

Editorial

Imatinib Therapy for Patients with Chronic Myelogenous Leukemia: Are Patients Living Longer?

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Chronic myelogenous leukemia (CML) is a clonal hematopoietic disorder characterized by the reciprocal translocation involving chromosomes 9 and 22. As a result of this translocation, a novel fusion gene, BCR-ABL is created and the constitutive activity of this tyrosine kinase plays a central role in the pathogenesis of the disease process. Without bone marrow transplantation, the median survival among patients with CML has previously only been 3–5 years. The majority of deaths arise from progression to advanced-stage disease characterized by rapid proliferation and blastic transformation to either myeloid or lymphoid blast crisis. Once patients enter the terminal blast stage, conventional treatments are ineffective, and expected survival is very short.

Imatinib mesylate (Gleevec) is a tyrosine kinase inhibitor that interferes with the enzymatic activity of the BCR-ABL gene product. By inhibiting BCR-ABL kinase activity, imatinib effectively blocks the proliferation signal within leukemic progenitor cells and induces apoptotic cell death in cells expressing this activated kinase (1). Imatinib thus leads to rapid and selective CML cell death *in vitro* and *in vivo*, and the clinical effectiveness of this new agent has been demonstrated in large-scale clinical trials (2). In 454 patients with chronic phase CML who were refractory or intolerant to IFN- α , 95% of patients achieved a complete hematological remission, 60% achieved a major cytogenetic response, and 41% achieved a complete cytogenetic remission when treated with imatinib. In this study, the 18-month progression-free survival was 89%, and overall 2-year survival was approximately 95%. Only 2% of patients stopped treatment with imatinib because of drug-related toxicities. These impressive results were confirmed in the International Randomized Study of IFN *versus* STI571 (IRIS). In the IRIS study, 1106 patients with newly diagnosed chronic phase CML were prospectively randomized to receive either imatinib or IFN plus cytarabine (3). The complete cytogenetic remission rate was 73.8% for patients receiving imatinib compared with only 8.5% for patients on IFN plus cytarabine. Because of the

superior response rates and excellent tolerability of imatinib, the majority of patients initially assigned to receive IFN plus cytarabine subsequently switched to imatinib. The median duration of therapy for the IFN plus cytarabine group was only 8 months. Due to the high crossover rate, it is not likely that a significant difference in survival will ever be observed in the IRIS study.

Before the development of imatinib, the majority of patients with chronic phase CML who were not candidates for stem cell transplantation were treated with IFN, with or without cytarabine. This was based on the results of prospective randomized trials that demonstrated the superiority of IFN therapy to treatment with either hydroxyurea or busulfan (4, 5). In these studies, IFN therapy not only delayed the time of disease progression but also prolonged overall survival. Although only a small fraction of patients treated with IFN achieved a complete cytogenetic remission, the demonstration of improved survival in prospective randomized trials established IFN as the standard therapy for chronic phase CML.

Although imatinib clearly provides a higher likelihood of achieving complete cytogenetic remissions than IFN, for reasons noted above, it is not likely that improved survival will ever be demonstrated in prospective randomized trials. For this reason, Kantarjian *et al.* (6) undertook a detailed analysis of survival after imatinib therapy in comparison with historical results in similar cohorts of patients. As reported in this issue of *Clinical Cancer Research*, two historical groups were selected for analysis. The first group included 204 patients with early chronic phase CML treated with IFN-based regimens at M. D. Anderson between 1982 and 1992. The second group included 95 patients in late chronic phase who received IFN-based regimens after previous therapy with non-IFN regimens. In both cases, results were compared with patients who received imatinib after being refractory or intolerant to IFN. Although both historical groups were not entirely similar to the imatinib treatment groups, both early and late chronic phase groups are sufficiently similar to allow a valid retrospective comparison. In both comparisons, imatinib therapy was associated with a significant improvement in survival. Importantly, improved survival with imatinib becomes evident within the first 2 years of therapy and was found even though the control groups included some patients who had gone on to receive allogeneic stem cell transplants.

In a recent report, Marin *et al.*, (7) also undertook a retrospective comparison of 143 patients treated with imatinib after failure of IFN with 246 control patients who received conventional therapy. This study also demonstrated a survival advantage for patients who received imatinib, but this was found primarily in patients who achieved a cytogenetic response after 6 months of therapy. Cytogenetic responders represent the majority of patients receiving imatinib, but patients in the Hammersmith study who did not achieve a cytogenetic response after 6 months of imatinib had worse survival than historical controls

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(7). Kantarjian *et al.* also examined this specific issue with different results. Imatinib treated patients in the M. D. Anderson study had improved survival whether or not they had achieved a cytogenetic response. Although further follow-up of imatinib-treated patients is certainly necessary, both retrospective studies provide convincing evidence that imatinib therapy provides a survival advantage for both early and late stage chronic phase CML. When combined with the single large prospective randomized study demonstrating vastly superior cytogenetic responses and markedly lower levels of minimal residual disease with imatinib, there is little doubt that imatinib should now be established as “standard” therapy for chronic phase CML in patients not eligible for stem cell transplantation.

Having demonstrated the clinical superiority of imatinib therapy for chronic phase CML, there still remain many unresolved issues. One important issue is the persistence of minimal residual disease and durability of cytogenetic and molecular responses in patients responding to imatinib. Previous studies using quantitative PCR demonstrated a 2-log reduction in BCR-ABL transcripts after 1 year of imatinib therapy in cytogenetic responders that was not seen in cytogenetic non-responders (8). Quantitative PCR monitoring in the IRIS study showed that complete cytogenetic remission with imatinib was associated with a 2.5-log reduction in BCR-ABL transcripts (9). Continued treatment with imatinib resulted in further reductions in minimal residual disease, but few, if any, responding patients actually become PCR negative for BCR-ABL transcripts during imatinib therapy. Increasing numbers of patients may become PCR negative with more prolonged imatinib treatment, but thus far >95% of responding patients continue to have evidence of minimal residual disease after 2 years of treatment. Some of these patients will undoubtedly develop imatinib-resistant disease, but previous experience with assessment of minimal residual disease after allogeneic stem cell transplantation suggests that low levels of PCR-detectable disease in CML precursor cells can persist for many years in some patients without progression to clinical relapse (10). Further follow-up of the large numbers of patients enrolled on all of the imatinib trials will be needed to accurately define the durability of response to this potent therapeutic agent for chronic phase CML.

Because almost all imatinib responders continue to have evidence of persistent disease, many efforts are underway to develop strategies for elimination of minimal residual disease in these patients. These include evaluation of higher-dose imatinib regimens, use of other agents in combination with imatinib, additional BCR-ABL kinase inhibitors, and a variety of immunological approaches. Since residual CML cells appear to be particularly sensitive to immunological targeting by donor B cells as well as T cells after allogeneic stem cell transplantation (11), it is hoped that immunological approaches will be similarly effective in imatinib responders.

Establishing the clinical superiority of imatinib over conventional therapy does not entirely resolve the issue of when to recommend potentially “curative” allogeneic stem cell transplantation for patients with chronic phase CML. Although the toxicity associated with allogeneic stem cell transplantation continues to improve, this remains an intensive treatment mo-

dality associated with significant morbidity and mortality. Ideally, close monitoring of response to imatinib might identify those individuals who are not likely to have long-term benefit from this treatment. Recent analysis of quantitative PCR monitoring for BCR-ABL transcripts in the IRIS study found that 100% progression-free survival was maintained in complete cytogenetic responders who achieved at least a 3-log reduction in BCR-ABL transcripts. Progression-free survival was significantly worse in patients who achieved a <3-log reduction in BCR-ABL transcripts, but this was still associated with a 95% progression-free survival at 24 months. The small difference in progression-free survival between these two groups based on the level of molecular remission is not likely to be sufficient to discontinue imatinib in favor of allogeneic stem cell transplantation. However, these observations suggest that it may be possible to identify individuals at high risk for imatinib failure based on close monitoring of the quantitative response to imatinib. Additional studies characterizing outcomes based on the extent of both cytogenetic and molecular response will be necessary to identify these parameters and establish their impact on long-term survival for patients with CML in the post-imatinib era.

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