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Letter to the Editor

Patients' perspectives on the definition of cure in chronic myeloid leukemia

1. Introduction

The development of tyrosine kinase inhibitors (TKIs) markedly improved the prognosis of patients with chronic myeloid leukemia (CML) [1], and many healthcare professionals now consider its management as a chronic disease. Some experts have called deep remission sustained by TKI therapy a "functional cure" for CML, since optimally treated patients with CML have the same life expectancy as age-matched peers without CML [2]. However, the need for continuous TKI therapy may result in ongoing toxicities, limits on fertility, and financial hardship [3]. Discontinuation of TKI therapy is effective for some patients, without the need for additional treatment (treatment-free remission) [4]. Thus, other experts have called treatment-free remission the "functional" cure for CML [5]. Expert definitions of cure have related to treatment status and evidence of disease. To date, no research has examined patients' perspectives on cure in CML.

The H. Jean Khoury Cure CML Consortium (HJKC3) is a collaborative effort of physicians and researchers at 21 North American academic centers [6]. The HJKC3-0001 Chronic Myeloid Leukemia Patient Survey sought to understand patients' definition of cure and gauge patient priorities for future research in CML.

2. Methods

2.1. Data collection

English-speaking adults were recruited through invitations by HJKC3 physicians, CML advocacy groups (e.g., Leukemia and Lymphoma Society), and social media. Participants completed the self-administered questionnaire online via a secure online survey platform (Qualtrics®), which was also used to capture electronic consent. The survey was anonymous. Definition of cure and priorities for future research were measured with items we developed. The questionnaire was pre-tested by patients with CML who were members of the Patient Advisory Panel for the Life After Stopping TKIs clinical trial [7,8], and modifications were made to address their comments. Item wording is presented in the associated results tables. For the definition of cure item, patients could endorse more than one response option, with 4 options provided that related to treatment status and evidence of disease. For the research priorities items, the order of the different topics was randomized.and response options included "very important", "somewhat important", and "not at all important". Patient demographic, health, and CML treatment characteristics were also collected. Depending on skip patterns, participants who reported having been diagnosed with CML ("patients") were asked up to 59 items. Participants who reported no CML diagnosis were asked 18 items; however, as there were only 25 participants in this category, results from this group are not included. The Medical College of Wisconsin institutional review board approved this study.

2.2. Data analysis

Data were analyzed in SAS. Descriptive statistics are presented, including percentages, medians, and ranges.

3. Results

Four hundred and fifty-eight patients completed the questionnaire, with a median of 4 years since diagnosis of CML.(Table 1) Participants represented 45 of the 50 U.S. States (n = 441) and 16 other countries (n = 43). The median age of participants was 54 years; 88% of patients identified as non-Hispanic white, 2% as non-Hispanic black, 2% as non-Hispanic Asian, 4% other race, non-Hispanic, and 4% identified as Hispanic. More than half of participants had a college degree or more, and the majority (75%) were married, in a domestic partnership, or civil union. A minority of patients rated their overall health as fair (18%) or poor (4%), and overall quality of life had a similar distribution, with 23% rating quality of life as fair and 6% as poor.

All but three respondents had received treatment with a TKI. One quarter of the sample (26%) reported trying a TKI discontinuation, that is, having stopped their TKI medication for at least one month. Patients reported being willing to add additional treatments to their TKI in order to reach treatment-free remission; when presented with the possibility of stopping all future treatment for CML, 97% of patients were willing to add another oral medication to their TKI while 89% of patients would accept intravenous treatment in addition to a TKI.

3.1. Patient definition of cure

The overwhelming majority of patients considered cure as permanently stopping any CML treatment, with 90% who endorsed permanently stopping treatment with no evidence of disease and 8.5% endorsed permanently stopping treatment with some evidence of disease. Only 4% of patients endorsed a definition of cure that included taking a daily pill. (Patients were allowed to endorse multiple options.)

3.2. Research priorities

All but one patient (99%) said that more research was needed for CML. Management of CML that is not responding to treatment and understanding long term complications of CML medication were each endorsed as very important by over 90% patients (Table 2). Management of side effects of CML medication, stopping CML medication, taking less CML medication, and the impact of cost of CML medication were endorsed as very important by over 80% of patients. At least 50% of patients endorsed patient education, coping with CML, and fertility and pregnancy as very important.

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Table 1
Patient characteristics (n = 458).

Characteristic	No. (%)
Years since CML diagnosis, median (range)	4 (0–26)
Age, median (range)	54 (18–81)
Race/ethnicity	
Asian, non-Hispanic	9 (2.0)
Black, non-Hispanic	7 (1.5)
White, non-Hispanic	404 (88.2)
2 or more races, non-Hispanic	11 (2.4)
Other, non-Hispanic	10 (2.2)
Hispanic	17 (3.7)
Education level	
Less than high school	2 (0.4)
High school graduate or equivalent	40 (8.8)
Some college, no degree	101 (22.2)
2-year degree	66 (14.5)
4-year degree	109 (24.0)
Master's, professional, or doctoral degree	136 (29.9)
Marital status	
Married or in a domestic partnership or civil union	340 (75.2)
Widowed	16 (3.5)
Divorced	43 (9.5)
Separated	5 (1.1)
Never married	42 (9.3)
Overall self-rated health	
Excellent	42 (9.3)
Very good	127 (28.1)
Good	181 (40.0)
Fair	83 (18.4)
Poor	19 (4.2)
Overall self-rated quality of life	
Excellent	47 (10.4)
Very good	127 (28.0)
Good	148 (32.7)
Fair	103 (22.7)
Poor	28 (6.2)
Ever on TKI therapy	455 (99.3)
Ever stopped TKI therapy for > 1 month, No. (%)	119 (26.2)
Would add another oral medication to TKI	415 (97.2)
Would add an IV medication to TKI	383 (89.3)

Table 2
Patients' definition of cure and research priorities for CML (n = 458).

In your opinion, what is the definition of a cure for CML?*	**No. (%)**
Taking a pill daily with some evidence of disease	5 (1.1)
Taking a pill daily with no evidence of disease	13 (2.8)
Permanently stopping any CML treatment with some evidence of disease	39 (8.5)
Permanently stopping any CML treatment with no evidence of disease	411 (89.7)
How important is CML research for each item below?**	
Management of CML that is not responding to treatment	429 (93.7)
Understanding long term complications of CML medication	429 (93.7)
Management of side effects of CML medication	406 (88.6)
Stopping CML medication	405 (88.4)
Taking less CML medication	397 (86.7)
Impact of cost of CML medication	378 (82.5)
Patient education	316 (69.0)
Coping with CML	308 (67.2)
Fertility and pregnancy for people with CML	237 (51.7)

* Participants were allowed to select more than one response.
** Number and percent of participants (out of 458) who selected "very important".

4. Discussion

The advent of highly effective oral medication, TKIs, has been a tremendous success for patients with CML. Nevertheless, lifelong TKI therapy remains a source of disruption in many patients' lives. Survey responses suggest that patients with CML do not consider disease control with life-long oral TKI medication as a cure; rather, cure requires the absence of treatment. To reach a treatment-free remission, patients reported willingness to add additional therapies to their TKI, either orally or intravenously. There are several ongoing trials with promising early or preclinical results in this area. These include the addition of ruxolitinib [9] (NCT03654768) [10], venetoclax [11] (NCT02689440), or PD1 inhibitors [12] (NCT03516279) to TKIs to get patients to a deeper molecular response, toward the ultimate goal of treatment discontinuation and treatment-free remission. Patients in our survey universally supported more research in CML. Of particular importance to the most patients were addressing CML that is unresponsive to treatment and understanding long term complications of CML medication. TKI discontinuation and management of TKI side effects were also widely endorsed by patients as research priorities.

We acknowledge the limitations of our study. This was a convenience sample of English-speaking adults. Diagnosis of CML was self-reported and not externally validated by physicians. Participants tended to be younger, as the median age in our sample was 54 while the U.S. median is 65 years at diagnosis [13]. Due to an oversight, self-reported sex was not included on the questionnaire, so we were unable to describe results by sex, though we would not expect major difference in our study outcomes by sex.

5. Conclusion

Patients with CML indicated the importance of continuing CML research with an ultimate goal of cure. Nearly all patients defined cure in CML as permanently stopping any CML treatment with no evidence of disease. Additionally, patients' responses strongly support continued research, especially into long-term effects and adverse effects of treatment. The HJKC3 was initiated with the goal of curing CML; the current study further elucidates how patients interpret this term and thus can inform and guide future research priorities.

Ethics approval and consent

The Medical College of Wisconsin institutional review board (IRB) granted approval.

Competing interests

We wish to confirm that there are no known conflicts of interest associated with this publication. E.A. has served as a member of the advisory boards of Bristol-Myers Squibb, Novartis, Pfizer, and Takeda and has received research support to his institution from Bristol-Myers Squibb and Pfizer for work performed outside of the current study. V.K. has served as a consultant for Novartis, Pfizer, and Takeda for work performed outside of the current study. M.M. has served as a consultant for Bristol-Myers Squibb, Novartis, Pfizer, and Takeda and has received research support to his institution from Bristol-Myers Squibb and SPARC/Sun Pharma for work performed outside the current study.

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Kathryn E. Flynn*, Michael J. Mauro, Gemlyn George, Alexander Hinman, Arielle Baim, Vamsi Kota, Richard A. Larson, Jeffrey H. Lipton, James E. Thompson, Martha Wadleigh, Ehab Atallah

Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee 53226, United States

E-mail address: kflynn@mcw.edu (K.E. Flynn).

* Corresponding author.