Chapter 15

DISCONTINUATION OF TYROSINE KINASE INHIBITORS IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: WHERE ARE WE TODAY?

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HISTORY AND RATIONALE FOR DISCONTINUATION OF TYROSINE KINASE INHIBITORS

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasia caused by the fusion of the BCR and ABL1 genes, most frequently as the result of the reciprocal translocation t(9;22)(q34;q11). BCR-ABL1 fusion protein has tyrosine kinase (TK) activity and plays a major role in the development of CML. Treatment with tyrosine kinase inhibitors (TKIs) specifically inhibits this activity and effectively clears the malignant clone in most CML patients (1). TKIs have dramatically improved the outcome for CML patients (2, 3). Imatinib is the first TKI used in CML treatment, which was approved after the initial published data of the International Randomized Study of Interferon and STI571 (IRIS) trial (4). Nilotinib and dasatinib are second-generation TKIs (2G-TKIs), and they are more potent than imatinib with lower rates of transformation to advanced disease. These two TKIs have been shown to be superior to imatinib including the speed and the depth of responses, and they are approved in the frontline treatment of patients with CML-CP in some countries following 2 phase III prospective, randomized, company-sponsored trials (5, 6). With the inclusion of the third generation (3G) drug, ponatinib, TKIs have become the gold standard treatment against the disease and allogeneic hematopoietic stem cell transplantation (HSCT) has receded into the background despite its curative potential (7).

TKIs have some chronic toxicities that may, especially in the long-term, have a significant impact on patient quality of life (8). Moreover, real-life studies have shown problems of patient compliance with TKIs. Furthermore, the economic impact of life-long TKI therapy is quite significant, and although the price of imatinib is expected to fall with the introduction of generic formulations, long-

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There are some limitations of the current data. Clinical data on TKI discontinuation obtained from published studies are difficult to compare and the follow-up durations are not long enough to reach a conclusion. Almost all studies have found different predictive factors of TKI discontinuation success. Up-to-date studies in real life settings have been retrospective in design and may have some bias in patient selection. Clear recommendations on TKI discontinuation using rigorous evidence-based medicine will emerge in the near future with the goal of determining if, when and how patients may safely try to stop TKI in clinical practice. Therefore, questions concerning real-life settings will be answered with the accumulation of data on TKI discontinuation trials, either prospective or retrospective. Further research regarding parameters and biomarkers to predict successful TFR and guidelines for surveillance are essential.

REFERENCES

1. Dvorak P, Lysak D, Vokurka S. Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia patients - worldwide battlefield. Neoplasma 2015; 62(2): 167-71.
2. Bower H, Bjorkholm M, Dickman PW, et al. Life Expectancy of Patients With Chronic Myeloid Leukemia Approaches the Life Expectancy of the General Population. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016; 34(24): 2851-7.
3. Druker BJ. Current treatment approaches for chronic myelogenous leukemia. Cancer journal (Sudbury, Mass) 2001; 7 Suppl 1: S14-8.
4. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. The New England journal of medicine 2003; 348(11): 994-1004.
5. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. The New England journal of medicine 2010; 362(24): 2251-9.
6. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine 2010; 362(24): 2260-70.
7. Rosti G, Castagnetti F, Gugliotta G, et al. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? Nature reviews clinical oncology 2017; 14(3): 141.
8. Phillips KM, Pinilla-Ibarz J, Sotomayor E, et al. Quality of life outcomes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a controlled comparison. Supportive Care in Cancer 2013; 21(4): 1097-103.
9. Campiotti L, Suter MB, Guasti L, et al. Imatinib discontinuation in chronic myeloid leukaemia patients with undetectable BCR-ABL transcript level: A systematic review and a meta-analysis. European journal of cancer (Oxford, England : 1990) 2017; 77: 48-56.
10. Kimura S. Current status of ABL tyrosine kinase inhibitors stop studies for chronic myeloid leukemia. Stem cell investigation 2016; 3: 36.

11. Narra RK, Flynn KE, Atallah E. Chronic Myeloid Leukemia-the Promise of Tyrosine Kinase Inhibitor Discontinuation. Current hematologic malignancy reports 2017; 12(5): 415-23.
12. Bhalla S, Tremblay D, Mascarenhas J. Discontinuing Tyrosine Kinase Inhibitor Therapy in Chronic Myelogenous Leukemia: Current Understanding and Future Directions. Clinical lymphoma, myeloma & leukemia 2016; 16(9): 488-94.
13. Rea D, Ame S, Berger M, et al. Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia: Recommendations for clinical practice from the French Chronic Myeloid Leukemia Study Group. Cancer 2018.
14. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013; 122(6): 872-84.
15. Rousselot P. The story of tyrosine kinase inhibitors discontinuation in clinical practice. Leukemia & lymphoma 2018; 59(12): 2782-91.
16. Cerveira N, Loureiro B, Bizarro S, et al. Discontinuation of tyrosine kinase inhibitors in CML patients in real-world clinical practice at a single institution. BMC cancer 2018; 18(1): 1245.
17. Mahon FX, Rea D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. The Lancet Oncology 2010; 11(11): 1029-35.
18. Etienne G, Guilhot J, Rea D, et al. Long-Term Follow-Up of the French Stop Imatinib (STIM1) Study in Patients With Chronic Myeloid Leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017; 35(3): 298-305.
19. Ross DM, Branford S, Seymour JF, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. Blood 2013: blood-2013-02-483750.
20. Takahashi N, Tauchi T, Kitamura K, et al. Deeper molecular response is a predictive factor for treatment-free remission after imatinib discontinuation in patients with chronic phase chronic myeloid leukemia: the JALSG-STIM213 study. International journal of hematology 2018; 107(2): 185-93.
21. Imagawa J, Tanaka H, Okada M, et al. Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year (DADI trial): a multicentre phase 2 trial. The Lancet Haematology 2015; 2(12): e528-35.
22. Okada M, Imagawa J, Tanaka H, et al. Final 3-year Results of the Dasatinib Discontinuation Trial in Patients With Chronic Myeloid Leukemia Who Received Dasatinib as a Second-line Treatment. Clinical Lymphoma Myeloma and Leukemia 2018; 18(5): 353-60. e1.
23. Shah NP, Paquette R, Müller MC, et al. Treatment-free remission (TFR) in patients with chronic phase chronic myeloid leukemia (CML-CP) and in stable deep molecular response (DMR) to dasatinib-the DASFREE Study. Blood 2016 vol. 128 no. 22 1895.
24. Kumagai T, Nakaseko C, Nishiwaki K, et al. Discontinuation of dasatinib after deep molecular response for over 2 years in patients with chronic myelogenous leukemia and the unique profiles of lymphocyte subsets for successful discontinuation: a prospective, multicenter Japanese trial (D-STOP Trial). Blood 2016 vol. 128 no. 22 791.

25. Rea D, Nicolini FE, Tulliez M, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. Blood 2017; 129(7): 846-54.
26. Hochhaus A, Masszi T, Giles FJ, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. Leukemia 2017; 31(7): 1525-31.
27. Mahon F-X, Boquimpani C, Kim D-W, et al. Treatment-free remission after second-line nilotinib treatment in patients with chronic myeloid leukemia in chronic phase: results from a single-group, phase 2, open-label study. Annals of internal medicine 2018.
28. Mahon F-x, Richter J, Guilhot J, et al. Cessation of tyrosine kinase inhibitors treatment in chronic myeloid leukemia patients with deep molecular response: results of the Euro-Ski trial. Am Soc Hematology 2016.
29. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. The Lancet Oncology 2018; 19(6): 747-57.
30. Rousselot P, Charbonnier A, Cony-Makhoul P, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. Journal of clinical oncology 2013; 32(5): 424-30.
31. Hernández-Boluda JC, Pereira A, Pastor-Galán I, et al. Feasibility of treatment discontinuation in chronic myeloid leukemia in clinical practice: results from a nationwide series of 236 patients. Blood Cancer Journal 2018; 8(10): 91.
32. Atallah E, Schiffer CA, Weinfurt KP, et al. Design and rationale for the life after stopping tyrosine kinase inhibitors (LAST) study, a prospective, single-group longitudinal study in patients with chronic myeloid leukemia. BMC cancer 2018; 18(1): 359.
33. Takahashi N, Kyo T, Maeda Y, et al. Discontinuation of imatinib in Japanese patients with chronic myeloid leukemia. Haematologica 2012; 97(6): 903-6.
34. Benjamini O, Kantarjian H, Rios MB, et al. Patient-driven discontinuation of tyrosine kinase inhibitors: single institution experience. Leukemia & lymphoma 2014; 55(12): 2879-86.
35. Rege Cambrin G, Fava C, Dogliotti I, et al. Imatinib discontinuation in chronic myeloid leukemia: a retrospective analysis on patients in clinical practice. Haematologica 2015; 100(S1): 232-.
36. Chomel JC, Bonnet ML, Sorel N, et al. Leukemic stem cell persistence in chronic myeloid leukemia patients in deep molecular response induced by tyrosine kinase inhibitors and the impact of therapy discontinuation. Oncotarget 2016; 7(23): 35293-301.
37. Eşkazan AE. Evolving treatment strategies in CML–moving from early and deep molecular responses to TKI discontinuation and treatment-free remission: is there a need for longer-term trial outcomes? British journal of clinical pharmacology 2018.
38. Breccia M, Colafigli G, Molica M, et al. Timing and deepness of response to tyrosine kinase inhibitors as a measure of potential treatment discontinuation in chronic myeloid leukemia patients managed in the real-life. American journal of hematology 2017; 92(12): E668-e70.
39. Branford S, Yeung DT, Ross DM, et al. Early molecular response and female sex strongly predict stable undetectable BCR-ABL1, the criteria for imatinib discontinu-

ation in patients with CML. Blood 2013; 121(19): 3818-24.
40. Riva S, Mazzocco K, Pravettoni G. Rationale and protocol of CML study: cognitive and emotional impact of discontinuation of therapy in patients with chronic myeloid leukemia. Tumori 2016; 102(2): 217-21.
41. Sogawa R, Kimura S, Yakabe R, et al. Anxiety and depression associated with tyrosine kinase inhibitor discontinuation in patients with chronic myeloid leukemia. International journal of clinical oncology 2018; 23(5): 974-9.
42. NCCN Clinical Practice Guidelines in Oncology. Chronic Myeloid Leukemia. Version 1.2019 — August 1, 2018. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
43. Hochhaus A, Saussele S, Rosti G, et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2017; 28(suppl_4): iv41-iv51.