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Chronic Myeloid Leukemia in the Imatinib Era

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The results of imatinib (Gleevec) (formerly STI571) therapy for chronic myeloid leukemia (CML) have continued to improve and have surpassed almost everyone's predictions. However, the long-term results with imatinib and its ability to cure CML as a single agent are unknown. These issues will be discussed along with potential strategies to improve the cure rate, using imatinib as a building block to achieve this goal.

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THE RESULTS of imatinib (Gleevec or Glivec, Novartis, Switzerland) (formerly STI571) therapy for chronic myeloid leukemia (CML) have continued to improve and have surpassed almost everyone's predictions. From phase I to phase II trials of chronic phase patients who failed interferon therapy, the complete cytogenetic response (CCR) rate increased from 13%³ to 41%,⁶ and in phase III studies, 68% of newly diagnosed chronic phase patients achieved a CCR.² Further, with a progression-free survival rate of 98.5% in the first year of therapy and an overall survival rate of greater than 99%, it is hard to argue against using imatinib as front-line therapy for most, if not all, newly diagnosed chronic-phase CML patients. The data from the phase III study served as the basis for regulatory agencies in the United States and Europe to approve the use of imatinib for newly diagnosed chronic-phase CML patients.

Many have said that the main unanswered question for imatinib is the durability of cytogenetic responses. If CCRs to imatinib are not durable, then there is obviously much room for improvement. But, if CCRs are as durable as they are for interferon, then the majority of patients with CML would have a life expectancy of greater than 10 years. Thus, imatinib could become much like insulin for a diabetic. This is a major advance. But is this good enough? Would diabetic patients rather take insulin for the rest of their lives or be cured? Similarly, would a CML pa-

tient really want to take imatinib for a lifetime? Would there be side effects from long-term therapy? Would resistance eventually develop? My belief is that we are dealing with a formidable enemy that under selective pressure will develop resistance and that most patients would opt for curative therapy, especially if there were a relatively nontoxic cure. However, if cytogenetic responses are quite durable, how much toxicity is acceptable to achieve a cure? Equally as important, are there prognostic features that correlate with duration of cytogenetic responses to assist in identifying patients that would be the best candidates for more aggressive therapy? One of the issues that will also need to be addressed is whether molecular negativity is a more appropriate goal for therapy or whether specific levels of positivity would

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predict the likelihood of relapse. Specifically, if a threshold level or lower is obtained, would relapse become unlikely, or do patients need persistent polymerase chain reaction (PCR) negativity to be cured, or will even PCR-negative patients relapse and after how long?

The assumption from the preceding paragraph is that imatinib as a single agent, at 400 mg per day, while highly efficacious, may not be a curative therapy for the majority of CML patients. So how do we cure more patients? Ideally, the first step would be to determine why patients have persistent, low levels of leukemia while on therapy with imatinib. Among newly diagnosed, chronic-phase CML patients, 68% achieve a CCR, but less than 10% become PCR-negative for transcripts, at a level of detection of one cell per million. Why do these cells persist? Are stem cells resistant to imatinib due to quiescence?⁴ Do high levels of P-glycoprotein expression on stem cells mediate resistance? Could low levels of kinase activity prevent cells from proliferating, but not induce apoptosis? Are there point mutations in the ABL kinase, as seen in relapsed patients, that are insensitive to imatinib? If this is the case, are these mutant kinases less pathogenic or partially sensitive to imatinib, thus accounting for long times to relapse? If we understand the mechanisms that allow persistence of the positive clone, we should then be able to design rational strategies to eradicate the disease. This could include treatments that induce cellular proliferation, P-glycoprotein inhibitors, more potent ABL kinase inhibitors, or combinations of ABL kinase inhibitors.

In the meantime, empirical approaches will be tried. The current favorites include high-dose imatinib, and imatinib in combination with interferon or cytarabine. Each of these approaches has some attractive features. High-dose imatinib, 600 or 800 mg, has shown some promise,⁵ but if cellular quiescence is a major mechanism of persistence, then this approach is unlikely to yield significantly better results than the standard dose.

The combination of interferon and imatinib is attractive as it combines the best two nontransplant therapies. Presumably, by attacking the leukemia with two different agents, cross-resistance would be prevented. Preliminary experience with this combination has shown that imatinib at 400 mg with low doses of interferon is reasonably well tolerated, but is quite myelosuppressive.^{7,8} One of our thoughts is to add granulocyte-macrophage colony-stimulating factor (GM-CSF) to imatinib plus interferon, as data suggest that results for the combination are better than with interferon alone.⁹ GM-CSF, by providing a growth stimulus, might overcome resistance due to quiescence. The other attractive feature of GM-CSF is its ability to stimulate dendritic cells that could present CML antigens. In addition, most patients

with a specific human leukocyte antigen (HLA)-type treated with imatinib do not develop immunity to a myeloblastin-derived nonapeptide, while patients treated with interferon do.¹ Thus, interferon in combination with imatinib could induce tumor immunity; however, the sequencing of the combination might be important to observe this effect.

The combination of imatinib with cytarabine also has the advantage of attacking the leukemia by two different mechanisms. In the HOVON study (Dutch Hematology Association), intermediate doses of cytarabine are being used, which puts significant regenerative pressure on the marrow. Again, if cellular quiescence is a major mediator of disease persistence, then this approach could be extremely successful. To evaluate the possibilities discussed above, a prospective, randomized phase III trial has been designed to compare standard therapy for newly diagnosed chronic-phase CML patients treated with 400 mg of imatinib per day to higher dose therapy, versus imatinib at 400 mg/d with interferon, versus 400 mg/d of imatinib with low-dose cytarabine. This study is expected to be activated in 2003.

However, it would seem that the best approach to curing CML would be to combine the best two therapies, imatinib plus allogeneic stem cell transplantation, for those patients who are potential allogeneic transplant candidates. The success of transplantation is dependent on alloimmunity. This is most evident from the data for identical twin transplants and T-cell-depleted transplants, where relapse rates are significantly higher. Ideally, the precise determinants on a CML cell that are required for alloimmunity would be identified and this information would be used to generate specific immunotherapy. In the meantime, allogeneic stem cell transplants are becoming safer. For example, complications from high-dose therapy can be minimized in nonmyeloablative stem cell transplants, but graft-versus-host-disease continues to be a significant problem. An approach that we are exploring is whether graft-versus-host disease could be lessened with a partial T-cell depletion. The relapse rate would be higher with a T-cell-depleted transplant. However, if patients were treated to minimal residual disease with imatinib, then underwent a nonmyeloablative, T-cell-depleted transplant, this might be sufficient to eradicate minimal residual disease. If necessary, T-cell infusions could be provided post-transplant, after chimerism is established. If the mortality from this procedure were 5% or less, and a high rate of durable molecular remissions were achieved, this would be an extremely attractive treatment approach.

Even if imatinib is not curative as a single agent, it is a quantum advance in the treatment of CML and the prospect for a cure of this disease is closer than ever.

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