Front-Line TKI Therapy for Chronic-Phase CML: the Luxury of Choice

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Physicians now have the luxury of focusing attention on maximizing outcomes that are already quite favorable, and of devoting more attention to improving quality of life and addressing questions of cost-effectiveness.

The modern era of targeted tyrosine kinase inhibitor (TKI) therapy for the treatment of human malignancies was ushered in by the BCR-ABL TKI imatinib (Gleevec) in glorious fashion by Brian Druker and colleagues.[1] Upon its approval in 2001, imatinib was rapidly adopted (despite an absence of long-term outcome and safety data) as first-line therapy for newly diagnosed chronic myeloid leukemia (CML) patients in chronic phase—even for younger patients who were excellent candidates for the established curative procedure of allogeneic stem-cell transplantation. The enthusiasm for imatinib was largely based on its ease of administration, its good tolerability (particularly relative to interferon), and most notably, its efficacy. Complete cytogenetic response (CCyR), which had previously been recognized as a surrogate marker of progression-free and overall survival—and which remains a critical goal of treatment today—was achieved in the majority of patients treated with imatinib.[2] Longer-term follow-up has provided firm justification for the initial optimism regarding imatinib in cases of chronic phase CML. With 8 years of follow-up, it appears that the likelihood of dying of CML is approximately equivalent to the likelihood of dying of other causes,[3] and it is hoped that with longer follow-up and more access to effective next-generation TKIs, the majority of chronic-phase CML patients, in stark contrast to historical experience, will die of causes unrelated to CML or its treatment.

However, longer follow-up has also shown that a substantial proportion of patients discontinue imatinib because of treatment failure or toxicity.[3] It is important to note that definitions of imatinib failure have evolved as clinical trial data have matured, and many patients who continued imatinib in the landmark International Randomized Study of Interferon and STI571 (IRIS study) would have been removed relatively early for treatment failure had treatment milestones that incorporate a current understanding of imatinib failure been employed at the time. For instance, approximately 25% of patients treated with front-line imatinib fail to achieve CCyR by 18 months,[4] a widely accepted (and perhaps conservative) definition of treatment failure. While the incidence of discontinuation for imatinib-associated grade 3/4 nonhematologic toxicity is low, as Goldman and Marin state, a large proportion of patients experience bothersome grade 2 side effects (fatigue, myalgias, gastrointestinal disturbances),[4] frequently on a chronic basis. Given the current expert recommendations that imatinib should be continued indefinitely in chronic-phase CML patients who respond to and tolerate the drug adequately, the issue of lower-grade side effects takes on added significance. The welcome addition of the second-generation TKIs dasatinib (Sprycel) and nilotinib (Tasigna) have given patients more options, and in many (but not all) cases, these agents are better tolerated than imatinib. Although the follow-up data available for these agents may always be less mature compared with the data on imatinib, it should be noted that the longest presented follow-up of imatinib is 8 years,[3] whereas 6- and 4-year follow-up data for dasatinib[5] and nilotinib,[6] respectively, in the second-line have been presented. The recent anecdotal emergence of concerning post-marketing toxicities (pulmonary arterial hypertension with dasatinib,[7-9] peripheral arterial occlusive disease with nilotinib[10,11]) in patients treated with these agents needs to be kept in mind. To date, there do not seem to be serious late-emerging toxicities with imatinib, although severe side effects, such as fulminant hepatic failure, became apparent many years ago.[12,13]

Goldman and Marin have nicely summarized first-line trials of nilotinib and dasatinib, which have demonstrated that both these agents are superior to imatinib at achieving rapid cytogenetic and molecular responses.[14,15] But should these agents be used preferentially in newly diagnosed chronic-phase CML patients? The higher cytogenetic and (more convincing) molecular response rates...
associated with the newer TKIs may portend better long-term prognosis, but the available follow-up is too short to detect meaningful differences. One reasonable approach, particularly for younger patients, would be to assume that the higher molecular response rates associated with nilotinib and dasatinib will be associated with better long-term outcomes (and perhaps with more patients being “operationally cured,” as this term is defined by Goldman and Marin) when extended follow-up data become available, and to therefore preferentially treat younger patients with a second-generation TKI. However, as Goldman and Marin state, the economics of treatment decisions cannot be ignored: both nilotinib and dasatinib are more expensive than imatinib, a difference expected to become more dramatic once imatinib is no longer patent-protected in late 2015. Incorporating this concern, as well as the observation that many patients indeed do well on imatinib, an alternative approach would be to preferentially initiate imatinib, particularly in regions where cost concerns are paramount, and to switch to second-generation TKIs those patients who fail to meet an early treatment milestone (BCR-ABL transcript reduction to ≤ 10% on the International Scale at 3 months), which appears in many studies to reliably distinguish patients likely to do well on imatinib treatment. It should be noted, however, that the ability to safely discontinue TKI therapy would be predicted to offer both substantial healthcare savings and maximal quality of life to CML patients, and in this regard, the true cost-effectiveness of second-generation agents may be difficult to gauge at the present time.

Although both nilotinib and dasatinib appear to be associated with a lower incidence of blast phase transformation, the most dreaded complication of CML, the percentage of patients who may be “protected” from transformation by the newer agents relative to imatinib thus far appears to be small (~1% to 3%),[16,17] and it is reasonable to hope that a 3-month “trial” of imatinib would minimize the opportunity cost associated with initiating imatinib, with respect to disease transformation risk. In practice, this might enable identification of the ~50% of patients who are expected to do well on imatinib in the long term. Because kinase domain mutation within BCR-ABL represents a common mechanism of loss of response to TKI therapy,[18,19] from a scientific perspective, it is tempting to speculate that the newer TKIs, which are vulnerable to only ~5 different drug-resistant mutations,[20-22] will result in better progression-free and overall survival than imatinib, which is vulnerable to ~100 different drug-resistant mutations.[23] At the present time, however, there is no clinical evidence to support this prediction, given that data from only 3 years of study follow-up are currently available. It is possible that longer follow-up may reveal meaningful differences in these parameters. Should this be the case, it will be very interesting to see how the investigational third-generation TKI ponatinib fares relative to imatinib with respect to progression-free survival in previously untreated chronic-phase CML patients—since ponatinib appears to be invulnerable to single substitutions in the BCR-ABL kinase domain[24] and may therefore represent a best-in-class agent in this regard.

The availability of numerous effective TKI options is particularly good news for patients. Gratifyingly, the management of chronic-phase CML is becoming similar to that of hypertension, for which there are several effective and generally tolerable agents; having a choice of agent allows preservation of both efficacy and, importantly, quality of life. Physicians now have the luxury of focusing attention on maximizing outcomes that are already quite favorable, and of devoting more attention to improving quality of life and addressing questions of cost-effectiveness. As Goldman and Marin imply, further research is necessary to achieve these important goals.

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