Which TKI Should Be Recommended as Initial Treatment for CML in Chronic Phase?

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Resistance due to new mutations in the genes coding for the targeted proteins, as well as to changes in other signaling pathways, often develops, and newer drugs and perhaps combination approaches may be needed.

The lessons learned from the specifically “targeted” treatment of patients with chronic myeloid leukemia (CML) using imatinib (Gleevec) are now being applied with sometimes dramatic success in a variety of other tumors in which critical driving mutations have been identified, including some, such as malignant melanoma and lung cancer, that are notoriously resistant to other treatments. Sadly, but as might have been predicted from the experience in more advanced-stage CML, resistance due to new mutations in the genes coding for the targeted proteins, as well as to changes in other signaling pathways, often develops, and newer drugs and perhaps combination approaches may be needed.

The overall results with tyrosine kinase inhibitors (TKIs) in CML in chronic phase remain excellent, however, and Drs. Goldman and Marin nicely summarize the results of current treatments and the dilemmas posed by the availability of three (and perhaps soon four) alternatives to imatinib—although they do not actually tell us what they would recommend to the next newly diagnosed patient whom they will see in their practice. Some points of reference for my further discussion:

1. Approximately 60% of newly diagnosed CML patients will remain in complete cytogenetic remission and continuing on imatinib 5+ years after treatment is begun, with an extremely low rate of relapse if they continue to take the drug.[1] Some patients will have variably bothersome symptoms, particularly fatigue and muscle cramps, although serious late side effects have not occurred with now up to 12 years of follow-up.

2. With the recent US Food and Drug Administration (FDA) approval of bosutinib (Bosulif) for patients with CML who do not respond to or who are intolerant of imatinib, there are now three drugs available for second-line treatment. Approximately 40% to 50% of patients treated with these drugs will achieve complete cytogenetic responses, with occasional patients responding to an alternative tyrosine kinase inhibitor (TKI) as third-line therapy if particular BCR/ABL kinase mutations are present.[2-5] Responses have been higher in the patients who were intolerant of imatinib and seem to be durable. Of interest is that, at least in my experience, most patients who are switched report that they have fewer constitutional symptoms than they had with imatinib. Among the newer TKIs, the longest reported follow-up is with dasatinib (Sprycel), and although progression-free survival is ~60% at 6 years, only about 30% of the original cohort of patients are continuing to receive dasatinib.[6] Thus, there are still a significant number of chronic-phase patients with unsatisfactory outcomes using the treatment sequence of imatinib followed by an alternative TKI if needed, with poorer results in patients who present in advanced chronic or accelerated phases. We do not know whether the outcome would be better using the more potent TKIs as initial therapy. Randomized trials comparing imatinib to dasatinib or nilotinib (Tasigna) or bosutinib have shown very similar results, with molecularly deeper and more rapid responses using the newer drugs, although in some trials the differences became smaller with longer follow-up.[7-9] Again, as was noted above regarding the use of these drugs in the second-line setting, ~25% of patients were no longer receiving the second-generation drugs within 1 to 2 years of follow-up, because of either side effects or worsening disease. Unfortunately, as is common in pharmaceutical company-sponsored trials, there is less detailed follow-up of the patients who went “off study.” One could surmise that patients intolerant of treatment were switched to imatinib or dasatinib/nilotinib; it is not obvious how to manage patients whose disease progressed on the newer agents except for the use of experimental treatments or referral for allogeneic transplant.

The overall survival in chronic-phase patients in whom TKI therapy has “failed” remains around 60%
to 70+%[6]—considerably higher than would have been expected in the pre-TKI era—and it is of interest to speculate that exposure to TKIs somehow slows the rate of acquisition of the additional mutations associated with blast crisis. Nonetheless, it is likely that the “clock is ticking” in patients without sustained complete cytogenetic responses. It is not unusual in oncology (as in medicine generally) to have to make recommendations about treatment based on incomplete data and/or imperfect trials—or in the case of chronic diseases such as CML, on the basis of relatively short follow-up. Based on the consistency among the three randomized trials,[7-9] I generally recommend either dasatinib or nilotinib to newly diagnosed patients and certainly to all patients who present with more advanced chronic-phase disease as defined by Sokol risk group. The efficacy results do not favor one drug or the other; the choice is occasionally governed by the presence of pretreatment conditions that might favor one of the drugs over the others on account of their differing toxicity profiles. We have noted that some patients express a preference for the more convenient once-a-day dosing with dasatinib. One factor affecting treatment decisions, somewhat unique to the United States, is the variable and sometimes appreciable size of patient co-pays for outpatient anticancer drugs. If patients expect to have sizable out-of-pocket costs, I am comfortable with starting with imatinib and switching if necessary. Certainly, this will become an even more important societal issue when generic imatinib becomes available, with a presumed (and hopefully major) decrease in the cost of this agent. Hopefully, at that time, we will have more mature follow-up data from the randomized trials and perhaps better criteria for selection of patients who can do well on imatinib alone.

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## References

**REFERENCES**


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