Patient- and physician-reported pain after tyrosine kinase inhibitor discontinuation among patients with chronic myeloid leukemia

Kathryn E. Flynn,[1] Ehab Atallah,[1] Li Lin,[2] Neil P. Shah,[3] Richard T. Silver,[4] Richard A. Larson,[5] Javier Pinilla-Ibarz,[6] James E. Thompson,[7] Vivian G. Oehler,[8] Jerald P. Radich,[8] Vamsi Kota,[9] Michael J. Mauro,[10] Charles A. Schiffer,[11] Jorge Cortes,[9] and Kevin P. Weinfurt[2]

[1]Medical College of Wisconsin, Milwaukee, WI; [2]Duke University School of Medicine, Durham, NC; [3]University of California at San Francisco, San Francisco, CA; [4]Weill Cornell Medicine, New York, NY; [5]University of Chicago, Chicago, IL; [6]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [7]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [8]Fred Hutchinson Cancer Center, Seattle, WA; [9]Georgia Cancer Center at Augusta University, Augusta, GA; [10]Memorial Sloan Kettering Cancer Center, New York, NY and [11]Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA

Correspondence: K. E. Flynn
kflynn@mcw.edu

Received: November 17, 2021.
Accepted: April 22, 2022.
Prepublished: May 5, 2022.

https://doi.org/10.3324/haematol.2021.280377

Online Supplementary Appendix

Methods

Measures

Physician-reported Adverse Events

Any AE that the treating physician determined was related to TKI discontinuation was reported on the AE electronic case report form in the Oncore Clinical Trial Management System. AE monitoring continued until restarting TKI or study completion. All patients were followed for a minimum of 36 months; depending on when patients enrolled, they may have been followed for up to 60 months.

Patient-reported Pain

Patient reported outcomes (PROs) were assessed at screening when patients were on a TKI. After TKI discontinuation, they were assessed at months 1, 2, 3, 4, 5, 6, 8,12, 18, 24, 30, and 36. For patients who restarted a TKI, PROs were assessed in conjunction with disease monitoring (RQ-PCR blood testing), approximately every 3 months for 1 year, then every 6 months thereafter. PRO assessments were self-administered via REDCap,[1] primarily on a study iPad at the clinic/lab, though alternatives were allowed to reduce missing data, including via REDCap outside the clinic or (rarely) on paper. To measure musculoskeletal pain, we used a single item from the European Organization for Research and Treatment of Cancer (EORTC)-CML24, which uses a one-week recall period and asks, “have you had aches or pains in your muscles or joints?” with ordinal response options of 1=not at all, 2=a little bit, 3=quite a bit, and 4=very much. We also assessed how much pain affected daily life using the PROMIS® Pain Interference computerized adaptive test. PROMIS measures are scored on a standardized scale, where 50 corresponds to the average in the U.S. general population (standard deviation

+/-10).[2] The average pain interference score for adults without any chronic conditions is 46.[3] A score below 50 is considered within normal limits, 50-55 is mild, 55-65 is moderate, and >65 is severe pain interference.

Pain Medications

On the 3-month PRO assessment for those in TFR (still off TKI), we included a series of questions asking about changes in medications since TKI discontinuation: “Since you joined the LAST study 3 months ago and stopped taking your TKI, have you started taking any new prescription medications?” and “Since you joined the LAST study 3 months ago and stopped taking your TKI, have you started taking any new over-the-counter medications or supplements?”

Statistical Approach

Polyserial correlation was used to characterize the relationship between the single musculoskeletal pain item and PROMIS Pain Interference score at baseline. The agreement in pain classifications by each source of information was examined through cross-tabulations and McNemar’s tests for association. The probability of molecular relapse-free survival was calculated using the Kaplan-Meier estimator, defined as the time from TKI discontinuation to loss of major molecular remission. As previously described,[4] we defined loss of major molecular remission as a single value greater than 0.1%BCR-ABL1 based on the International Scale ratio, based on RQ-PCR performed on peripheral blood samples.

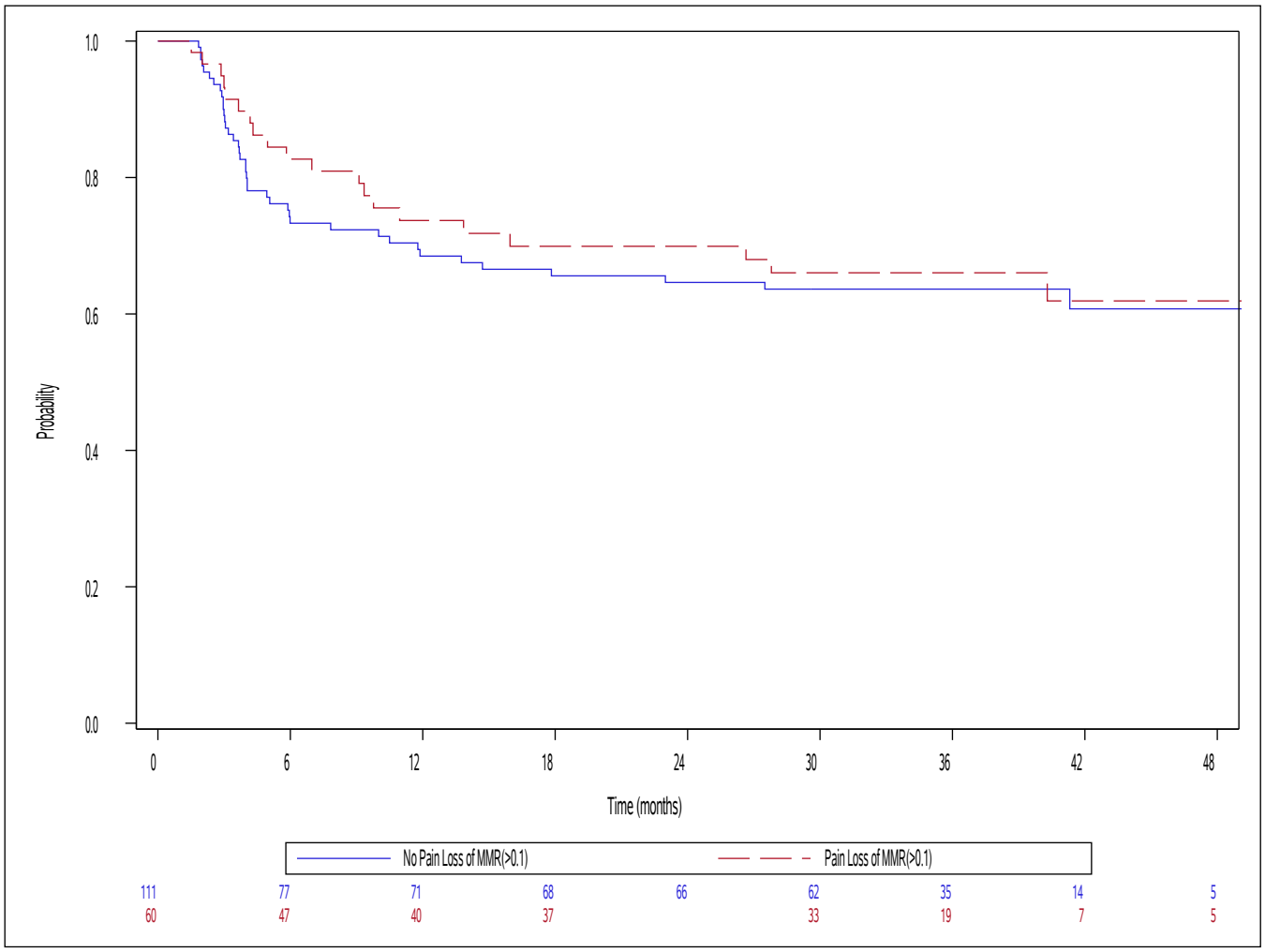
Results

The polyserial correlation between the single EORTC CML musculoskeletal pain item and the PROMIS Pain Interference score at baseline was 0.74 (95% CI 0.662-0.818).

Supplementary Table S1. Agreement between patient-reported increases in pain and addition of a pain medication within 3 months of discontinuation of tyrosine kinase inhibitors

	Added medication for pain (n=154)	
	No	Yes
Patient-reported increased pain (1+)		
No	49 (31.8)	6 (3.9)
Yes	87 (56.6)	12 (7.8)
Patient-reported increased pain (2+)		
No	120 (77.9)	14 (9.1)
Yes	16 (10.4)	4 (2.6)
Total	136 (88.3)	18 (11.7)

Supplementary Figure S1. Probability of Loss of Major Molecular Remission



References

1. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.
2. Cella D, Riley, W., Stone, A., Rothrock, N., Reeve, B., Yount, S., Amtmann, D., Bode, R., Buysse, D., Choi, S., Cook, K., DeVellis, R., DeWalt, D., Fries, J. F., Gershon, R., Hahn, E. A., Pilkonis, P., Revicki, D., Rose, M., Weinfurt, K., Hays, R., Lai, J-S. The Patient Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008 *Journal of Clinical Epidemiology.* 2010;63(11):1179-1194.
3. Rothrock NE, Hays RD, Spritzer K, Yount SE, Riley W, Cella D. Relative to the general US population, chronic diseases are associated with poorer health-related quality of life as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS). *J Clin Epidemiol.* 2010;63(11):1195-1204.
4. Atallah E, Schiffer CA, Radich JP, et al. Assessment of Outcomes After Stopping Tyrosine Kinase Inhibitors Among Patients With Chronic Myeloid Leukemia: A Nonrandomized Clinical Trial. *JAMA Oncol.* 2021;7(1):42-50.