatment with dasatinib. If cytogenetic testing reveals <1 log reduction in BCR-ABL level, a mutational analysis should be performed. In the event of BCR-ABL mutations, the TKI agent specific to that mutation should be administered (Figure 2). However, the committee could not reach a consensus on a single therapy in the event that no mutations are identified and recommended comorbidity-based TKI selection. Similarly, in the case of intolerance to dasatinib, contraindications should be avoided in the event of comorbid conditions when selecting the appropriate TKI.

Disease Progression

In the case of disease progression with imatinib for low/intermediate-risk CP-CML, the committee determined that a mutational analysis should be performed. In the event of BCR-ABL mutations, the TKI agent specific to that mutation should be administered, as noted in the algorithm (Figure 2). If no mutations are identified, the default treatment should be dasatinib if there are no comorbid conditions. Contraindications should be avoided in the event of comorbid conditions as described in the algorithm. In the case of disease progression with dasatinib for high-risk CP-CML, the committee determined that a mutational analysis should be performed. In the event of BCR-ABL mutations, the TKI agent specific to that mutation should be administered. If no mutations are identified, contraindications should be avoided in the event of comorbid conditions when selecting the appropriate TKI (Figure 2).

Despite the success in selecting single-agent standards of care as default treatment for the uncomplicated first- and second-line therapies, such was not the case for third-line therapy and beyond. The literature review and personal experiences were too varied to establish a consensus choice beyond imatinib and dasatinib other than restricting ponatinib to those patients with the specific target mutation T315I. Thus, the committee failed to reach a consensus regarding third-line therapies.

CONCLUSION

The live meeting concluded in less than 5 hours. The experience of the committee members with all approved TKI agents allowed for robust conversation and revealed some
very different impressions of the agents, especially with regard to adverse events. The literature review and consensus building process resulted in less debate and more rapid resolution to the subsequent branches of the treatment algorithm. Mutational testing and comorbidity-based treatment selection became the standard response at each branch point.

Despite heated debate, the participants ended the meeting amicably and were somewhat surprised by what had been accomplished. Few believed at the start that consensus could be achieved around a single option for the vast majority of patients receiving first- and second-line therapies. The participants expressed confidence that such a pathway could be presented to and accepted by the majority of oncologists and hematologists with whom they practice. They believed that the 80% compliance threshold was the most critical element in the pathway design and, if clearly communicated, should result in high levels of adoption and compliance.

This experience is consistent with published literature and validates the willingness and ability of community practitioners to actively participate in clinical pathway development. Mock pathways conducted in the described fashion provide an opportunity for interested stakeholders, whether they be payers, providers, pharmaceutical companies, or even patients, to observe the processes by which oncologists determine initial and subsequent diagnostic tests critical to treatment selection, timing and extent of such testing, the most appropriate treatment for each line of therapy, definition of treatment failure, and criteria for subsequent treatment selection.

REFERENCES