Chronic Myelogenous Leukemia

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Natural History
Chronic myelogenous leukemia (CML) is a disorder of hematopoietic stem cells accounting for 15% of adult leukemias. The median age at presentation is between 50 and 60 years; 12% to 30% of patients at diagnosis are older than 60 years.

Chronic myelogenous leukemia classically progresses through 3 phases, becoming more resistant to treatment in each successive phase. The majority of patients present in the chronic phase, which may last 4 to 6 years and is often asymptomatic at diagnosis. In the accelerated phase, symptoms become worse and immature blasts increase in the peripheral blood. The duration of this phase may last as long as a year. The final and fatal blastic phase (>30% blasts in the bone marrow or peripheral blood) has features of an acute leukemia including fever, weight loss, bleeding, and anemia; this phase may last 3 to 6 months.

Pathophysiology
The Philadelphia (Ph') chromosome was first described in 1960 in patients with CML as a shortened chromosome that was later discovered to be chromosome 9, accounting for 15% of adult leukemias. The median age at presentation is between 50 and 60 years; 12% to 30% of patients at diagnosis are older than 60 years.

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Monitoring With Bcr-Abl
Patients with CML currently may be monitored by hematologic, cytogenetic (karyotype), and molecular tests such as FISH (fluorescence in situ hybridization) and RT-PCR (reverse transcriptase-polymerase chain reaction). Based on these assays, therapy outcome may be defined in terms of hematologic remission (normalization of blood cell counts and spleen size), varying degrees of cytogenetic response (decline in percentage of Ph' cells), or a molecular remission (PCR negative). Cytogenetic analysis is tedious, but has become useful in predicting survival outcome.7-9 Polymerase chain reaction is a highly sensitive assay and can detect a single Ph' cell in 10000 to 100000 normal cells.10 Bcr-Abl messenger RNA (mRNA) transcripts can now be quantitated and followed over time by newly developed PCR assays to predict eventual relapse in patients who have undergone transplantation.11 Although the predictive significance of these assays in nontransplant therapies of CML has not been fully clarified.

Evolution of Therapy in CML
Prior to the 1950s, splenic irradiation was the mainstay of CML therapy but it had minimal effect on survival (TABLE).12 In 1953, busulfan was introduced for palliation of chronic-phase CML.14 Ten years later, hydroxyurea, a ribonucleotide reductase inhibitor, became available15 and was favored over busulfan because it had fewer adverse effects and improved survival.15,22 However, since neither drug affected either cytogenetic response or progression to blast crisis,15,22 more effective therapy was needed. Allogeneic stem cell transplantation (SCT) for CML was first performed in the 1970s, initially with identical twin transplants25 and subsequently with HLA-matched sibling transplants.25 Since few patients were eligible for SCT, alternative treatment was desired, and in the early 1980s α-interferon (IFN)–based therapy was introduced.20

Currently, allogeneic matched sibling SCT is favored for young (<30-40 years old) patients in chronic phase who are within 1 year of diagnosis. These patients can have "cure" rates of 50% to 55% at 10 years.27 For older patients, the transplant-associated mortality rate is 30% to 50%, which is higher than the mortality rate in younger patients.28,29 Even with the long-term event-free survival rates seen with allogeneic SCT, 10% to 20% of the patients who receive one will experience a disease relapse, which generally occurs within 3 years of trans-
After the translocation between chromosomes 9 and 22, the Bcr-Abl fusion gene undergoes transcription. The resulting chimeric Bcr-Abl messenger RNA (mRNA) is then translated into the Bcr-Abl tyrosine kinase protein, which enhances altered cell proliferation, adhesion, and survival.

Table. Evolution of Discoveries and Therapies in Chronic Myelogenous Leukemia*

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<td>1980-present</td>
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*SCT indicates stem cell transplant; STI-571, signal transduction inhibitor 571. †Only for patients eligible for SCT. ‡Ellipses indicate not yet available.

Plantation. Treatment choices include α-IFN, infusion of donor lymphocytes, or a second SCT. Infusion of donor lymphocytes is most effective when given within the first 2 years of the SCT. Lymphocytes from the original donor are transfused and induce complete remission through graft-vs-tumor effect in 60% to 80% of patients who relapse with active chronic-phase CML.

Although allogeneic SCT from siblings is the best chance for cure for CML patients in chronic phase, only 15% to 20% of patients are candidates for this treatment given the limitations of age or lack of HLA-matched related donors failing to provide therapeutic solutions for the majority of patients with CML. For patients not eligible for SCT, α-IFN plus hydroxyurea and/or cytarabine can be used. Combination therapy with α-IFN and cytarabine has a slight survival advantage over α-IFN alone. α-Interferon was first used clinically in 1983 after reports of activity in CML. A single-center study later demonstrated that α-IFN induced complete hematologic (80%) and complete cytogenetic (26%) responses in patients with chronic-phase CML and similar responses were confirmed by other investigators.

Median time to complete hematologic remission is 6 to 7 months and 12 to 17 months for complete cytogenetic remission. Survival rates are higher in patients receiving α-IFN than in patients receiving busulfan or hydroxyurea alone. The most remarkable impact on survival has been demonstrated among patients with low-risk disease, where survival rates have exceeded 9 years. Furthermore, greater than 80% of those who demonstrate a complete cytogenetic response to α-IFN are alive for more than 10 years.

**Novel Therapies**

The search for more effective treatment has continued because of the limita-
tions of current therapies—many patients are not eligible for a potentially curative allogeneic SCT, SCT is associated with life-threatening toxicities, and α-IFN is seldom curative and also associated with morbidity. In 1996, this effort led to the development of relatively specific Bcr-Abl tyrosine kinase inhibitors. One of these, a 2-phenylaminopyrimidine, was a potent relatively selective inhibitor of the Bcr-Abl tyrosine kinase. This compound, CGP 57148B (Novartis, Basel, Switzerland), demonstrated inhibition of proliferation of Bcr-Abl expressing cells as well as inhibition of Bcr-Abl (+) tumor formation in profoundly immunodeficient mice. CGP 57148B (later named STI-571, signal transduction inhibitor 571) had little in vivo toxicity in animals and did not hinder the growth of normal cells. Further investigation of this compound has revealed that STI-571 binds to the adenosine triphosphate–binding site of Abl, thus inhibiting the phosphorylation of substrates and subsequent malignant transformation (Figure 2). Although STI-571 is relatively specific for Bcr-Abl tyrosine kinases and is active against platelet-derived growth factor receptor kinase and c-kit receptor kinase, it is inactive against a large number of other tyrosine kinases.

Because of the promising in vitro and in vivo data, a phase 1 study of STI-571 began in patients with chronic-phase CML resistant to or intolerant of α-IFN. A total of 53 of 54 patients experienced complete hematologic remissions. Cyogenetic responses, were seen in 54% of patients. Complete hematologic remissions have continued in 51 of the 53 patients after a median follow-up of 265 days. These results are surprising in light of the fact that these patients had long-standing disease (3 years on average from diagnosis). The adverse effects of STI-571 observed in the study included nausea, vomiting, and fluid retention; a maximal tolerated dose was not reached. Preliminary data from a phase 2 study of STI-571 evaluating cytogenetic responses in patients with Ph (+) CML for whom α-IFN had not been successful are also promising. After 6 months of therapy, a major cytogenetic response was observed in 56% of the 290 evaluable patients. Phase 2 studies that included patients with accelerated-phase CML have demonstrated an overall hematological response rate of 78%; a complete hematologic remission has been demonstrated in 22 patients. STI-571 has also been evaluated in patients with blastic-phase CML and Ph (+) ALL. Fifty-five percent of patients with CML in blastic phase demonstrated a response; 22% of these were complete responses. Even though 14 of 20 patients with Ph (+) ALL or lymphoid blast crisis experienced a response, all but 1 have relapsed while receiving therapy. A phase 3 trial is under way to investigate the use of STI-571 as front-line treatment of newly diagnosed patients with CML in chronic phase. It will compare STI-571 with the combination of α-IFN and cytarabine.

In May 2001, the Food and Drug Administration approved STI-571 under the name Gleevec (Novartis, East Hanover, NJ) for patients with chronic-phase CML who are resistant to or intolerant of α-IFN as well as for patients with more advanced stages of CML.

New Agents

A number of novel agents are still under investigation for the treatment of CML. Homoharringtonine, a plant alkaloid, has shown activity in patients in the early and late chronic phases of CML. A potent hypomethylating agent called decitabine has also demonstrated activity in patients with CML in accelerated and blastic phases. Of 5 patients with blastic-phase CML treated with troxacitabine, a cytosine analog, 2 have returned to chronic phase. Immuno therapy with specific vaccines is also under investigation.

Conclusions

Over the past century, our understanding of CML pathogenesis and therapeutic strategies for CML has evolved considerably. Chronic myelogenous leukemia is one of the few diseases in...
which a specific cytogenetic and molecular abnormality has been implicated in the pathogenesis of the disease. The presence of a constitutively active Bcr-Abl tyrosine kinase in the tumor cells has led to the first targeted molecular therapy of its kind. This drug has the advantage, compared with traditional antineoplastic agents, of being able to target abnormal cells and spare normal cells.

Clinical trials have shown very promising results of STI-571 in Bcr-Abl (+) leukemias in all phases. The most durable responses have been seen in patients with chronic-phase CML who are resistant to or intolerant of α-IFN, but remarkable responses have also been seen in accelerated and blastic phases of the disease. The success of this inhibitor has underscored the significance of molecular based therapy. It may be the first in a series of new compounds that operate in a similar mode of action in a variety of other malignancies. Additional research should help determine the optimal role for STI-571, whether it be alone, in combination with α-IFN and cytarabine, or as first-line therapy for CML.

REFERENCES


