

**Determining and Addressing Adherence to the NCCN Guidelines for Chronic Phase
CML**

PI: Benjamin Brewer, PsyD.

Institution: University of Colorado Anschutz Medical Campus- Department of Medicine

Dates of Project: 5/1/14- 7/1/16

Funding Source: Support from Pfizer IGLC and the NCCN

Structured Abstract

Purpose: The purpose of this study was to determine the baseline rate of appropriate monitoring of CP-CML by BCR-ABL1 transcripts in peripheral blood using RT-PCR in accordance with the NCCN guidelines at four practices across Colorado. It also tested a novel behavior change intervention in these practices and accounted for impact on the adherence rate and medical provider knowledge at the practice sites.

Scope: Nationally between 31 and 51 percent of patients with CML are monitored in accordance with the NCCN guidelines. Low adherence to these guidelines is associated with disease progression, TKI resistance and poor medical outcomes

Methods: EMR data was collected at four practice sites to determine the baseline and one year post intervention follow up. An interactive presentation designed to improve medical provider knowledge of and adherence to the NCCN guidelines for treatment of CP-CML was administered at each practice site. Pre-Post and 6 month follow up tests were used to evaluate changes in provider knowledge.

Results: Four practices sites had pre-intervention adherence to timely monitoring of BCR-ABL by RT-PCR rates of 47, 46, 66 and 14 percent. Post-intervention monitoring was also suboptimal. Physician and provider training was successful at improving the knowledge of medical teams about effective CML treatment and monitoring. The difference between pre and post measurements is significant, $z= 5.311$, $p <.000$. indicating improved provider knowledge.

Purpose (Objectives of Study)

The literature on the clinical practice of physicians treating Chronic Phase Chronic Myeloid Leukemia (CP-CML) suggests several major gaps between identified best practices and the real world practices of physicians. The most significant gap identified in the literature is the lack of appropriate monitoring of the BCR-ABL1 translocation by qPCR in CP-CML. A second major concern identified in the literature is the problem of patient adherence to Tyrosine Kinase Inhibitor (TKI) medications over time. A third concern is a lack of physician knowledge about how to interpret data from BCR-ABL1 when monitoring is conducted correctly and how to make the correct choice of TKI medication based on this information.

This study addressed these three concerns using a novel interactive behavior change intervention for physicians, midlevel providers and nurses that was offered in-person to each of the four practices in the study. Additionally, this study determined the baseline rates of physician adherence to NCCN guidelines for monitoring of BCR-ABL1 in CP-CML patients at four practices across the state.

Scope

Background and Context

The treatment of CP-CML with TKI's represents the beginning of an era of targeted molecular treatments that require appropriate monitoring of gene markers by physicians and will also require patients to adhere to a daily medication regimen and medical follow-up appointments for monitoring. This new style of treatment requires significant practice change from the old approach where patients often received treatment with chemotherapy administered onsite and required less monitoring over time. This new style of treatment has created three major gaps identified in the literature on CP-CML.

The three sections below are summarized briefly here and represent the most salient gaps in practice vs. recommended practice for the care of patients with CP-CML identified in a national needs assessment and the NCCN guidelines.^{1,12} Gap 1: The most significant practice deficit identified nationally for the treatment of CP-CML is the low rate of proper monitoring of BCR-ABL1 by community oncologists (31%). Monitoring of this marker by peripheral blood is vital to assess treatment response and guide treatment decisions. Gap 2: The second major concern identified is the lack of physician and midlevel provider's understanding of how to assess and address patient adherence to their TKI medications. Gap 3: A third major deficit is the physicians appropriate choice of first-line TKI and a lack of knowledge about when to switch TKI's and which TKI represents the best choice in the event of TKI resistance or lack of disease response.

Gap 1: Physician non-adherence to NCCN guidelines for monitoring of BCR-ABL1

The NCCN guidelines currently recommend testing for BCR-ABL1 with qPCR in CP-CML patients every three months after initiating therapy, regardless of treatment response. A recent report by the Annenberg Center for Health Sciences found that only 31% of community physicians and 52% of academic medicine physicians in the U.S. were correctly tracking this vital marker of treatment response in peripheral blood.¹ Most were not adequately using this molecular analysis to track their patient's response to TKI therapy and many were performing unnecessary bone marrow biopsies to conduct monitoring, usually on a suboptimal timeline.- CP-CML monitoring was also found to be suboptimal in a recent study with 1,200 CML patients. This study found that 41% of patients on a TKI did not receive qPCR monitoring of BCR-ABL1 within one year of treatment initiation, while 31.9% had 1-2 tests in that year and 27% had 3-4 tests. This study also compared patients in the "no tests" group to patients in the "3-4 tests" group, and found that the latter group had 37% fewer inpatient admissions for CP-CML related concerns, suggesting that monitoring in accordance with NCCN guidelines for qPCR testing is economically and medically useful.-

Gap 2: Physicians lack knowledge of how to effectively assess and then promote the adherence of their CP-CML patients taking TKI medications.

Patient adherence to oral TKI medication is strongly associated with overall treatment response and likely remains one of the primary factors effecting the loss of Major

Molecular Remission (MMR) or lack of response to treatment. The ADAGIO study examined the adherence of patients to imatinib and compared their reported level of adherence to their actual pill consumption. 64% of patients reported perfect adherence to their medication, however only 14% of this group actually achieved perfect adherence. 71% of patients in the study were found to be taking less than the prescribed dosage.³

Poor adherence has a substantial impact on treatment response. In one study, patients with less than or equal to 90% adherence to medication were found to have only a 28.4% rate of MMR to treatment in comparison with a 94.5% rate for those with greater than 90% adherence.⁴ 90% adherence is the equivalent of taking 27/30 doses in a 30 day month.

Gap 3: Community physicians have been shown to lack information about first-line TKI choice, the importance of early and deep molecular response when starting treatment and when to switch TKI medication.

Community oncology physicians may encounter only a few CP-CML patients per year and thus keeping up with current recommendations for TKI selection may be challenging. In a recent needs assessment, 62% of oncologists continued to use imatinib as a first line treatment for their CML patients when second-generation TKI's such as dasatinib and nilotinib have been shown to produce an earlier and deeper molecular response with data and recommendations that show that may be better tolerated.¹ Providers were also not sufficiently aware that dasatinib and nilotinib were recommended by the NCCN guidelines for patients with high risk disease and were associated with earlier and deeper molecular remission. There is also evidence that physicians lack the ability to differentiate the appropriate clinical actions when patients become resistant to a first-line TKI. Many were unaware of the need to conduct a mutational analysis and the TKI recommendations for specific mutations. Difficulty interpreting and appropriately determining the meaning of increases on qPCR monitoring using the International Scale has been identified as another concern.¹

Settings

This study occurred at four hematologic oncology practice sites across the state of Colorado. These sites represent a wide array of practice type and population characteristics and are geographically distributed around the state. The sites were selected due to their location, the population served and known treatment of CML patients. Three of these sites have recently become affiliated with the University of Colorado Health System but remain geographically and demographically diverse.

The University of Colorado Cancer Center (UCCC) is located in Aurora, Colorado. The UCCC is an NCI-designated comprehensive regional cancer center for the Rocky Mountain region. It is located on the Anschutz Medical Campus, a major tertiary care center for the Rocky Mountain Region.

The Cancer Center of the Rockies is Located in Fort Collins, Colorado, this community oncology practice serves a wide area in Northern Colorado and Southern Wyoming. This center is a new member of the University Health System and is similar to many large oncology practices. This center uses EPIC as it's EMR and is connected to University Hospital and Memorial Hospital so that records from one center are visible across the system.

The Cancer Center at Memorial Hospital is located in Colorado Springs, Colorado. This site represents a large community oncology practice and is also a new member of the University Health System. This center serves the community in Southeastern and South Central Colorado over a wide area that includes many rural locations.

St. Mary's Regional Cancer Center is located in Grand Junction, Colorado. This site represents a large regional hematologic malignancies practice that has recently become affiliated with the University of Colorado bone marrow transplant program and will begin doing autologous stem cell transplants in collaboration with University of Colorado Cancer Center. St. Mary's serves patients from across the western slope of Colorado that come from broad geographic region that is largely rural.

Participants

This intervention was provided directly to a total of 50 oncologists, hematologists, midlevel providers and other members of care teams directly involved in patient care or treatment decision-making at four practices across the state of Colorado. These four practices treat a large number of patients in a community setting, share a common EMR (EPIC), although Grand Junction was found to have an incompatible form of EPIC for direct data pulls.

Data from the four practices was pulled regarding CML patients and the rate of testing for BCR-ABL1 by RT-PCR. The total number of CML patients in the study was 132 and reflects the number of CML patients treated and documented in the EMR at these sites during the baseline and follow up periods of this study.

Site	Total n	% (n) with Diagnosis Date
Site A	13	92% (12)
Site B	36	78% (28)
Site C	24	0% (0)
Site D	59	75% (44)
Total	132	64% (84)

Incidence and Prevalence

The *prevalence* of CML in the population is relatively low and estimated by rough calculations to be about 1,333 patients living with the disease in the state of Colorado

for 2014. The success of TKI medications in treating CP-CML now means that the overall prevalence of the disease in the population will rise over time, as the vast majority of people with the disease are able to live out a nearly normal lifespan. This ongoing increase in the number of people living with CP-CML highlights the importance of correctly addressing the behavioral factors that optimize the long-term treatment outcomes for patients. In the United States, although the annual incidence of CP-CML remains stable at approximately 1/100,000 people, the prevalence of CML is estimated to increase from approximately 70,000 people in 2010 to a plateau of approximately 181,000 by the year 2050.¹⁵

Methods

Study Design and Collection of Data Sources

One year of baseline data for BCR-ABL1 assessment by qPCR was pulled from all four medical centers in this study. All of the centers in this study recently implemented EPIC and each medical center in the study had a different “go live” date for EPIC. The retrospective baseline data collection began on the date that the last hospital in the study switched to using EPIC in their oncology clinics. This date is **November 2nd, 2013** for Memorial Hospital in Colorado Springs Colorado. Of note this date is approximately six months from the date of funding of this project which was May of 2014. This allowed six months of baseline data to be collected retrospectively prior to the potential funding of the project.

Due to the low prevalence of CML and the relatively small catchment of the practice sites, a one-year baseline was needed to ensure sufficient power and accurately document the baseline rate of BCR-ABL1 assessment in comparison to the testing rate recommended in the NCCN guidelines (every three months or 4 times per year). Six months of retrospective data (before the date of funding) and six months of prospective data (after funding) were combined to make this one-year baseline. An additional one-year was required after the intervention to the practices to look for changes in the rate of physician’s ordering BCR-ABL1 monitoring in the practices.

Data Extraction from EPIC (EMR)

Baseline data including diagnostic and billing data, was obtained using ICD-9/10 codes for CML and data from the EMR of the four medical centers in this study. At Grand Junction a different implementation of EPIC prohibited the direct pull of this data and data were hand counted by a practice researcher using an existing list of CML patients. This data was very different than that provided by the other practice sites and there is uncertainty associated with its accuracy. Specifically the list the patients were pulled from may not have included all the patients in the

Data about BCR-ABL1 monitoring by qPCR was obtained by using the physician order for testing BCR-ABL1 assessment by qPCR from peripheral blood. This test will be evaluated

against the ideal four time points per year recommended by the NCCN, to determine the baseline rate of each practices adherence to the NCCN guidelines.

Pre and post-tests immediately before and after the trainings will document immediate changes in provider knowledge. A follow-up post-test, conducted at 6 months, documented changes in provider knowledge from the intervention. Data from the pre-post and 6-month post tests will be entered into a separate relational database to determine provider changes in knowledge about the content of the presentation and the maintenance of any changes in knowledge at 6-months.

Expected Change in Provider Knowledge and Behavior

Based on prior study of changes in provider knowledge and the difficulty of creating behavior change in medical providers, changes in knowledge were expected to be significantly greater than those found in behavior.¹²

Interventions

The four medical practices were given a novel interactive presentation using a clicker system for live audience polling. During these presentations this system appeared effective in maintaining close attention to the presentation and generated good questions as providers were forced to think through clinical scenarios regarding treatment of CP-CML in accordance with the NCCN guidelines. During this presentation practices learned their baseline rate of adherence to these guidelines and this data was updated during a follow up presentation to the practice leaders at each site at 6 months from the initial intervention. These follow up sessions did include a formal presentation but also utilized a semi-structured qualitative interview with at least one practice leader from each site to explore their perception of the barriers to appropriate monitoring of CML at their site. These sessions were audio recorded and may be coded to identify addressable concerns. At times these discussions included barriers that were immediately modifiable to improve adherence and in these instances brainstorming techniques were used to identify possible areas of practice change.

Measures

The impact on knowledge change as a result of the presentation was assessed using a matched Pre-Post-6 month post-test designed for this study.

Limitations

There were a number of significant limitations to this study. Initially it had been assumed that the since the four sites shared an EMR (EPIC) that data collection would be straight forward and consistent at each site. However after initial attempts to pull data it was discovered that St. Mary's Hospital in Grand Junction, Colorado used a different version of EPIC and also kept some of their medical records in a old EMR called Mosaic. We were unable to direct pull data from this site as a consequence. To compensate for this and allow this site to partially continue in the study data regarding CML patients was hand tabulated and collected using an exiting list of CML patients. This

data appears very different from the data pulled from the other three sites. This was explored with the Grand Junction site and this data was pulled from an existing nurse generated list of CML patients. It is very possible there was error introduced into the hand count due to his list. Specifically it may be that not all CML patients treated at the site were on the list and that patients who were listed likely got better follow up care. When during the data analysis portion of our study it became necessary to determine the date of diagnosis this data was not available from the Grand Junction site.

The pre-post analysis data appears very solid and shows strong gains in the knowledge of providers at various levels across the practices. We had more difficulty getting the 6 month follow up post tests returned due to staffing changes and difficulty getting the same group of people who had attended the first presentation re-assembled due to scheduling issues.

The major barrier to this project is that the final data over the two-year study show a continuous decline in rates of adherence based on the time since diagnosis (seemingly independent of the intervention). To attempt to control for this, a manual chart review to determine date of diagnosis was conducted across all patients in the three sites where this was possible. This resulted in a subsample analysis that was further complicated by the date of diagnosis data being widely and very non-normally distributed. This necessitated the creation of categories for patients based on how long they had had a diagnosis of CML and if they entered the practice pre or post intervention. Due to the low incidence of CML in the population there were very few patients who entered the study after the intervention, allowing only a descriptive analysis to be conducted. Some of the data from this analysis appear encouraging but no clear statements can be made with statistical confidence.

Results

Principal Findings

- Four practices sites had pre-intervention adherence to timely monitoring of BCR-ABL by RT-PCR rates of 47, 46, 66 and 14 percent. Post-intervention monitoring was also suboptimal.
- Trends in this population indicate that the longer a patient is seen in a clinic the lower their individual rate of adherence to BCR-ABL monitoring.
- Physician and provider training was successful at improving the knowledge of medical teams about effective CML treatment and monitoring. The difference between pre and post measurements is significant, $z = 5.311$, $p < .000$.
- A wide variety of barriers were identified in qualitative interviews with practice leaders . Consistent themes included:

- lab draws being done incorrectly by local labs
- patient adherence to testing even when ordered by a medical provider
- decreased patient desire for testing once disease was stable
- inability of practices to ensure patients schedule and attend timely follow-up visits.

Table 1. Patient count by practice site

Site	Total (n)	Subsample with Diagnosis Date (% (n))
Site A	13	92% (12)
Site B	36	78% (28)
Site C	24	0% (0)
Site D	59	75% (44)
Total	132	64% (84)

Table 2. Rate of BCR-ABL Testing among total opportunities for testing.

Site	Patients (n)	Rate Pre- Intervention	Rate Post - Intervention
Site A	13	47	27
Site B	36	46	19
Site C	24	66	0
Site D	59	14	12

Table 3. Rate of BCR-ABL Testing Stratified by Patient Entry to Practice.

Site	Entry to Practice	N	Rate Pre- Intervention	Rate Post - Intervention
Site A	Pre- Intervention	10	47	18
	Post- Intervention	3	N/A	75
Site B	Pre- Intervention	33	46	17

Site	Entry to Practice	N	Rate Pre-Intervention	Rate Post - Intervention
	Post-Intervention	3	N/A	67
Site C	Pre-Intervention	24	66	0
	Post-Intervention	0	N/A	N/A
Site D	Pre-Intervention	51	14	6
	Post-Intervention	8	N/A	50

Discussion & Conclusions

Preliminary analysis suggests that this study effectively documented the baseline rate of adherence for monitoring of BCR-ABL1 by RT-PCR at four practices across Colorado. As anticipated, the rate of adherence for monitoring of BCR-ABL1 by RT-PCR was suboptimal at all practice sites. Estimated rates within community practices were higher than many of the values reported in the literature for this population; however, the monitoring rate as measured in this study at an academic medical center (14%) was far lower than the national average of 51%.

Analysis of the pre-post tests suggest the effectiveness of the intervention at changing physician knowledge but the study does not appear to confirm a change in physician behavior as these results are inconclusive due to the data analysis issue described in the barriers section.

This study appears to show that the longer a patient is in a medical practice the less they are monitored for BCR-ABL1. This finding has not been described before in the literature to our knowledge but is an important factor for future research on CML and the long

term monitoring of this disease. It may be that patients and medical teams become more complacent about monitoring due to

Based on the results as analyzed so far, physician training does appear to increase knowledge about the effective management and monitoring of CML. However, these gains in knowledge did not appear to translate into changes in monitoring. Many of the data appear to indicate a lower rate of adherence in the year post-intervention. This is likely due to factors not measured as part of this project or that have not yet been accounted for as part of our originally planned analysis. A preliminary subsample analysis attempted to control for time since diagnosis as this appeared to be a relevant factor in adherence to the monitoring guidelines. This subsample of patients had insufficient numbers to power an interpretable analysis.

Significance

The preliminary findings of this project suggest that interactive presentations with data feedback to medical practitioners is an effective intervention for increasing provider knowledge, but not for improved adherence to monitoring guidelines. Our findings contribute a better understanding of the monitoring trends among patients living with CML and emphasize the importance maintaining adherence over time.

Implications

The preliminary findings of this study suggest the need for exploration of new and innovative interventions for increasing adherence to NCCN guidelines for BCR-ABL monitoring of CML among patients taking TKI medications. Provider trainings should not be pursued as a primary means of increasing monitoring rates. Additionally, particular attention should be given to the development of interventions specific to increasing monitoring among CML survivors living with a diagnosis for more than 5 years.

List of Publications

Findings of this study have not yet been prepared for publication. The researchers anticipate the preparation of a manuscript for submission by the end of 2016.