First-Line Treatment for Patients With CML in Chronic Phase: Second-Generation TKIs Are the Therapy of Choice

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How often do we choose the “second best” treatment as initial therapy for our patients with cancer? The management of chronic myeloid leukemia (CML) should be no different. It is a malignancy that historically has been associated with a median survival of only 4 to 5 years from diagnosis in patients with chronic phase disease. Imatinib as initial therapy has resulted in excellent patient outcomes and has changed the treatment paradigms for CML. However, the drug is far from perfect.

From the 8-year follow-up data of the IRIS trial (unfortunately, the last data that will be available, as this study has been terminated), “only” 83% of patients achieved a complete cytogenetic response (CCyR), and approximately 15% of those who achieved a CCyR eventually lost it. CCyR is unquestionably the minimum acceptable response one should accept in the setting of frontline therapy. In addition, approximately 5% of patients are truly unable to tolerate their treatment. (I am not including here patients with chronic low-grade adverse events, even though these patients are frequently switched to a different inhibitor, often with a rapidity that might do more harm than good.) Thus, at the very least, 37% of patients have an unacceptable outcome.

The reported rate of event-free survival at 8 years is 81%, but this estimate is from a Kaplan-Meier calculation that, as we all know, overestimates the actual rate. In addition, the definition of “events” clearly leaves out instances that we all consider inadequate, such as failure to achieve a CCyR or even a major cytogenetic response, or loss of a CCyR, or intolerance. When a more comprehensive definition is used, the event-free survival rate is approximately 60% at best (with even this rate based on a Kaplan-Meier estimate). Compared with interferon, this is still an outstanding result, but we are no longer comparing newer treatment options with interferon, and we should always aim for the best outcome for all our patients.

The frequent—and valid—argument for why these events are not so dreadful is that we have excellent salvage therapy using the second-generation tyrosine kinase inhibitors (TKIs). However, what the data show is that the rate of CCyR with dasatinib, nilotinib, or bosutinib among patients who experience imatinib resistance is only approximately 40% to 45%, and it is slightly higher for patients with intolerance to imatinib. Of course, many patients who achieve these responses eventually lose their response, leaving us with at best the ability to rescue approximately one-third of the patients with imatinib failure. A third-line TKI provides even lower response rates, and these tend to be of much shorter duration. If we consider a good outcome for only approximately 70% of our patients as acceptable, we should probably refocus our thinking.

In CML, the objective is long-term benefits. These are not seen in the first 2 or 3 years or even 5 to 7 years of treatment. We should aim for normal life expectancy for all patients. We know from single-arm studies, and particularly from randomized trials, that second-generation TKIs provide improved results in every category that is relevant: rates of CCyR, major molecular response, time to response, rate of transformation, etc. For example, for one of the recent darlings of “optimal response” for CML patients, the response at 3 months, the rate of patients with the “evil” of a BCR-ABL transcript level >10% (or the gross equivalent, lack of a major cytogenetic response) at this timepoint is at least twice as high with imatinib compared with the new agents, and these imatinib-treated patients have a significantly worse outcome. Also, what many now consider the new...
goal of therapy, complete molecular response, is also much more commonly achieved with any of the second-generation TKIs than with imatinib. True, there is not yet a survival benefit for patients treated with these options rather than imatinib, given the short follow-up period available, but it is not unreasonable to expect to identify a survival benefit sometime in the future. Thus, I believe these agents take us closer to our goal of optimal outcome for all patients with CML. If I were a patient with CML, I would definitely take one of these TKIs as initial therapy, instead of taking a chance that my pinch hitter (imatinib) will bail me out.

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