10 Years of Progress in Chronic Myelogenous Leukemia

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Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm with an incidence of 1 to 2 cases per 100,000 adults. It accounts for approximately 15% of newly diagnosed cases of leukemia in adults. Central to the pathogenesis of CML is the fusion of the Abelson murine leukemia (ABL) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22. This fusion results in expression of an oncoprotein, BCR-ABL. BCR-ABL is a constitutively active tyrosine kinase that promotes growth and replication through downstream pathways such as RAS, RAF, JUN kinase, MYC, and STAT. This influences leukemogenesis by creating a cytokine-independent cell cycle with aberrant apoptotic signals in response to cytokine withdrawal.

Until little more than a decade ago, drug therapy for CML was limited to nonspecific agents such as busulfan, hydroxyurea, and interferon-alfa (INF-α). INF-α use led to disease regression and improved survival but was hindered by a multitude of toxicities. Allogeneic stem cell transplantation was a curative intervention, but carried a high risk of morbidity and mortality. Further, it is only an option for patients with excellent performance status and an appropriate stem cell donor.

Small molecule tyrosine kinase inhibitors (TKIs) were developed to exploit the presence of the aberrantly expressed BCR-ABL protein in CML cells. This “targeted” approach was found to dramatically alter the natural history of the disease, improving 10-year overall survival rates from approximately 20% to 80% or 90%. This article describes current frontline options for CML and new compounds under investigation for the management of resistant disease.

Frontline Treatment Options

Three TKIs are currently commercially available for the treatment of CML: imatinib, dasatinib, and nilotinib. Current guidelines endorse all 3 as viable options for initial management of CML in the chronic phase (CML-CP).

Imatinib

Imatinib mesylate (Gleevec, Novartis Pharmaceuticals Corporation) was the first TKI to receive approval by the FDA for the treatment of patients with CML-CP. It acts via competitive inhibition at the adenosine triphosphate (ATP) binding site of the Bcr-Abl protein, which results in inhibition of phosphorylation of proteins involved in cell signal transduction. Imatinib efficiently inhibits the BCR-ABL kinase but also blocks the platelet-derived growth factor receptor (PDGFR) and the C-KIT tyrosine kinase.

The International Randomized Study of Interferon and STI571 (IRIS) study is considered a landmark clinical trial for TKI use in CML. Investigators randomized 1106 patients to receive imatinib, 400 mg/d, or INF-α plus low-dose subcutaneous cytarabine. After a median follow-up of 19 months, relevant outcomes for patients receiving imatinib were significantly better than for those treated with INF-α plus cytarabine; notably, the rates of complete cytogenetic response (CCyR; 74% vs. 9%; P < .001) and freedom from progression to accelerated phase or blast crisis at 12 months (99% vs. 93%; P < .001). Further highlighting the challenge of using INF-α was the high crossover rate to imatinib due to intolerance. The responses to imatinib

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were also durable, as shown in an 8-year follow-up of the IRIS study.\textsuperscript{11} Estimated event-free survival was 81%, and overall survival was 93% when only CML-related deaths were considered.

As impressive as the results using imatinib were, however, only 55% of patients in the IRIS study remained on therapy at 8 years, which underscored the need for additional options for patients who could not tolerate imatinib or for whom it failed. This led to development of second-generation TKIs.

**Dasatinib**

Dasatinib (Sprycel, Bristol-Myers Squibb) is an oral second-generation TKI that is 350 times more potent than imatinib in vitro.\textsuperscript{14-16} It is also known to inhibit the Src family of kinases, which may also be important in blunting critical cell signaling pathways.\textsuperscript{17} Although it was initially evaluated in the salvage setting, clinicians and researchers were excited to test the possibility that frontline use of the more potent inhibitors might further improve outcomes compared with imatinib.

The DASISION trial was a randomized, phase III, international study comparing imatinib, 400 mg/d, versus dasatinib, 100 mg/d, in patients with newly diagnosed CML-CP.\textsuperscript{18} The primary end point of the study was confirmed CCyR at 12 months, which was achieved in a higher percentage of patients on dasatinib (77% vs. 66%; \(P = .007\)). Dasatinib also induced more major molecular responses (MMR) than imatinib. Importantly, with 18 months of follow-up, the benefits of dasatinib persisted.\textsuperscript{19}

**Nilotinib**

Nilotinib (Tasigna, Novartis Pharmaceuticals Corporation) is a structural analog of imatinib, although its affinity for the ATP binding site on BCR-ABL is up to 50 times more potent in vitro.\textsuperscript{15,20} As with dasatinib, nilotinib initially showed ability to induce hematologic and cytogenetic responses in patients in whom imatinib failed. An investigation of nilotinib's potential role in the frontline setting followed.

ENESTnd was a randomized, phase III, international study comparing imatinib, 400 mg/d, versus dasatinib, 100 mg/d, in patients with newly diagnosed CML-CP.\textsuperscript{18} The primary end point of the study was confirmed CCyR at 12 months, which was achieved in a higher percentage of patients on dasatinib (77% vs. 66%; \(P = .007\)). Dasatinib also induced more major molecular responses (MMR) than imatinib. Importantly, with 18 months of follow-up, the benefits of dasatinib persisted.\textsuperscript{19}

**Management of TKI Resistance: New Agents**

Drug resistance may be a problem that increases due to widespread use of all the commercially available TKIs. One of the most common mechanisms of resistance involves point mutations in the kinase domain of BCR-ABL, which impairs the activity of the available TKIs. Use of second-generation TKIs can overcome most of the mutations that confer resistance to imatinib, although novel mutations rendering the leukemia resistant to dasatinib or nilotinib have emerged. One important mutation, T315I, is known as the “gatekeeper” mutation, because it displays resistance to all currently available TKIs. Patients who develop this mutation have a poor prognosis, so it is important to continue efforts to bolster the therapeutic arsenal.

Ponatinib (formerly AP24534) is a rationally designed TKI shown to efficiently inhibit BCR-ABL and many additional important tyrosine kinases, including FLT3, PDGFR, vascular endothelial growth factor, and C-KIT.\textsuperscript{22,23} Perhaps most notably, ponatinib is active against CML harboring the T315I mutation, offering a viable option
for patients who previously had few. Results from the international phase II PACE trial were recently presented at the annual ASH meeting. Most patients were highly exposed to TKIs, with 94% having 2 prior failed TKIs, and 57% having 3 prior failed TKIs. In the entire cohort (which included patients with Philadelphia chromosome–positive acute lymphoblastic leukemia), 106 patients had a T315I mutation. The drug exhibited significant antileukemia activity, with major cytogenetic responses achieved in 57% of patients with CML-CP and the T315I mutation. Follow-up is ongoing.

Several novel agents are under development that may be useful as single agents or as part of a combination approach. DCC-2036 is known as a “switch pocket inhibitor,” which acts by binding in the area responsible for the conformational change between inactive and active Bcr-Abl protein. It appears to be active in CML cells with the T315I mutation. Other new agents include omacetaxine, a non-TKI that disrupts protein synthesis and induces cellular apoptosis. Additional agents and classes that may lead to meaningful improvements in survival include, but are not limited to, aurora kinase inhibitors, farnesyl transferase inhibitors, hedgehog inhibitors, and hypomethylating agents.

Can CML Be Cured?
TKI therapy revolutionized CML but is currently considered a lifelong treatment. As patients underwent longer treatment and monitoring techniques improved, however, researchers noted that some patients had little if any detectable disease (ie, complete molecular response [CMR]) several years after starting therapy. This observation led investigators to consider whether discontinuing TKIs might be feasible and curing CML possible. The Stop Imatinib (STIM) trial evaluated patients with documented CMR for more than 2 years. Patients enrolled on this study stopped imatinib and were followed closely for molecular relapse. Sixty-nine patients with at least 12 months of follow-up were included, and 41% remained in CMR after stopping the TKI.

An update to the STIM trial was recently presented at the annual ASH meeting. Of 100 patients with sufficient follow-up, 61% experienced molecular relapse, with most relapses occurring within 7 months of imatinib discontinuation. Two factors that predicted continued CMR after TKI cessation included Sokal risk score and duration of imatinib therapy. Low-risk patients who had received more than 60 months of imatinib therapy were more likely to remain in CMR after stopping. These data indicate that stopping TKI is feasible and that some patients may actually be cured. Nevertheless, TKI therapy currently should only be stopped in the context of a clinical trial.

Current Practice and Future Perspectives
With the publication of recent updates to the DASISION and ENESTnd trials, the question often arises about optimal choice for frontline management of CML-CP. Based on faster attainment of CCyR and a trend for less progression to accelerated phase or blast crisis, the current recommendation is to use a second-generation TKI for frontline management. For patients who progress to accelerated phase/blast crisis, treatment options are limited and the overall prognosis is poor. Therefore, a primary goal of first-line therapy should be to prevent progression. However, second-generation TKIs are expensive, and imatinib may be available generically within a few years. Clinicians also know that a large number of patients will have optimal responses to imatinib therapy. Therefore, future research could work to identify baseline factors that indicate which patients will benefit most from upfront treatment with a second-generation TKI. New therapies will be tested alone and in combination with TKIs.
so patient outcomes continue to improve. The pursuit of a cure for all patients will continue, and the criteria for safely discontinuing TKIs will receive further attention.

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