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.

We have seen considerable progress in recent years in the management of malignant disease in general, but in few areas has the progress been quite as remarkable as in the management of chronic myeloid leukemia (CML). At one time, treatment of CML consisted primarily of chemotherapy, which changed the natural history of the disease little if at all. This evolved to a time when selected patients could be treated and often "cured" by allo-geneic stem cell transplantation (allo-SCT). Most recently we have witnessed the introduction of molecularly targeted therapy—with results well summarized in the accompanying paper by Savona and Talpaz—which seems to offer the prospect of substantial prolongation of life for the majority of patients ineligible for transplant. Indeed, this approach has been so successful that it has displaced transplant as primary therapy for all but a very few patients.

In this paper, I will briefly summarize memories of treatment with busulfan (Myleran), hydroxyurea, and interferon-alpha, outline the role of allo-SCT in the 1990s, and speculate about the direction of further therapy.

End of the 20th Century
In the 1970s, there was universal agreement that CML was inexorably fatal. Moreover, it is worth noting that few hematologists at the time even considered the possibility that it might be curable. The usual approach on both sides of the Atlantic was to administer busulfan,[1,2] but with caution, because it was well recognized that overdosage could induce an irreversible bone marrow aplasia. Some suspected that busulfan, a known mutagen, might actually expedite blastic transformation, but this was not widely regarded as a contraindication to its use. Hydroxyurea was preferred by some,[3] but the fact that the leukocyte count rose so rapidly if hydroxyurea was interrupted for any reason was regarded as a disadvantage.

The demonstration in 1979 by Fefer and colleagues in Seattle that patients with CML in chronic phase achieved complete cytogenetic remission after high-dose chemotherapy and transplant of hematopoietic stem cells from their respective identical twins was an important landmark in the management of CML.[4] This led rapidly to the design and implementation of programs to treat CML in chronic phase by allo-SCT using HLA-identical siblings and HLA-matched unrelated donors. It gradually became clear that although transplant-related complications and mortality remained risks for patients undergoing the procedure, relapses were comparatively infrequent, and many patients became long-term leukemia-free survivors. For the next 20 years (1980-2000), treatment policy for patients with CML involved transplant if possible and interferon-alpha, alone or in combination with other agents, for those deemed ineligible for transplant on grounds of age or absence of a suitably matched donor.

The use of interferon-alpha purified from lymphoblastoid cell lines was introduced by Talpaz and colleagues in Houston in 1983.[5,6] Interferon-alpha was relatively toxic, in both the short and long term, but it induced durable Philadelphia chromosome (Ph)-negativity in a significant minority of patients, who survived substantially longer than those who achieved no cytogenetic benefit. Of great interest was the observation that a small percentage of patients who achieved Ph-negativity...
continued in complete cytogenetic remission even after the drug was stopped.[7] Efforts to improve the results of standard-dose interferon-alpha involved escalating the dosage and adding other agents, such as cytarabine, but the real benefit of these approaches was small or nonexistent.[8,9]

State of the Art
The pharmaceutical company Ciba-Geigy (now Novartis) initiated a program in the early 1990s to identify small molecules for clinical use that might inhibit relevant tyrosine kinases. At the time, many observers expressed doubts as to whether such a program could ever yield useful information or therapeutic agents. However, Brian Druker, then at the Dana-Farber Cancer Institute in Boston, directed the attention of scientists at Ciba-Geigy to the crucial role of the BCR-ABL gene in CML, and after some years of work on the lead compound, the result was an agent (CGP57148B) that appeared to selectively inhibit the proliferation of CML cell lines while leaving control lines unaffected.[10-13] The compound, then renamed signal transduction inhibitor (STI)571, was first used to treat CML patients judged to be resistant to interferon-alpha in June 1998, and within a few months it was clear that it could induce Ph-negativity in a relatively high proportion of those who received higher doses of the agent.[14] This led to the launch of a prospective randomized trial for patients newly diagnosed with CML in chronic phase who received either STI571, now renamed imatinib mesylate (Gleevec), or the combination of interferon-alpha plus cytarabine as primary therapy.[15] The comparative toxicity of the control arm and the speed with which patients treated with imatinib obtained chromosomal responses led to a high rate of crossover from the interferon-alpha/cytarabine arm to the imatinib arm, and as a prospective comparison, the study collapsed.

Patients were, however, analyzable on an "intention-to-treat" basis and it seems now that all patients treated with imatinib, whether they received the drug at initial randomization or after failing or withdrawing from the control arm, are still alive at 5 years from the start of therapy—very much superior to any comparable historical control population.[16] Imatinib has thus become the treatment of choice for all or almost all newly diagnosed patients with CML in chronic phase. Transplant can be considered for eligible patients who fail to respond well to imatinib.

What Issues Remain?
First, results in the majority of CML patients seem so good that one wonders whether CML may not have been converted into a chronic disease readily controllable for years or decades with a single agent such as imatinib. Conversely, will long-term treatment with imatinib reveal cumulative toxicities that are not yet apparent? Possibly.
Second, will it be possible to stop imatinib in good responders after some years of treatment? The experience with interferon-alpha suggested that a small number of patients remained in long-term remission after adequate treatment with that agent. Will the same be true for imatinib, or might the proportion of treatment-free responders actually be larger? Could one perhaps maintain the remission with some form of immunotherapy after stopping imatinib? These are questions that must be addressed in the future.
Third, what can we do for the patient who fails to respond to imatinib as initial therapy or who, having initially responded, loses his or her response? Such patients should presumably be considered for treatment with one or another of the second generation of tyrosine kinase inhibitors, namely, dasatinib or nilotinib. These two agents are both substantially more active than imatinib, and both are active against the majority of Ph-positive subclones bearing kinase domain mutations, which are considered in some cases to be the primary cause of acquired resistance to imatinib. The most notorious kinase domain mutation—the so-called gatekeeper amino-acid mutation, a threonine-to-isoleucine mutation at position 315 (T315I)—confers resistance to imatinib but seems also ineluctably to escape inhibition by dasatinib and nilotinib.
There is a third generation of tyrosine kinase inhibitors, including some that are active against the T315I mutant clone, and some of these are now entering clinical trials. Whether they make a significant difference in the management of patients who fail to respond to imatinib therapy and whether they help in the management of patients who are resistant to imatinib per primum (most of whom have no demonstrable kinase domain mutations) remains to be seen. It is quite possible that optimal therapy will prove to involve the use of two or more tyrosine kinase inhibitors used in combination or in tandem.
What is certain is that the advent of imatinib has fundamentally altered the therapeutic strategy for CML patients and promises substantial prolongation of life in comparison with previous treatments. It has also redirected therapeutic research efforts in CML and has had an impact on research strategies.
for other neoplastic diseases. It is most salutary that the 21st century has begun with a recognition
that the use of small molecules designed on the basis of known molecular mechanisms underlying
malignancy should replace the empiric use of much less specific cytotoxic drugs.

—John M. Goldman, DM

Disclosures:
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