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ORIGINAL RESEARCH

A Pharmacist-Led Oral Chemotherapy Program's Impact on Chronic Myeloid Leukemia Patient Satisfaction, Adherence, and Outcomes

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Abstract

Patients with chronic myeloid leukemia (CML) can be treated with oral tyrosine kinase inhibitors (TKIs). Pharmacist-led oral chemotherapy programs (POCPs) can improve TKI adherence rates, but evaluation of patient satisfaction with such programs is rare. The purpose of this analysis was to compare the satisfaction of patients with CML taking TKIs enrolled in a POCP program with that of those not enrolled. Secondary objectives were to assess adherence rates, patient-reported value, early molecular response (EMR) rates, and major molecular response (MMR) rates. This study utilized an anonymous telephone survey of patients who had taken TKIs for at least 3 months. Molecular response was determined by chart review. Of 40 patients surveyed, 50% were enrolled in the POCP, and the POCP group had more African Americans than the non-POCP group. More patients in the POCP were satisfied with their care than in the non-POCP group (100% vs. 75%, $p = .047$). There were no differences in high patient-reported adherence (55% vs. 60%, $p = 1.000$), patient-reported value for integrated services (95% vs. 90%, $p = 1.000$), achievement of EMR (75% vs. 75%, $p = 1.000$), or MMR (85% vs. 85%, $p = 1.000$). Patients in the POCP received more structured clinical pharmacy services; however, both groups felt the clinical pharmacist played a major role in their care (85% vs. 90%, $p = 1.000$). Patients in the non-POCP group reported lower satisfaction than those enrolled resulting from fragmented care that was likely due to external specialty pharmacies. Irrespective of POCP enrollment, patients reported clinical pharmacists play a major role in their therapy and value integration of their specialty pharmacy and medical team.

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The number of specialty drugs on the market has increased dramatically over the past decade, and specialty drugs are expected to make up over 50% of the pharmaceutical industry's revenue by 2020 (Galante, 2018). This has prompted the growth of specialty pharmacies, especially in oncology. 60% of oncology practices associated with a health-care system have a dispensing pharmacy that generates 35% of the practice's revenue (Galante, 2018). Nonetheless, specialty pharmacies are not immune to the transition to value-based care and must address challenges arising from fragmented care, patient nonadherence, and patient satisfaction in order to improve patient experience, continuity of care, and outcomes (Galante, 2018).

Along with the rise of other specialty pharmacy drugs, several oncology drugs have been developed, including tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML; Woessner et al., 2011). Although hematopoietic stem cell transplantation remains the only curative option for CML therapy, oral TKIs have transformed CML from a progressive disease with a high mortality rate into a chronic condition with dramatically reduced mortality rates (An et al., 2010; Chen et al., 2013; Druker et al., 2006).

Treatment for CML with oral TKIs is lifelong; continued adherence to oral TKI therapies has been shown to be an independent predictor of major molecular response (MMR) and complete cytogenetic response (CCyR) rates (Marin et al., 2010). In a study by Marin and colleagues (2010), adherence was assessed with a microelectronic monitoring system (MEMS) and expressed as the percentage of TKI that was taken compared with what was prescribed. There was a strong correlation between adherence rates (≤ 90% or > 90%) and the 6-year probability of an MMR (28.4% vs. 94.5%, $p < .001$) and CMR (0% vs. 43.8%, $p < .002$); no molecular responses were observed in this study when adherence was ≤ 80% ($p < .001$; Marin et al., 2010).

Nonetheless, adherence remains a challenge even for patients who have taken oral TKIs for over 2 years (Marin et al., 2010). Primary nonadherence is common in one third or more of CML patients, while general adherence rates range from 16% to 100% (Greer et al., 2016). Although many factors impact adherence rates in CML patients, medication possession ratios were observed to be lower in women, patients with higher cancer complexity, and decreased as the number of a patient's concomitant medications increased (Darkow et al., 2007). Fragmented care can further negatively impact medication adherence rates by preventing patients from receiving their medication in a timely manner. Treatment interruptions and nonadherence have been associated with increased medical and health-care costs (Darkow et al., 2007). Thus, ensuring oral chemotherapy adherence remains a major challenge to achieving optimal care while avoiding the detrimental effects of nonadherence.

PHARMACIST-LED ORAL CHEMOTHERAPY PROGRAMS

Previous studies have demonstrated the benefit of pharmacist-led oral chemotherapy programs (POCPs) on oral medication adherence in patients with CML compared with standard of care (Lam & Cheung, 2016; Muluneh et al., 2018). In a trial conducted by Muluneh and colleagues (2018), a POCP led to patient-reported adherence rates of over 90%, which were validated with medication possession ratio rates. Furthermore, this led to higher MMR rates (83.3%) in the CML population within the POCP compared with rates published in clinical trials (average 60%; Muluneh et al., 2018).

In another trial of 56 patients receiving oral anticancer medication for CML, the group overseen by the oncology pharmacist also resulted in a statistically higher percentage of imatinib (Gleevec) adherence rates compared with standard of care (88.6% vs. 65.8%, $p = .0046$; Lam & Cheung, 2016). These POCPs were able to obtain higher adherence rates compared with standard of care; the high adherence rates were well above the threshold that has previously been associated with poor outcomes (Ibrahim et al., 2012). However, little has been done to evaluate patient satisfaction with POCPs or to determine if patients have personal interest in or desire to engage with POCPs in an attempt to reduce fragmented health care.

The purpose of this trial was to evaluate how an enhanced level of care with an established POCP embedded within an outpatient clinic in a large academic medical center impacted composite satisfaction scores in patients with CML who

were taking oral chemotherapy compared with participants not enrolled in the program and who were only receiving standard of care.

METHODS

Study Population

Patients were included in this prospective study with subsequent retrospective chart review if they were aged 18 years or older, diagnosed with CML, and were receiving active treatment with imatinib, nilotinib (Tasigna), bosutinib (Bosulif), or dasatinib (Sprycel) at the University of North Carolina Medical Center as of September 1, 2014, and who had been receiving active treatment for at least 3 months. Patients were excluded from the analysis if they were not fluent in English, had cognitive impairments, were incarcerated, or were taking one of the TKI therapies in combination with other chemotherapy agents.

Study Design

This was a nonrandomized, single-center, noninterventional, observational study. Approval was obtained from the hospital's institutional review board and protocol review committee prior to the commencement of the research project. Patients gave their verbal consent prior to initiating the telephone survey and were allowed to withdraw their consent at any time during the survey. Data were gathered using a verbal telephone survey from June 2018 to August 2018. Retrospective review of the electronic medical record (EMR) was used to assess patient data that was documented in the EMR from September 2014 through August 2018. An initial report was created with assistance from the pharmacy analytics team who utilized the EMR to identify 209 patients taking oral TKIs. Patients were screened and included in the study as seen in Figure 1.

POCP Format

In order for patients to be eligible for enrollment into the POCP, they must have received a counseling session from an oncology clinical pharmacist about their oral chemotherapy medication prior to initiation, received their oral chemotherapy medication from the specialty pharmacy associated with the medical center (the ability to fill a prescription from the specialty pharmacy was dependent on a patient's insurance coverage), received at least one subsequent counseling session with follow-up from the oncology clinical pharmacist, and been clinically managed by a clinical pharmacist at the medical center to meet the accreditation of the specialty pharmacy associated with the medical center. Participants who were not eligible to enroll in the POCP received standard of care, which included a counseling session from an oncology clinical pharmacist about their oral chemotherapy mediation prior to initiation. These patients could still be seen by a clinical pharmacist as needed at the discretion of the patient's attending provider. Additional details regarding care provided for patients in the POCP and non-POCP groups can be seen in Figure 2.

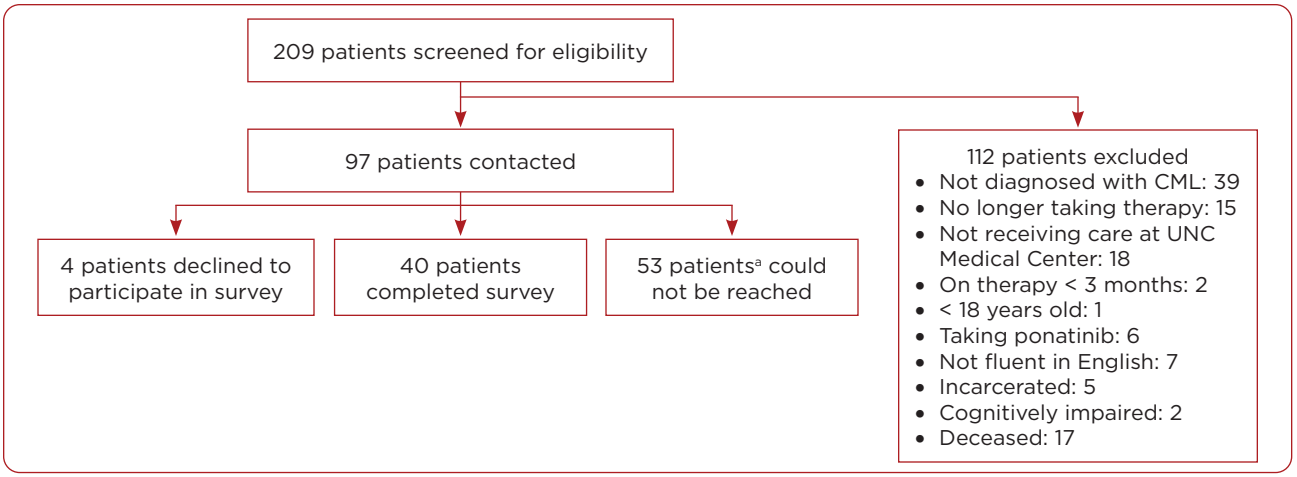

Figure 1. Patient CONSORT: Screening and inclusion. CML = chronic myeloid leukemia; UNC = University of North Carolina.
[a]Patients were called at least three times before it was determined they could not be reached.

Survey Instrument and Measures

A telephone survey was designed to assess patients' satisfaction with their care, self-reported adherence, and perceived value of pharmacy integration within their care team. Applicable questions from the telephone survey and scoring are in Table 1. "Satisfaction" and "value" questions were presented in a Likert-style format. Composite scores of ≥ 15 and ≥ 6 were considered a positive finding, respectively. All score designations were assigned *a priori*.

Adherence was assessed using the validated four-item Morisky Green Levine (MGL) Medi-

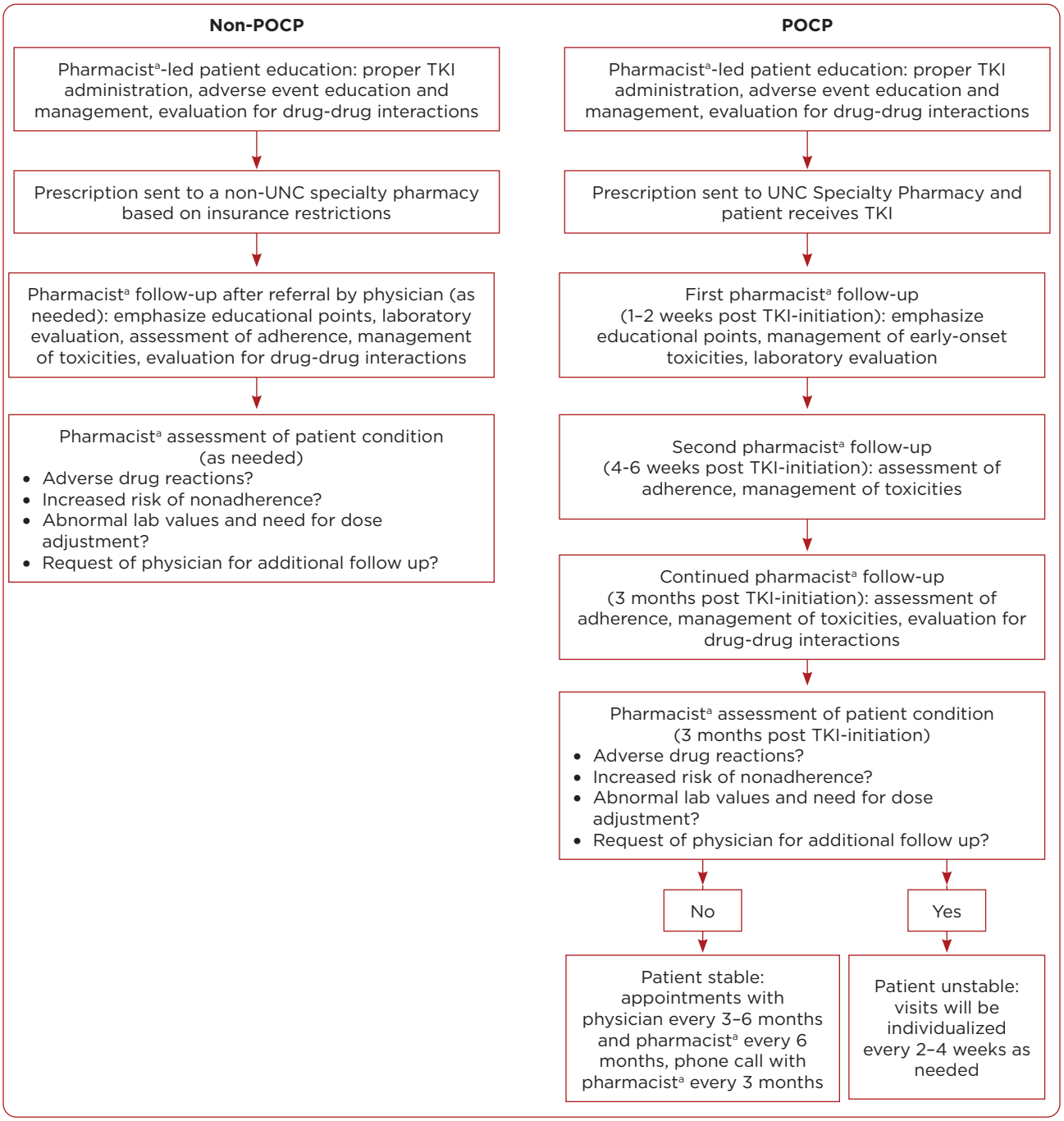

Figure 2. Care models of non-POCP and POCP groups. POCP = pharmacist-led oral chemotherapy program; TKI = tyrosine kinase inhibitor.
[a]Clinical pharmacist embedded in the leukemia clinic.

Table 1. Telephone Survey Questions Assessing Satisfaction, Adherence, Value, and Pharmacist Role

1. How satisfied are you with the service you receive at your specialty pharmacy?[a]
   - ❍ Extremely satisfied
   - ❍ Somewhat satisfied
   - ❍ Somewhat dissatisfied
   - ❍ Extremely dissatisfied

2. Are you satisfied with the current refill process of your specialty pharmacy?[a]
   - ❍ Extremely satisfied
   - ❍ Somewhat satisfied
   - ❍ Somewhat dissatisfied
   - ❍ Extremely dissatisfied

3. How frustrated are you with the delays you may have experienced in receiving your oral CML cancer medications from your specialty pharmacy over the past 3 months?[a]
   - ❍ Not frustrated at all
   - ❍ Slightly frustrated
   - ❍ Somewhat frustrated
   - ❍ Extremely frustrated

4. Is the communication between you and your specialty pharmacy about your oral CML cancer medications sufficient for your needs?[a]
   - ❍ Meets all of my needs
   - ❍ Meets most of my needs
   - ❍ Does not meet most of my needs
   - ❍ Meets none of my needs

5. Is the communication between your specialty pharmacy and your medical providers about your oral cancer medications sufficient for your needs?[a]
   - ❍ Meets all of my needs
   - ❍ Meets most of my needs
   - ❍ Does not meet most of my needs
   - ❍ Meets none of my needs

6. In the past 3 months, have you done the following things?[b]

Do you ever forget to take your medicine?	Yes	No
Are you careless at times about taking your medicine?	Yes	No
When you feel better do you sometimes stop taking your medicine?	Yes	No
Sometimes if you feel worse when you take your medicine, do you stop taking it?	Yes	No

7. Do you think it is valuable for your medical team to have access to your specialty pharmacy system?[c]
   - ❍ Extremely valuable
   - ❍ Somewhat valuable
   - ❍ Not really valuable
   - ❍ No value at all

8. Do you think it is valuable for your specialty pharmacy system to have access to your medical team (though medical notes, etc)?[c]
   - ❍ Extremely valuable
   - ❍ Somewhat valuable
   - ❍ Not really valuable
   - ❍ No value at all

9. How important a role do you feel your clinical pharmacist plays in your cancer therapy?[d]
   - ❍ Major role
   - ❍ Moderate role
   - ❍ Minor role
   - ❍ No role

Note. [a]Questions assessing satisfaction. [b]Four-item Morisky Green Levine tool assessing adherence. [c]Questions assessing value. [d]Questions assessing pharmacist role.

cation Adherence Scale (Morisky et al., 1986). A score of 1 was assigned for every question within the MGL tool that was answered "yes," while a score of 0 was assigned for every question within the MGL tool that was answered "no." The numerical value of each question within the MGL tool was then summed. A score of 0 is indicative of high patient-reported adherence, a score of 1 to 2 is indicative of medium patient-reported adherence, and a score of 3 to 4 is indicative of low patient-reported adherence (Morisky et al., 1986).

Pertinent information gathered during the telephone survey also included background information regarding a patient's oral chemotherapy regimen, how patients obtained their oral chemotherapy medication, as well as how and from whom patients obtained information about their oral chemotherapy regimen. Additional data were gathered retrospectively via chart review of patients' EMRs to determine patient demographics (age, sex, race, ethnicity), CML diagnosis date, and polymerase chain reaction (PCR) results 3 months after initiating therapy, 12 months after initiating therapy (if able), and the most recent PCR results to assess the achievement of early molecular response (EMR) or MMR. Early molecular response was defined as having achieved at least a 1-log reduction (BCR-ABL/ABL ratio ≤ 10%) by 3 months, while MMR was defined as a 3-log reduction in BCR-ABL/ABL transcript levels in accordance with the common definitions in published literature (Marin et al., 2010). The percentage of participants who achieved or maintained EMR as well as the percentage of participants who achieved MMR were determined and compared between those in the POCP and those receiving standard of care.

Statistical Analysis

The trial, which included both a participant questionnaire and subsequent retrospective chart review, had the primary objective of determining whether a POCP improved rates of patient-reported satisfaction with their care. Secondary objectives were to evaluate patient-reported adherence, value, EMR, and MMR rates in participants enrolled in the POCP compared with the rates of participants not enrolled in the program.

The composite satisfaction score was anticipated to be 90% within the POCP group. A Fisher's Exact Test with a 0.05 two-sided significance level was determined to have 80% power to detect the difference between the composite satisfaction scores of those enrolled in the POCP and those in the non-POCP group when the sample size was 30 patients in each group (60 patients total). Descriptive statistics were used to characterize the patient population. Fisher's Exact Tests were used to compare satisfaction for categorical variables and Wilcoxon Rank Sum tests for continuous variables. A p value of $< .05$ was considered statistically significant.

RESULTS

A total of 40 patients who met the inclusion criteria agreed to participate in the study; 20 were enrolled in the POCP and 20 were in the non-POCP group. Patient demographics are described in Table 2. The average age in the POCP was 57.4 years (standard deviation ± 13.97) and 53.3 years (standard deviation ± 11.84) in the non-POCP group. More patients in the non-POCP group were female (55%), had 4-year degrees (60%), and had commercial insurance (75%) than in the POCP group (female: 45%, 4-year degrees: 30%, commercial insurance 45%); however, these differences were not statistically significant. Most patients lived with other people, and there was no statistically significant difference between the current oral chemotherapy patients were taking or the duration of the current oral chemotherapy between the POCP and the non-POCP groups. The only statistically significant difference between groups was race, where 50% of the patients enrolled in the POCP were African American and only 20% of those in the non-POCP group were African American ($p = .014$).

The primary outcome, patient satisfaction with care, can be seen in Table 3. 100% of the 20 patients enrolled in the POCP were satisfied with their care, while only 75% of the 20 patients in the non-POCP group were satisfied with their care ($p = .047$). Differences in race could not be controlled for because of the small sample size and small percentage of patients who were not satisfied with their care. All 12 African American patients as well as the Native American patient were satisfied. Of the 12 white patients in the POCP, 10 white patients were satisfied, while only 12 of the 17 white patients (70%) in the non-POCP group

Table 2. Patient Demographic Data

Variable	POCP (n = 20)	Non-POCP (n = 20)	*p* value
Age (years), average (± SD)	57.35 (± 13.97)	53.25 (± 11.84)	.215
Gender, male, n (%)	11 (55%)	9 (45%)	.752
Race, n (%)			.014
African American	10 (50%)	2 (10%)	
Caucasian	10 (50%)	17 (85%)	
Native American	0 (0%)	1 (5%)	
Living status, n (%)			.451
Live with others	14 (70%)	17 (85%)	
Live by themselves	6 (30%)	3 (15%)	
Level of education, n (%)			.111
2-year degree or less	14 (70%)	8 (40%)	
4-year degree or more	6 (30%)	12 (60%)	
Type of insurance, commercial, n (%)	9 (45%)	15 (75%)	.105
Current oral chemotherapy treatment, n (%)			.357
Imatinib	5 (25%)	8 (40%)	
Dasatinib	4 (20%)	5 (25%)	
Bosutinib	7 (35%)	2 (10%)	
Nilotinib	4 (20%)	5 (25%)	
Duration of current therapy, n (%)			.909
< 6 months	1 (5%)	2 (10%)	
6 months to 1 year	6 (30%)	5 (25%)	
1 year	6 (30%)	6 (30%)	
2 years	2 (10%)	1 (5%)	
3 years	0 (0%)	2 (10%)	
4 years	1 (5%)	1 (5%)	
> 4 years	4 (20%)	3 (15%)	

Note. POCP = pharmacist-led oral chemotherapy program; SD = standard deviation.

Table 3. Comparison of Composite Survey Scores and Molecular Response

Variable	POCP (n = 20)	Non-POCP (n = 20)	*p* value
Satisfied with care received[a], n (%)	20 (100%)	15 (75%)	0.047
High patient-reported adherence, n (%)	11 (55%)	12 (60%)	1.000
Valued pharmacist integration in care team, n (%)	19 (95%)	18 (90%)	1.000
Early molecular response rate achieved[b], n (%)	15 (75%)	15 (75%)	1.000
Major molecular response rate achieved[c], n (%)	17 (85%)	17 (85%)	1.000

Note. POCP = pharmacist-led oral chemotherapy program.
[a]Primary endpoint.
[b]Early molecular response = ratio of BCR-ABL to ABL mRNA < 10% at 3 months after therapy initiation.
[c]Major molecular response = ratio of BCR-ABL to ABL mRNA < 0.1%.

were satisfied with their care. Table 3 also shows secondary outcomes, including high patient-reported adherence (POCP: 55% and non-POCP: 60%, $p = 1.000$), patient value of pharmacist integration in their care team (POCP: 95% and non-POCP: 90%, $p = 1.000$), EMR rate achieved (POCP: 75%, non-POCP: 75%, $p = 1.000$), and MMR rate achieved (POCP: 85%, non-POCP: 85%, $p = 1.000$).

One question within the telephone survey in Table 1 assessed the role (minor, moderate, or major) patients believed the clinical pharmacist played in their care. Additional analysis evaluating these results can be seen in Figure 3. Of all 40 patients surveyed in total, only one patient perceived the clinical pharmacist as having a minor role in their care, while 35 patients (87.5%) believed the clinical pharmacist played a major role in their care. The belief that the clinical pharmacist played a major role in care was not limited or exclusive to those enrolled in the POCP; 17 patients in the POCP felt this way, while 18 patients in the non-POCP group also thought the clinical pharmacist played a major role.

DISCUSSION

The characteristics of patients enrolled in the POCP compared with those in the non-POCP group were balanced in all aspects except race, where there were more African Americans enrolled in the POCP than in the non-POCP group. While there was a trend towards more patients in the non-POCP group having a higher level of education and more likely to have commercial insurance, which have the potential to impact adherence rates and thus outcomes, neither of these between-group differences were statistically significant (Geissler et al., 2017).

Using a Closed-Loop Dispensing Model in the POCP Improved Satisfaction Rates

This analysis demonstrated that patients enrolled in the POCP who received their oral TKI from the

medical center's specialty pharmacy and thus had enhanced pharmacy integration were more likely to be satisfied with the care they received than patients in the non-POCP group. A 25% increase in satisfaction between the POCP and non-POCP groups was observed in this analysis and was statistically significant. This increase in satisfaction was irrespective of the fact that both patients enrolled in the POCP and in the non-POCP group could be seen by and be managed by the clinical pharmacist. The importance of patient satisfaction should not be underestimated, as it has previously been found that patients who have high satisfaction rates after interactions with their treating doctor regarding information about CML have higher adherence rates to their oral chemotherapy (Geissler et al., 2017). Furthermore, those patients who feel that their treating doctor is approachable to discuss the challenges of taking medication are also more likely to be adherent to their oral chemotherapy medication (Geissler et al., 2017).

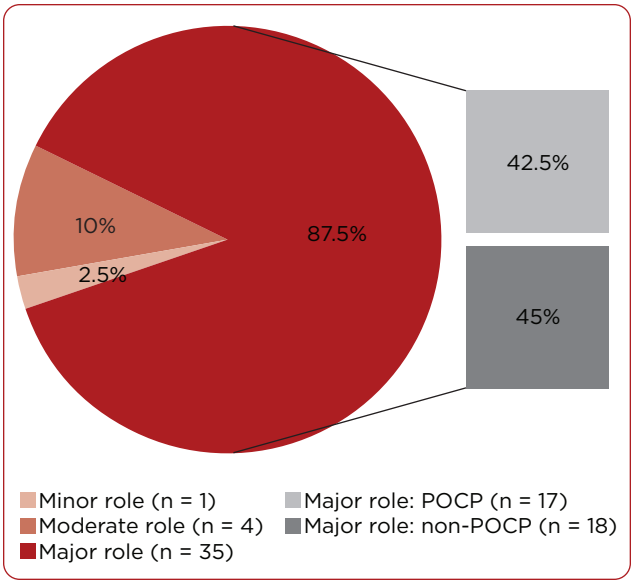

Figure 3. Patient perception: Role of pharmacist (clinical pharmacist embedded in the leukemia clinic) in their care. POCP = pharmacist-led oral chemotherapy program.

Active Involvement by the Clinical Pharmacist Overcomes Fragmented Care

Despite lack of satisfaction in the non-POCP group, presumably driven by fragmented care, adherence rates in the non-POCP group remained high and consistent with previously published data at other medical centers, likely due to the clinical pharmacist, since most patients in both groups said the clinical pharmacist played a major role in their care (Greer et al., 2016). However, several factors could explain any potential discrepancies. The small sample size might not have been reflective of the larger patient population. Different methods were utilized to assess adherence in this study compared with the 2018 study by Muluneh and colleagues (four-item MGL tool vs. a patient-reported survey verified with a medication possession ratio). Additionally, patient-reported adherence rates in this study were not validated with medication possession ratios as they were previously (Muluneh et al., 2018).

Both patients enrolled in the POCP and those in the non-POCP group reported the clinical pharmacist played a major role in their care and valued pharmacy integration, from both the clinical pharmacist and the specialty pharmacy, with their medical team. This is likely because both patients enrolled in POCP and those in the non-POCP group had interactions with the clinical pharmacist. However, patients in the non-POCP group used external specialty pharmacies that did not have the same access to patients' medical records, resulting in more fragmented care and likely explaining inferior satisfaction rates. Both groups could receive information and education from, be assessed by, and be followed by the clinical pharmacist; those within the POCP simply received more regular, scheduled, and consistent management from the clinical pharmacist. This embedded pharmacist role within the leukemia clinic has contributed to the high adherence rates and outcomes seen previously (Muluneh et al., 2018). The high MMR rates within both the POCP and the non-POCP group (85% for each group) are consistent with prior studies at the same institution and are higher than rates in other published clinical trials (Cortes et al., 2018; Kantarjian et al., 2010; Muluneh et al., 2018; O'Brien et al., 2003; Radich et al., 2012).

Limitations

There were several limitations to this study, most notably the small sample size and the inability to enroll enough patients to reach power due to fewer than anticipated willing participants.

Furthermore, differences in race between the POCP and non-POCP groups could not be controlled. While a validated method to assess adherence (the four-item MGL tool) was used, the remainder of the survey questions were created by the authors with assistance from a survey research laboratory that provided expertise in questionnaire design but were nonetheless not validated beforehand. The survey was given verbally over the phone, which inherently introduces bias due to the potential for patients to perceive their response as not truly anonymous. Although the individual verbalizing the survey questions and recording responses was unknown to participants and stated that their response would not impact the care patients received, it is impossible to know exactly how, if at all, this may have impacted patients' responses. Finally, the number of interactions or follow-ups the clinical pharmacist had with each patient, both those enrolled in the POCP and those not enrolled, was not quantified. This information could have clarified the extent of involvement the clinical pharmacist played within the non-POCP group, which could then have been controlled for when comparing and attempting to differentiate results and outcomes between the two groups. Despite these limitations, this analysis demonstrated that patients enrolled in the POCP were more likely to be satisfied with the care they received, which was the primary endpoint of the analysis and which reached statistical significance.

Directions for Future Research and Implications for Practice

This study was not powered to detect a difference in clinical outcomes. The humanistic impact of a POCP is undoubtedly important and can impact other quantitative measures such as adherence and possibly outcomes (Geissler et al., 2017). Future studies should enroll a larger patient population and include multiple institutions with closed-loop models utilizing institutional specialty pharmacies and regular pharmacist intervention. Ideally, these comparative studies would be powered to detect a difference in patient adherence to oral TKIs as well as in clinical outcomes such as EMR or MMR rates. As health care continues to shift away from the fee-for-service system towards a fee-for-performance system, controlling factors such as adherence, which has been shown to impact patient outcomes, will become even more important. The use of models like the closed-loop POCP has the potential to become the new gold standard in improving not only patient satisfaction with care but also patient outcomes.

CONCLUSIONS

This analysis showed significant improvement in composite satisfaction scores for patients enrolled in a POCP compared with those not enrolled in such a program. There were no significant differences in patient-reported adherence or molecular response rates (EMR or MMR) between groups, possibly due to clinical pharmacist intervention, as both groups reported the clinical pharmacist played a major role in their care. Patients valued pharmacy services that were integrated with their medical care team. Additional studies with larger patient populations are needed to assess what impact POCPs that utilize closed-loop institutional specialty pharmacies and regular pharmacist intervention have on clinical outcomes, including adherence and outcomes, before this model becomes standard of care.

Disclosure

The authors have no conflicts of interest to disclose.

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