Chronic Myeloid Leukemia: Changing the Treatment Paradigms

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Molecular discoveries and clinical advances over the past few decades have made the treatment of chronic myeloid leukemia (CML) one of the great success stories of modern medicine. Before the 1980s, the focus was on maintaining normal white blood cell counts with agents such as hydroxyurea and busulfan. With the use of interferon, treatment strategies turned more toward cytogenetic remission. In 1998, targeted therapy was introduced to this setting with the first studies of imatinib mesylate. Since then, treatment objectives have shifted toward the attainment of molecular remission. In this review, we consider the variety of approaches to treating CML, efforts to minimize treatment failures, and possible future directions in therapy.

When Drs. Nowell and Hungerford first suggested a causal relationship between a chromosome abnormality and chronic granulocytic leukemia[1] (now termed chronic myeloid leukemia, or CML), an era of cancer genetics began. Over the course of the next 20 years, the Philadelphia chromosome, named after the city where it was discovered, became the hallmark of CML, and the focal point for many discoveries. In 1973, it was defined as t(9;22), a reciprocal chromosomal translocation.[2] A decade later, laboratories in the Netherlands and the United States localized the ABL proto-oncogene on chromosome 9 and the breakpoint cluster region (BCR) on chromosome 22 as focal points of the fusion gene product.[3-5]

Subsequent molecular discoveries and clinical advances have made the treatment of CML one of the great success stories of modern medicine. The development of therapy for CML in the clinic largely matches the scientific discoveries in the laboratory. Before the 1980s, the focus was on maintaining normal white blood cell counts, typically with hydroxyurea and busulfan (Myleran). In the era of interferon, cytogenetic remission became the focal point of therapy. Targeted therapy was introduced in 1998 with the first studies of imatinib mesylate (Gleevec), and since then, the objectives of therapy have rapidly shifted toward the achievement of molecular remission.

Interferon and Bone Marrow Transplantation

In 1983, interferon-alpha was first found to have activity against CML.[6] This finding was quickly expanded, and in early studies, hematologic and cytogenetic responses of 71% and 39%, respectively, were reached.[7] Randomized studies comparing interferon-alpha to traditional chemotherapy with busulfan and hydroxyurea echoed these findings; interferon-alpha prolonged the time to disease progression by 28 months and led to some long-term complete responses.[8] Dormant myeloid progenitors were seen in CML patients with interferon-alpha-induced remissions, and immunologic mechanisms leading to tumor dormancy were proposed as a cause of sustained remission with interferon-alpha therapy.[9] Indeed, long-term remissions off therapy, perhaps indicative of cure, were noted in 7.6% of the interferon-treated patients.[10]

Bone marrow transplant (BMT) is not intended to be a primary topic of discussion in this review (which focuses on nontransplant therapeutic approaches), but it is important to recognize the role of BMT in the management of CML. In some patients, BMT offered durable, long-term remissions, and in a significant proportion of patients who were candidates for transplant, the procedure was curative. The scope of BMT remained limited, given the restricted availability of matched-sibling and unrelated donors and the associated transplant-related morbidity and mortality.[11-13] A regimen of interferon alfa-2b (Intron A) plus cytarabine offered the first real survival advantage in the treatment of CML,[7,14] and this approach was augmented by judicious use of transplantation, which still provides benefit in select patients who fail targeted therapy.

Molecular Advances: The Imatinib Era

Lugo et al discovered a relationship between cell-signaling via BCR-ABL tyrosine-kinase phosphorylation and the generation of oncogenic protein products in the BCR-ABL cells.[15] Resulting drug development targeted this specific tyrosine kinase. In vitro screening for a selective BCR-ABL tyrosine inhibitor led to the discovery of molecules with inhibitory effects on BCR-ABL cells in vitro[14,16] and further development of STI571, or imatinib, which was first used successfully in a phase I trial published in 2001.
In this study, 53 of 54 patients receiving more than 300 mg of imatinib daily achieved a complete hematologic response.[17] This activity was later confirmed in phase II studies.[18-20] CML patients in chronic phase who had been previously treated with interferon-alpha had remarkable remission rates with imatinib, and the US Food and Drug Administration (FDA) approved the drug for treatment of previously treated CML patients.[21,22] Imatinib was then explored in newly diagnosed CML patients in the ongoing controlled study IRIS (International Randomized study of Interferon-alpha plus cytarabine vs STI571), which compared imatinib to standard of care-interferon alfa-2b plus cytarabine. Imatinib was approved as first-line therapy for CML after interval results in this trial exhibited significantly higher rates of complete cytogenetic response in the imatinib group (81% vs 32%) and an improved toxicity profile.[10,23,24]

At the time of the initial interval IRIS results, we had limited information on the durability of the remissions, the impact on survival, and the nature of resistance. With almost 5 years of follow-up since the start of the IRIS study, the natural history of the disease with imatinib therapy is better articulated. Complete hematologic response rates have surpassed 90%, and over 86% of newly diagnosed CML patients have achieved a complete cytogenetic response, with an additional 6% developing a partial cytogenetic response while on imatinib (Figure 1).[25] Since the outset of the IRIS trial, approximately 4% of patients have developed resistance or progression annually. These risks are reduced among patients with a complete cytogenetic response, but significantly increased in those who do not have at least a partial cytogenetic response. With only 5 years of follow-up, the long-term outcome of therapy is still unknown, but the impact of imatinib on survival, thus far, appears to be dramatic.

Minimizing Treatment Failures

As relapse to accelerated phase or blastic crisis is associated with incomplete cytogenetic response, increasing the rates of complete cytogenetic and molecular responses has been the goal. First attempts at this were done with imatinib dose escalation. The maximal tolerated dose of imatinib was not reached in the initial phase I trial of the drug, and standard 400-mg once-daily dosing has not been established as the optimal therapeutic dose. In a recent single-arm study, high-dose imatinib (400 mg twice daily) led to a 38% complete molecular response rate.[26] This represents a sixfold increase over historical data in patients treated with 400 mg once daily,[23] and has led to the design of a multicenter randomized study comparing the two dose schedules.
Overcoming resistance to imatinib was also shown in a study incorporating dose escalation to 1,200 mg,[27] and a recent phase II study showed greater than a 40% improvement in major molecular response at 24 months' follow-up among patients receiving imatinib ≥ 600 mg daily vs those receiving imatinib ≤ 600 mg daily over the course of the initial 12 months of therapy.[28] Early utilization of high-dose imatinib may improve the overall molecular response rate, reduce the risk of the emergence of imatinib-resistant clones, and overcome relatively resistant cell clones, which seem to respond in a dose-dependent manner.[29] The gains need to be weighed against the increased toxicity profile and rates of compliance.

Some imatinib resistance cannot be overridden by increasing imatinib doses, however, and these resistant clones are commonly seen in relapsing and progressive disease.[30] Imatinib resistance has most commonly been associated with a rise in BCR-ABL protein products, loss of complete cytogenetic response, and increase in white blood cell counts.[31,32] This resistance is frequently due to point mutations within the ABL kinase domain. Over 30 such mutations have been identified, and they lead to mutant ABL kinase that adopts a conformational change in the kinase domain and subsequent destabilization of the binding complex, which may sterically block imatinib from the binding site.[30,33] These mutant BCR-ABL clones have led to the development of more potent, "second-generation" selective kinase inhibitors.

**Next-Generation Agents**

Two of these agents—nilotinib (AMN107) and dasatinib (BMS 354825)—are currently under clinical investigation. Nilotinib is a relatively selective BCR-ABL tyrosine kinase inhibitor, which binds to the inactive conformation of the ABL kinase with 30-fold more potency than imatinib. In contrast, dasatinib is a dual SRC kinase and ABL kinase inhibitor that binds to the ABL kinase in its inactive and active conformation with 325 times the inhibitory capacity of imatinib.[34] Both of these agents have exhibited activity in in vitro and in vivo preclinical cell proliferation and phosphorylation studies against all imatinib-resistant BCR-ABL mutants, with the exception of T315I.[34-36] Dasatinib also inhibits SRC kinases, which are cell-signaling molecules that have independent oncogenic potential in CML.[37]

In separate phase I trials, the use of nilotinib and dasatinib in imatinib-resistant (or intolerant) CML patients has revealed nearly 90% hematologic response rates in the chronic phase of CML, and substantial activity in the advanced stages of the disease.[38,39] The phase II trials (SRC-ABL Tyrosine kinase inhibition Activity Research Trials, or START studies) of dasatinib for imatinib-resistant chronic phase, accelerated phase, myeloid blast crisis, and Philadelphia chromosome-positive acute lymphocytic leukemia show similarly positive preliminary results.[40-42] BCR-ABL mutant T315I confers a particular conformational change and subsequent hindrance to imatinib, nilotinib, and dasatinib from their shared target within the ATP-binding pocket. A search for new inhibitors that overcome or avoid this hindrance is underway, and early potential successes are described below. Further Considerations of Imatinib Resistance

Although the data suggest a marked prolongation of survival with imatinib therapy, there is growing evidence that the malignant clone is not fully eradicated in the majority of patients.[23,43-45] Furthermore, the cessation of imatinib therapy, although not extensively studied, seems to lead to molecular and cytogenetic recurrence.[46,47] Given the frequent relapse after cessation of imatinib therapy in patients with a complete molecular response, imatinib seems unlikely to be a curative therapy for CML. Rather, when given as single agent, imatinib appears to be more precisely a suppressive therapy.

Although greater than 90% of CD34+ cells are sensitive to imatinib in a dose-dependent manner, the primitive CML self-renewing stem cells are refractory to the inhibitory effect of imatinib.[43,48] Holyoake et al recently demonstrated that CD34+ cells are more sensitive to dasatinib than to imatinib. In these experiments, however, the most primitive, quiescent CD34+/CD38− cells were not affected.[48] This work provides an explanation for the presence of a residual imatinib-refractory population of cells, and it suggests a lack of sensitivity of BCR-ABL kinase to the effect of kinase inhibitors in these cells. Further investigation of the CML stem cell should lead to additional clinical advancements.

**Future Directions**

Imatinib has altered the natural history of CML. It is probably the most cogent example of therapy directed against a dominant, oncogenic target. Challenges today concern CML that escapes suppression via imatinib (ie, resistance) and how to deal with minimal residual disease. As discussed above, second-generation ABL kinase inhibitors can overcome imatinib resistance in most patients with chronic phase CML and in some patients with advanced stages of the disease. Clinically, their effect on primitive CML stem cells remains in question. Further, the limited experience with these
agents prohibits conjecture as to disease response when therapy is stopped after complete molecular response is reached. The tyrphostin kinase inhibitor adaphostin (NSC680410) was originally developed to compete with substrate, rather than ATP at the BCR-ABL tyrosine kinase binding site, but it has also been found to have BCR-ABL-independent efficacy through reactive oxygen species. It has been found effective against wild-type BCR-ABL and all known mutations including T315I.\[49\] GNF-2, which inhibits the Abl-kinase via an allosteric, non-ATP-competitive mechanism, may be another agent with potential to overcome resistance induced by T315I mutations.\[50\] Additional small molecules targeting the BCR-ABL-signaling pathway are under development as well.\[51\]

In conclusion, targeted therapy has provided a minimally invasive mechanism to suppress CML in most patients, but for the reasons mentioned above, cure has not been seen with this treatment. Given a developing armamentarium of targeted therapies to quiet active disease, new clinical focus should be on the development of therapy to cure CML. Exploring the nuances of allogeneic stem cell transplant and interferon-alpha therapies against the CML stem cell requires rigorous study. These therapies have yielded the only reported cures of this disease. Clinical trials combining the use of targeted therapy to achieve a complete molecular response, followed by interferon alfa-2b to eradicate the malignant CML stem cell, are now underway.

**Disclosures:**
The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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