Is It Downhill from Here? Eliminating Leukemic Stem Cells and Curing Chronic Myeloid Leukemia

Catherine C. Smith and Neil P. Shah

Patients with chronic phase chronic myeloid leukemia who respond to imatinib have a rapid initial decrease in BCR-ABL transcript levels (α), followed by a slow decline (β). The rate of β decrease is consistent with declining leukemic stem cells and may predict which patients may safely discontinue therapy. Clin Cancer Res; 17(21); 6605–7. ©2011 AACR.

In this issue of Clinical Cancer Research, Stein and colleagues (1) report that most patients with newly diagnosed chronic phase chronic myeloid leukemia (CML) treated with imatinib experience a biphasic decline in BCR-ABL transcripts. This decline is composed of a rapid initial decrease over months, followed by a gradual decrease over years, consistent with the hypothesis that a slow decline in leukemic stem cells (LSC) occurs in patients responding to tyrosine kinase inhibitor (TKI) treatment.

With the success of TKI therapy in achieving sustained deep molecular remissions in a substantial proportion of patients with chronic phase CML, the achievement of “cure” in some patients has become an alluring possibility to consider. Further, mounting reports (2, 3), including 1 multicenter nonrandomized clinical trial (4), suggest that some patients who experience durable complete molecular response (CMR; defined as consistently undetectable BCR-ABL transcript levels determined by a quantitative PCR test harboring 4.5- to 5-log sensitivity) may discontinue imatinib therapy without disease recurrence over several years at a minimum. The question of whether such patients are truly cured will require longer clinical follow-up. It is postulated that disease cure will necessitate eradication of long-term disease-repopulating LSCs. However, in vitro experiments have suggested that quiescent stem cells are insensitive to TKI (5).

Multiple studies have reported a biphasic dynamic of BCR-ABL transcript decline (rapid initial decline followed by more gradual decline) in most patients treated with imatinib (6, 7), which seems to be consistent with a model of swift disappearance of a cycling cell population, followed by gradual decline in a less proliferative population of cells. Stein and colleagues (1) describe BCR-ABL transcript kinetics in 477 patients with chronic phase CML enrolled in the International Randomized Study of Interferon versus STI571 (IRIS) study who had at least one BCR-ABL transcript measurement. The authors confirm that most patients are fast responders to imatinib, with more than half (59%; 282 out of 477) showing a biphasic decline in BCR-ABL transcript levels composed of a rapid slope (α), followed by a slower decline (β). The β-slope value was calculated at −0.69 per year, rendering the half-life of the slow compartment >1 year. Significantly, a steeper rate of β decline correlated with improved survival. The authors then determined whether these observations can be explained by 1 of 3 distinct models: (i) the proliferating-quiescent hypothesis, in which initial response is due to loss of proliferating LSCs and the late response is due to quiescent LSCs that die upon becoming proliferative (7); (ii) the early-stem cell hypothesis, in which initial response is due to the death of early progenitors derived from LSCs and late response is due to death of LSCs that become proliferative (8); and (iii) the late-early progenitor hypothesis, in which initial response is due to death of late progenitors evolved from early progenitors, late response is due to death of early progenitors, and LSCs are unaffected (6). Each model predicts different early progenitor kinetics, ranging from a half-life of 5 to 17 days (early-stem and proliferating-quiescent models) to a half-life of 180 days (late-early progenitor model). On the basis of experimental observations that early progenitor kinetics exist on the order of weeks (9), the authors conclude that the population responsible for the β decline must be LSCs, as they are known to persist in the bone marrow for years.

The data of Stein and colleagues (1) suggest that eventual eradication of LSCs may be possible on TKI therapy and, moreover, that patients with BCR-ABL transcript levels showing a steep β slope may be the best candidates for TKI discontinuation, as they are expected to have eliminated a larger proportion of leukemia-initiating LSCs (Fig. 1). It is important to note that discontinuation of TKI has significant implications for patients beyond the semantic definition of cure. First, the current recommendation of life-long, continuous therapy is difficult for many patients who...
experience continuing side effects, desire to have children, or simply wish to be free from daily medication. Additionally, the dramatic improvements in life expectancy of patients with chronic phase CML as a result of TKI therapy, minimizing societal costs of these TKIs becomes increasingly important. The possibility of discontinuing TKI therapy in a proportion of patients for a prolonged period, and potentially indefinitely, is therefore very appealing. The ability to accurately predict which patients may or may not experience overt disease relapse upon TKI discontinuation based on the slope of transcript decline could provide valuable direction in an area in which very little clinical guidance currently exists. However, the predictive value of any test would need to be shown prospectively using transcript levels obtained throughout TKI administration, and it would require long-term follow-up of patients after treatment discontinuation. Given the relatively indolent nature of chronic phase CML, which is believed to require years from initiation before becoming clinically apparent, the current recommendation that responding patients with chronic phase CML continue TKI therapy is not likely to change in the near future, even for patients in persistent CMR, apart from participating in clinical trials.

Another intriguing possibility is that achievement of CMR may not be necessary for long-term disease control. The current international standard for CMR is a 4.5-log reduction in BCR-ABL transcript level (0.0032% international standard), but in a study of 8 patients who maintained CMR for a median of 2 years (range, 12–41 months) after discontinuation of imatinib, a more sensitive method of detection using patient-specific PCR of genomic DNA detected persistence of BCR-ABL on one or more occasions in 7 of 8 patients, presumably indicating the presence of a nonproliferating BCR-ABL–containing cell population in these patients (10). The assumption has been that these persistent cells represent quiescent LSC, which may reactivate at any time and which may be held in check by immune-related mechanisms. However, long-lived memory T and B cells are known to persist in vivo for years. In a murine study, polyclonal naive CD4+ T cells were shown to persist for >1 year after adoptive transfer to congenic recipients (11). It, therefore, remains possible that memory T or B cells originally derived from a BCR-ABL–containing stem cell may contribute to persistence of transcripts that might gradually decline in some patients and would not be predicted to represent a source of disease relapse. To assess this possibility, TKI therapy

Figure 1. Kinetics of BCR-ABL transcript decline. 1, at diagnosis, hematopoiesis is largely driven by BCR-ABL–containing progenitors and LSCs. Upon initiation of imatinib, BCR-ABL transcript levels initially decline rapidly (α). 2, as patients reach complete hematologic and cytogenetic remission, normal hematopoiesis recovers, and the rate of BCR-ABL transcript decline slows down (β), consistent with a decline in BCR-ABL–containing LSC. 3, as BCR-ABL transcript levels become undetectable, CMR is reached. Over time, LSC may continue to decline, during which only quiescent LSC may remain (A) or may be completely eliminated (B). HSC, hematopoietic stem cell.
discontinuation studies in patients with persistent minimal-
ly detectable BCR-ABL transcript levels could be pursued.
The findings of Stein and colleagues (1) support the
possibility of eventual eradication of BCR-ABL–driven dis-
ease in patients with a deep molecular response to TKI
therapy, especially those who show a steep late decline in
BCR-ABL transcript level after a rapid initial decline. A
systematic prospective evaluation of treatment discontinu-
atation in patients with chronic phase CML who have
achieved persistent CMR (or perhaps near-CMR) on TKI
therapy coupled with correlation of the B-slope value is
warranted. The proportion of patients on imatinib with
durable CMR who would be eligible for the TKI discontin-
uation studies described previously is admittedly small, but
given the faster and deeper rates of molecular response
recently reported with frontline nilotinib and dasatinib
relative to imatinib in newly diagnosed patients with chron-
ic phase CML, safe discontinuation of therapy may be
feasible in a larger proportion of patients with chronic
phase CML in the near future.

Disclosure of Potential Conflicts of Interest

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