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Imatinib for Chronic Myeloid Leukemia: The Impact of Its Effectiveness and Long-term Side Effects

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The development of effective, selective therapies has long challenged researchers trying to improve treatment options for cancer patients. The allure of such therapies has always been that so-called "targeted therapies" would by their very nature limit toxic effects commonly associated with traditional cytotoxic agents. Moreover, if the targeted agents are effective, such therapies might improve clinical responses, alter disease biology, and ultimately improve survival for a multitude of cancer patients. The threats to such promising approaches include serious or unexpected toxic effects (ie, narrow therapeutic indices) or partially effective therapies that could allow the emergence of drug resistance.

To date, the success of imatinib mesylate (IM) in the treatment of chronic phase chronic myeloid leukemia (CML) remains the best example of successful targeted therapy. This is true despite challenges as a result of its toxicity profile and the finding that drug resistance does occur. IM has transformed this leukemia with a previously optimistic life expectancy of 4–6 years with interferon-based treatments (1) into a true chronic illness with overall survival rates that appear to be increasing each year. However, there are still concerns about long-term tolerability and long-term efficacy with IM. In this issue of the Journal, the article by Gambacorti-Passerini et al. (2) adds "real-life, long-term" tolerability data to

the many pieces of efficacy data that have emerged in the time since the very first phase I IM trial was published (3).

The independent, multicenter Imatinib Long Term Side Effects (ILTE) study assessed overall survival, loss of cytogenetic remission, attainment of negative Philadelphia chromosome hematopoiesis, serious adverse events (SAEs), and toxic effects not qualifying as SAEs (NSAEs) but judged by treating physicians as substantially affecting quality of life. More than 832 confirmed eligible patients were enrolled in the study, and there is now a median treatment duration of almost 6 years. The median dose of IM throughout the study was 400 mg/day with the average doses between 420 and 464 mg/day. Unfortunately, the doses reported appear to be the prescribed doses, and the study does not provide data on patient compliance, which has been a longstanding issue with tyrosine kinase inhibitor treatment in CML.

The ILTE patient population was selected to study both the durability of cytogenetic responses and the impact of any long-term side effects. The population included CML patients who initiated IM therapy before 2005 and who achieved complete cytogenetic remission by 2 years on therapy. However, only 42% of the patients were being treated with IM as their first line of therapy, and most had been previously treated with interferon. These characteristics of CML patient history–whether the patient is receiving IM as first- or second-line therapy, was treated originally with interferon, and has achieved complete cytogenetic remission by 2 years—are critically important when incorporating these data into clinical practice.

In this group of patients, discontinuation of IM was very rare, with less than 10% of patients coming off the drug and almost 25% of those doing so for the positive outcome of persistent polymerase chain reaction negativity. Discontinuation for untoward events was evenly split between general side effects (2.3%) and insufficient response (2.6%). As expected, the data demonstrated that NSAEs made up the majority of the adverse events compared with SAEs (approximately 6:1) and that, overall, IM was well-tolerated over 3247 person-years of therapy covered. The authors do suggest that the rate of IM discontinuation related to chronic NSAEs may increase over time given the more recent availability of second-generation agents. Remarkably, survival rates and the incidence of secondary malignancies in this patient cohort did not differ statistically significantly from the general population, which speaks to both the astounding effect IM has had on the clinical course of this disease and its negligible effect on the development of treatment-related malignancies, arguably the most tragic outcome of otherwise curative cytotoxic therapies.

How does this report help us to better understand the impact of single-agent TKIs in the treatment of CML? A large percentage of the study population were treated with IM as second-line therapy, the majority of whom had received prior therapy with interferon. There were no differences in the occurrence of NSAEs between patients receiving IM as first-line therapy and those receiving it as second-line therapy. However, it is not clear from the data reported whether or not SAEs were more common in patients receiving IM as first- or second-line therapy nor was it clear if prior interferon treatment improved the likelihood of achieving complete molecular remission. Long-term follow-up from early trials with single-agent interferon suggests that some patients who achieve molecular remission may be cured because they remain free of measurable disease after having stopped all therapy (4,5). Notably, the first reports of maintained molecular remissions after stopping IM suggested that prior treatment with interferon was an important factor. However, in a more recent follow-up, it is unclear that this early finding remains vital to the success of discontinuation of IM (6). A careful analysis of these two groups within the ILTE study may help to shed light on this issue.

How does this report help physicians and patients as we gravitate toward the use of second-generation TKIs as first-line therapy in newly diagnosed patients? Recent published findings (7,8) from phase III trials comparing primary therapy with each of the FDA-approved second-generation TKIs vs IM suggested that the second-generation drugs, Nilotinib and Dasatinib, were more effective based on achieving deeper molecular responses, which, until now, have been neither used nor validated as clinically meaningful primary endpoints for studies in CML. Both articles also reported little to no difference in the tolerability of each of the second-generation agents compared with IM (7,8). However, analysis of both trials has been limited by the lack of long-term outcomes and tolerability data like that provided by the ILTE study. Our group practice has continued to recommend IM as first-line therapy while waiting for more complete long-term toxicity and efficacy profiles of the second-line agents. Ultimately, the permanent designation of either (possibly both) second-generation agent as first-line therapy for newly diagnosed CML patients may depend more upon the confirmation that the rates of treatment failure from disease progression are lowered by these agents rather than simply achieving a specific level of molecular response.

Finally, how does this report help us with our focus on curing patients with CML? Although the authors did not address this in their discussion, I believe that this may be one of the most important contributions of the ILTE report. As much as any known medical therapy for leukemia, TKIs are profoundly effective drugs that induce durable responses in the majority of CML patients and do so in a tolerable manner. These agents create a platform from which we can entertain the possibility of curing CML patients outside of the setting of allogeneic stem cell transplantation. It is now time for clinical and laboratory investigators to build on this platform and work to turn good and great responses into cures. Two biologically rational approaches expected to play important roles in moving toward curing this disease are to effectively target the residual clonogenic CML stem cells that are not eliminated by TKIs (9,10) and immunomodulatory strategies that build on the curative potential of the "allo-effect" of stem cell transplants (11). Achieving states of stable minimal residual disease while leaving patients otherwise medically well, as reported by Gambacorti-Passerini et al. (2), is the ideal starting place.

References

1. Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. *N Engl J Med.* 1994;330(12):820–825.
2. Gambacorti-Passerini C, Antolini L, Mahon F-X, Guilhot F, Deininger M, Saglio G, et al. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. *J Natl Cancer Inst.* 2011;103(7). doi: 10.1093/jnci/djr060.

3. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344(14):1031–1037.
4. Bonifazi F, de Vivo A, Rosti G, et al. Chronic myeloid leukemia and interferon-alpha: a study of complete cytogenetic responders. *Blood.* 2001;98(10):3074–3081.
5. Mahon FX, Delbrel X, Cony-Makhoul P, et al. Follow-up of complete cytogenetic remission in patients with chronic myeloid leukemia after cessation of interferon alfa. *J Clin Oncol.* 2002;20(1):214–220.
6. 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. *Lancet Oncol.* 2010;11(11):1029–1035.
7. Cortes JE, Jones D, O'Brien S, et al. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. *J Clin Oncol.* 2010;28(3):392–397.
8. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med.* 2010;362(24):2260–2270.
9. Graham SM, Jorgensen HG, Allan E, et al. Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro. *Blood.* 2002;99(1):319–325.
10. Angstreich GR, Matsui W, Huff CA, et al. Effects of imatinib and interferon on primitive chronic myeloid leukaemia progenitors. *Br J Haematol.* 2005;130(3):373–381.
11. Slavin S, Naparstek E, Nagler A, et al. Allogeneic cell therapy for relapsed leukemia after bone marrow transplantation with donor peripheral blood lymphocytes. *Exp Hematol.* 1995;23(14):1553–1562.

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