Advances in the genetic and molecular characterizations of leukemias have enhanced our capabilities to develop targeted therapies. The most dramatic example of targeted therapy in cancer to date is the use of targeted BCR-ABL protein tyrosine kinase inhibitors (TKI), which has revolutionized the treatment of chronic myeloid leukemia (CML). Inhibition of the signaling activity of this kinase has proved to be a highly successful treatment target, transforming the prognosis of patients with CML. In contrast, acute myeloid leukemia (AML) is an extremely heterogeneous disease with outcomes that vary widely according to subtype of the disease. Targeted therapy with monoclonal antibodies and small molecule kinase inhibitors are promising strategies to help improve the cure rates in AML. In this review, we will highlight the results of recent clinical trials in which outcomes of CML and AML have been influenced significantly. Also, novel approaches to sequencing and combining available therapies will be covered. 

Until 2000, therapy for CML was limited to nonspecific agents such as busulfan, hydroxyurea, and interferon-α (IFN-α). IFN-α resulted in modest complete cytogenetic response (CCyR) rates (10%–25%), and improved survival but was hindered by modest activity and significant toxicities. Allogeneic stem cell transplantation (alloSCT) was curative but carried a high risk of morbidity and mortality, and was an option only for patients with good performance status and organ functions, and with appropriate donors.

Small-molecule tyrosine kinase inhibitors (TKIs) were developed to target the aberrantly expressed Bcr-Abl oncoprotein in CML cells. This dramatically altered the natural history of the disease, improving the estimated 10-year survival rate from 20% to 80%–90%. Acute myelocytic leukemia (AML) is a heterogeneous malignancy of the bone marrow, predominantly diagnosed in patients greater than 60 years of age. The leukemia karyotype is one of the most significant prognostic factors in AML. Patients are typically considered to have favorable, intermediate, or unfavorable disease based on karyotype, which ultimately influences the overall treatment plan. Molecular studies allow the identification of gene mutations that influence cell signaling, proliferation, and survival. Most notably, mutations in the FMS-like tyrosine kinase 3 (FLT3) have been associated with poor prognosis. Several small molecules specifically inhibit FLT3.

In this review, we will discuss frontline and salvage options for CML, and new compounds under investigation for the management of resistant disease. We will also highlight the novel and investigational agents under development that may ultimately improve outcomes of patients with AML, including FLT3 inhibitors and new and “old” monoclonal antibodies.
CML FRONTLINE TREATMENT OPTIONS

Three TKIs are commercially available for the frontline treatment of CML: imatinib, dasatinib, and nilotinib. Current guidelines endorse all three as excellent options for the initial management of CML in the chronic phase (CML-CP) (Table 1). Imatinib mesylate (Gleevec, Novartis Pharmaceutical Corp, East Hanover, NJ), was the first TKI to receive approval by the US Food and Drug Administration (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 oncoprotein, which results in the inhibition of phosphorylation of proteins involved in cell signal transduction. It efficiently inhibits the Bcr-Abl kinase activity but also blocks the platelet-derived growth factor receptor (PDGFR) and the C-KIT tyrosine kinase.\(^\text{15}\)\n
The International Randomized Study of IFN-\(\alpha\) and STI571 (IRIS) study is considered a landmark clinical trial for TKIs and CML.\(^\text{16}\) Investigators randomized 1,106 patients to receive imatinib 400 mg/d or IFN plus subcutaneous low-dose cytarabine. After a median follow-up of 19 months, relevant outcomes for patients receiving imatinib were significantly better than for those treated with IFN plus cytarabine, notably the rate of CCyR (74% \(v\) 9%, \(P < .001\)), and freedom from progression to accelerated phase (AP) or blast phase (BP) at 12 months (99% \(v\) 93%, \(P < .001\)). The responses to imatinib were also durable, as shown in an 8-year follow-up of the IRIS study.\(^\text{11}\) The estimated event-free survival rate was 81%; the overall survival (OS) rate was 93% when only CML-related deaths were considered.

While the results using imatinib were impressive, only 55% of patients enrolled remained on therapy at the 8-year follow-up time. This underscores the need for additional options for patients who had failed or were intolerant to imatinib, and led to the rational development of second-generation TKIs.

Dasatinib (Sprycel, Bristol-Myers Squibb, Princeton, NJ) is an oral, second-generation TKI that is 350 times more potent than imatinib in vitro.\(^\text{17–19}\) It also inhibits the Src family of kinases, which may also be important in blunting critical cell signaling pathways.\(^\text{20}\) Following the positive results in the salvage setting post imatinib failure, dasatinib was evaluated as frontline CML therapy.

The DASISION trial was a randomized, phase III, international study comparing imatinib 400 mg daily versus dasatinib 100 mg daily in newly diagnosed patients with CML-CP.\(^\text{21}\) The primary endpoint of the study was confirmed CCyR at 12 months, which was achieved in a higher percentage of patients randomized to dasatinib (77% \(v\) 66%, \(P = .007\)). Dasatinib was also able to induce higher rates of major molecular response (MMR) compared with imatinib.\(^\text{22}\) Like dasatinib, nilotinib initially demonstrated the ability to induce hematologic and cytogenetic responses in patients with CML post imatinib failure, leading to nilotinib therapy in the frontline setting.

The Phase III Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) trial was a randomized, phase III, international study comparing two doses of nilotinib (300 mg or 400 mg twice daily) to imatinib 400 mg once daily.\(^\text{24}\) The primary study endpoint was the rate of MMR at 12 months, which was achieved at higher rates on the nilotinib arms compared with imatinib (44% and 43% \(v\) 22%, \(P < .001\)). There was also less progression to AP or BP noted with nilotinib.\(^\text{25}\)

Management of TKI Resistance

A common mechanism of resistance to TKIs involves point mutations in the Bcr-Abl kinase domain, which impair the activity of the particular TKIs. Second-generation TKIs are able to overcome most of the mutations that confer resistance to imatinib, though novel mutations rendering the leukemia resistant to dasatinib and/or nilotinib have emerged (Table 2). One important mutation, T315I, known as a “gatekeeper” mutation, displays resistance to all currently available TKIs except ponatinib.

Before defining a patient as having imatinib resistance and modifying therapy, treatment compliance and drug–drug interactions should be excluded. Rates of imatinib adherence range from 75%–90%; lower adherence rates correlate with worse outcome.\(^\text{26–28}\) In one study of 87 patients with CML-CP treated with imatinib 400 mg daily, an adherence rate of 90% or less resulted in MMR in only 28% versus 94% with >90% adherence rates (\(P < .001\)).\(^\text{26}\) Complete molecular response (CMR) rates were 0% versus 44% (\(P = .002\)); no molecular responses were observed when adherence rates were 80% or lower. Lower adherence rates have been described in younger patients, those with adverse effects to therapy, and those who have required dose escalations.\(^\text{29}\)

Second-Generation TKIs

Nilotinib and dasatinib were first approved for use as second-line CML salvage following prior therapy including imatinib. Results of second-line nilotinib, dasatinib, and bosutinib therapies following imatinib failure are summarized in Table 2. Several noteworthy observations emerged. First, second-line treatment can yield high rates of response in patients who have inadequate response to imatinib, including high rates of MMR. Second, dose escalation of imatinib can improve response rates in patients with inadequate response to standard-dose imatinib but switching to second-line can be more effective.\(^\text{29}\) Several studies that evaluated second-line nilotinib\(^\text{30,31}\) or dasatinib\(^\text{30,32}\) and high-dose imatinib (400 mg twice daily) have demonstrated significantly higher rates of complete hematologic response (CHR), CCyR, and MMR with the
<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Primary Endpoint</th>
<th>Follow-Up Data</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>% MMR</td>
<td>% PFS</td>
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<tr>
<td><strong>IRIS</strong></td>
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<tr>
<td></td>
<td>Ima 400 mg qd</td>
<td>553</td>
<td>% PFS at 18 mo</td>
<td>6 yr/8 yr</td>
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<td></td>
<td></td>
<td></td>
<td>97</td>
<td>93/92</td>
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<tr>
<td></td>
<td>IFN + ara-c</td>
<td>553</td>
<td>91 ($P &lt; .001$)</td>
<td>2 yr/3 yr</td>
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<td>2 yr/3 yr</td>
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<td><strong>ENESTnd</strong></td>
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<td></td>
<td>Nilo 300 mg bid</td>
<td>282</td>
<td>% MMR at 12 mo</td>
<td>2 yr</td>
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<td></td>
<td></td>
<td></td>
<td>44</td>
<td>71/73</td>
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<tr>
<td></td>
<td>Nilo 400 mg bid</td>
<td>281</td>
<td>43</td>
<td>67/70</td>
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<tr>
<td></td>
<td>Ima 400 mg qd</td>
<td>283</td>
<td>22 ($P &lt; .001$ for both comparisons)</td>
<td>44 ($P &lt; .0001$ for both comparisons)/53 ($P &lt; .0001$ for both comparisons)</td>
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<td></td>
<td>96/94</td>
</tr>
<tr>
<td><strong>DASISION</strong></td>
<td></td>
<td></td>
<td>% CCyR at 12 mo</td>
<td>2 yr/3 yr</td>
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<tr>
<td></td>
<td>Dasa 100 mg qd</td>
<td>259</td>
<td>77</td>
<td>64</td>
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<tr>
<td></td>
<td>Ima 400 mg qd</td>
<td>260</td>
<td>Imatinib: 66 ($P = .007$) Secondary endpoint: MMR at 12 mo: Dasa: 46 Ima: 28 ($P &lt; .0001$)</td>
<td>46</td>
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Abbreviations: ima, imatinib; nilo, nilotinib; dasa, dasatinib; ara-c, cytarabine; IFN, interferon; MMR, major molecular response; PFS, progression-free survival; OS, overall survival.

*Free from progression to accelerated phase or blast crisis.*
<table>
<thead>
<tr>
<th>Response</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Bosutinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (mo)</td>
<td>15 4 12⁺</td>
<td>24 9 3 3</td>
<td>7 6 3</td>
<td>11 13 6</td>
</tr>
<tr>
<td>% Resistant to imatinib</td>
<td>74 93 91 88</td>
<td>70 80 82 82</td>
<td>69 NR⁺</td>
<td>96</td>
</tr>
<tr>
<td>% Hematologic Response</td>
<td>- 79 50 40</td>
<td>94 56 22 19</td>
<td>85 54 36</td>
<td>NR NR NR</td>
</tr>
<tr>
<td>CHR</td>
<td>91 45 27 29</td>
<td>76 31 11 13</td>
<td>81 54 36</td>
<td>NR MaHR: 57</td>
</tr>
<tr>
<td>NEL</td>
<td>- 19 7 6</td>
<td>- 12 1 0</td>
<td>- 0 NR</td>
<td>NR NR</td>
</tr>
<tr>
<td>% Cytogenetic Response</td>
<td>NR 44 36 52</td>
<td>NR NR NR NR</td>
<td>- NR NR</td>
<td>NR NR</td>
</tr>
<tr>
<td>Complete</td>
<td>49 32 26 46</td>
<td>46 20 29 32</td>
<td>34 27 35</td>
<td>46 55 36</td>
</tr>
<tr>
<td>Partial</td>
<td>11 7 7 6</td>
<td>15 12 10 16</td>
<td>13 20 18</td>
<td>NR NR NR</td>
</tr>
<tr>
<td>% Survival (at 12 mo)</td>
<td>96 82 50 50</td>
<td>87 67 42 42</td>
<td>98 60 50</td>
<td>91 42 35</td>
</tr>
</tbody>
</table>

Abbreviations: CP, chronic phase; AP, accelerated phase; MyBP, myeloid blast phase; LyBP, lymphoid blast phase; BP, blast phase; MaHR, major hematologic response; CHR, complete hematologic response; NEL, no evidence of leukemia; NR, not reported.
newer TKIs than with high-dose imatinib. Progression-free survival (PFS) was also better with the newer TKIs. In addition, earlier change to second-line TKI may be more effective than later change. In a retrospective pooled analysis of second-line dasatinib in patients resistant to or intolerant of imatinib, an earlier change to dasatinib after the loss of major cytogenetic response (MCyR) (early intervention group) resulted in higher rates of CHR, CCyR, and MMR, and better 24-month event-free survival (EFS), transformation-free survival (TFS), and OS, than later change after the loss of CHR (late intervention group).

**New Agents**

Ponatinib (formerly AP24534) is a rationally designed TKI that efficiently inhibits Bcr-Abl, as well as other important tyrosine kinases, including FLT3, PDGFR, VEGF, and C-KIT. Most notably, ponatinib is active against CML harboring the T315I mutation. In the phase II, international PACE trial, most patients were highly exposed to TKIs, 94% having failed two prior TKIs, and 57% having failed three prior TKIs. In the entire cohort (which included Philadelphia chromosome–positive acute lymphocytic leukemia), 106 patients had a T315I mutation. The drug exhibited significant anti-leukemia activity, with MCyRs achieved in 59% (complete in 46%) of the patients with CML-CP and T315I mutation. Results of the PACE trial are summarized in Table 2. Several novel agents under development may be useful as single agents or as part of a combination approach for CML. DCC-2036, a switch pocket inhibitor that acts by binding in the area responsible for the conformational change between inactive and active pocket inhibitor that acts by binding in the area responsible for the conformational change between inactive and active pocket inhibitor.

**Definition of Response and Failures to TKI Therapy**

Monitoring response to TKI therapy in CML is a critical component of patients’ outcomes. Responses to TKI treatment are described in terms of hematologic, cytogenetic, and molecular outcomes. Hematologic response is defined as normalization of white blood cell (WBC) count and splenomegaly. Cytogenetic response is determined by the percentage of cells with Philadelphia chromosome–positive (Ph+) metaphases, whereas assessment of molecular response relies on quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) to measure BCR-ABL transcripts, best expressed on the International Scale (IS). On the IS, a MMR is defined as a BCR-ABL transcript level of 0.1% or less, which represents a 3-log reduction from a standardized baseline. CMR was defined in the European LeukemiaNet (ELN) recommendations and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) as a BCR-ABL transcript level that is undetectable by qRT-PCR in an assay with adequate sensitivity (eg, 4.5 logs). However, as more-sensitive PCR assays have been developed, 4-, 4.5-, and even 5-log reductions in BCR-ABL are now detectable, which raises the question of the true meaning of CMR and whether transcript-level changes below the level of MMR are meaningful.

Treatment failure is defined by the ELN and NCCN Guidelines recommendations as not achieving the specific milestones at defined time points. These guidelines were largely based on response data from the IRIS study. The main differences between these guidelines is the fact that ELN defines failure and suboptimal response and includes an additional response category (warnings), whereas the NCCN Guidelines do not formally define suboptimal response but rather define target responses at specific time points. However, these recommendations continue to evolve. In our opinion, a simplified schema of response/failure would be more practical and less confusing (Table 3).

**SHOULD WE STRIVE FOR AN EARLIER AND DEEPER RESPONSE?**

Beyond cytogenetic response, the more stringent criteria of a molecular response (MR) may also offer prognostic information. Recently, much attention has focused on the potential for an early MR as indicative of favorable long-term outcomes, including survival, and for guiding treatment decisions.

The potential significance of MMR has been investigated extensively. Some studies noted that achievement of

<table>
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<tr>
<th>Time (mo)</th>
<th>Imatinib</th>
<th>Second-Generation TKI</th>
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</thead>
<tbody>
<tr>
<td>3-6</td>
<td>MCyR; BCR-ABL transcript levels ≤ 10% (IS)</td>
<td>CCyR; BCR-ABL transcript levels ≤ 1% (IS)</td>
</tr>
<tr>
<td>12</td>
<td>CCyR; BCR-ABL transcript levels ≤ 1% (IS)</td>
<td>CCyR; BCR-ABL transcript levels ≤ 1% (IS)</td>
</tr>
<tr>
<td>Later</td>
<td>CCyR; BCR-ABL transcript levels ≤ 1% (IS)</td>
<td>CCyR; BCR-ABL transcript levels ≤ 1% (IS)</td>
</tr>
</tbody>
</table>

Note. MCyR roughly = BCR-ABL ≤ 10% (IS); CCyR roughly = BCR-ABL ≤ 1% (IS).

Abbreviations: MCyR, major cytogenetic response (Ph ≤ 35%); CCyR, complete cytogenetic response (Ph=0%); IS, International Scale.
MMR at 12 or 18 months was not associated with any benefit in long-term OS, although other benefits were observed.\textsuperscript{47}–\textsuperscript{49} In an analysis of the 7-year follow-up data from the IRIS study, EFS and progression to AP/BP-CML could be predicted at 12 and 18 months by achievement of a MMR (BCR-ABL ≤ 0.1%, according to the IS) compared with no MMR.\textsuperscript{48} In the German CML Study IV of imatinib with or without IFN-α in newly diagnosed CP-CML, achieving an MMR by 12 months in addition of CCR plus MMR did not confer a significantly greater survival advantage.\textsuperscript{47}–\textsuperscript{49,51,52}

Hanfstein and coworkers further investigated the potential correlations between molecular and cytogenetic responses and survival in the German CML Study IV.\textsuperscript{53} They found that patients with >10% BCR-ABL (IS) at 3 months had an 87% 5-year survival rate, compared with 95% in patients with ≤10% BCR-ABL (IS) (P < .001) and 97% in patients with >1%–10% BCR-ABL (IS) (P = .012). At the 6-month landmark analysis, significant differences in 5-year survival were seen between patients achieving BCR-ABL (IS) ≤1% and those with >1%–10% (97% vs 90% survival; P = .002). Thus, failure to achieve BCR-ABL (IS) transcript levels of <10% at 3 months (equivalent to partial cytogenetic response) or ≤1% at 6 months (equivalent to CCR) imatinib should prompt consideration of more careful monitoring, and that such patients should be candidates for studies that evaluate the benefit of continuing imatinib versus a change to another TKI.

In an exploratory analysis of data from the DASISION trial, Saglio and coworkers reported that among patients newly diagnosed with CP-CML and initiated on TKI therapy (imatinib 400 mg or dasatinib 100 mg), those who achieved a reduction in BCR-ABL transcripts to ≤10% (IS) at 3 months had significantly improved 3-year survival outcomes compared with patients with BCR-ABL transcript levels >10%.\textsuperscript{54} Three-year OS for patients receiving imatinib was 96% (95% CI 88%, P = .0036) and for patients receiving dasatinib, it was 96% (95% CI 86%, P = .03). The risk of transformation within 3 months was also decreased in patients with BCR-ABL ≤10% (95% CI >10%) and ≤1% (95% CI >1%) at 3 months. Similar results have been demonstrated for nilotinib. In the analysis of 3-year follow-up data from the ENESTnd study, treatment with either nilotinib or imatinib was associated with a higher OS rate in patients with a 3-month BCR-ABL transcript level ≤10% compared with those with a >10% level.\textsuperscript{55}

The NCCN guidelines currently recommend that if the BCR-ABL/ABL ratio is >10% (by qPCR [IS]) at 3 months then the patient should be evaluated for treatment compliance and drug–drug interactions, and mutational analysis conducted, with the possibility of changing treatment.

Marin and coworkers have recently suggested that more precise predictive 3-month MR thresholds, specific to the individual TKIs, could be developed.\textsuperscript{54,56} In a 282 patients newly diagnosed with CP-CML and initiated on imatinib 400 mg (followed by dasatinib or nilotinib if imatinib failed), the authors identified BCR-ABL transcript thresholds for low and high risk for each clinical outcome investigated at the 8-year follow-up.\textsuperscript{56} For OS, the BCR-ABL/ABL transcript threshold was identified to be 9.84% at 3 months, 1.67% at 6 months, and 0.53% at 12 months. Attainment of a BCR-ABL transcript level below this threshold at 3 months was associated with a significantly increased 8-year OS rate (93%) for patients with BCR-ABL levels below this threshold (v 57% for those above; P < .001). The authors noted that the 6- and 12-month assessments did not further contribute to the identification of patients at high risk of progression.\textsuperscript{56,57}

In contrast we have reported that a 3-month response was not predictive of 3-year OS in patients treated with first-line TKIs (imatinib, nilotinib, and dasatinib).\textsuperscript{58} Notably, the outcome of analyses of OS, TFS by molecular and cytogenetic responses was the same whether the analyses were based on 3-month or 6-month responses, with the exception of a 6-month MR predicting an improved 3-year OS.\textsuperscript{59} Given that the differences may be minimal between 3 and 6 months and that the long-term outcome of early switching is still unclear, for patients who have a suboptimal response, it may be more beneficial to continue to monitor response until a trend becomes evident, rather than implement a treatment switch at 3 months.

In 2009, we reported the results of a study designed to examine the clinical significance of minimal residual disease, that is, the presence of detectable BCR-ABL transcript levels, in patients with CP-CML who had achieved a durable CCR (>18 months) with imatinib treatment.\textsuperscript{59} We showed that the majority of patients who achieve a stable CCR and experience an increase in BCR-ABL transcript levels will remain in CCR; however, a subset of these patients will lose an MMR or will never achieve an MMR. These patients are most at risk for subsequent CML progression. In terms of clinical practice, these results suggest that, in general, cytogenetic and molecular monitoring every 6 months is sufficient for patients with an MMR. More frequent monitoring (every 3 months) and possibly treatment escalation might be considered for those who achieve a CCR but not an MMR and who exhibit a ≥1-log increase in BCR-ABL transcript levels, and for those who lose an MMR. In clinical practice, modest increases in BCR-ABL transcript levels detected by molecular monitoring in patients with CCR should not automatically prompt a change in treatment—not least because of assay variability. Such an intervention could result in an unnecessary increase in toxicity or switch from a still-effective treatment.

**Can CML Be Cured?**

Despite revolutionizing the treatment of CML TKI therapy is currently considered a life-long treatment. As
patients were treated for longer and monitoring techniques improved, it became apparent that some patients have very little, if any detectable disease (ie, CMR) several years after starting therapy. This led investigators to consider discontinuing TKIs. The Stop Imatinib (STIM) trial evaluated patients with documented CMR for >2 years. Patients enrolled on this study stopped imatinib and were followed closely for molecular relapse. Of 100 patients evaluated, 61% of patients experienced molecular relapse, with most of them 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 greater than 60 months of imatinib were more likely to remain in CMR after stopping the TKI. This indicates that stopping TKI therapy is feasible, and some patients may actually be cured of the disease. However, this represents a minority of patients (~10%-15%). Nevertheless, at present, stopping TKI therapy should only be done in the context of a clinical trial. Clinical trials assessing the combination of TKIs with agents like the pegylated form of interferon, azacitidine, and ruxolitinib are ongoing in patients with minimal residual disease. Their aims in to target the leukemia stem cell and eradicate the minimal residual disease with the hope to stop therapy with a sustained drug-free remission.

Current Practice and Future Perspective

With the updates of the DASISION and ENESTnd trials, the question often arises as to the optimal choice for frontline management of CP-CML. Based on attainment of faster and higher rates of CCyR, MMR, and CMR, and a trend for lower progression rates to AP or BC, it is reasonable to use a second generation TKI for frontline management. For patients who progress to AP/BC, treatment options are limited, and the overall prognosis is poor. Therefore, a primary goal of first-line therapy is to prevent progression. However, second-generations TKIs are expensive, serious adverse events are being reported, and by 2015 generic formulations of imatinib will be available. A large number of patients have optimal responses to imatinib therapy. Therefore, future research could identify baseline factors that may 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 to continue to improve patient outcomes. The pursuit of a cure for all patients will continue, and the criteria for safe permanent discontinuation of TKIs will receive further attention.

TARGETED THERAPIES IN AML

FLT3 Inhibitors

FLT3, a receptor tyrosine kinase involved in cell signaling and proliferation, is expressed on the surface of AML cells. Because FLT3 is often mutated in AML blasts, investigators explored FLT3’s influence on AML pathophysiology and prognosis, and developed targeting new molecules to target FLT3 mutations. Two distinct types of activating mutations are internal tandem duplication (ITD) of the intracellular juxtamembrane region and point mutations in the tyrosine kinase domain (TKD). FLT3 ITDs have been associated with poor prognosis; TKDs point mutations do not significantly impact prognosis. Early alloSCT for FLT3 ITD patients in first complete remission (CR) may improve outcome. TKDs point mutations may confer resistance to small molecule FLT3 inhibitors. This area is rapidly evolving, and we will review what we find to be the most significant findings to date.

Lestaurtinib (formerly CEP-701), one of the first FLT3 inhibitors, was evaluated in a randomized, multicenter study comparing the drug combined with chemotherapy versus chemotherapy alone. Patients were enrolled if they had FLT3-mutated (ITD or point mutation) AML in first relapse. Chemotherapy was assigned according to the duration of first CR. Patients randomized to lestaurtinib received the drug starting 2 days after the completion of chemotherapy (day 7) at a dose of 80 mg orally every 12 hours. In total, 224 patients were randomized. Unfortunately, lestaurtinib failed to improve either the CR rate or OS, and was more toxic when compared to the control group (30-day mortality rate was twice as high in the lestaurtinib group, 12% v 6%). The negative results were attributed to the high protein binding affinity (hence low availability of free drug).

In the study, there was substantial variability in the steady state plasma levels of the drug; and remission rates correlated with in vivo FLT3 inhibition, which was achieved in 50% of patients. Plasma levels of FLT3 ligand (FL) were increased drastically following intensive chemotherapy, and such high concentrations of FL impaired FLT3 inhibition (negative feedback loop). These three findings suggest that optimized molecules and sequence schedules were needed.

Another nonselective FLT3 inhibitor, midostaurin, was also evaluated in relapsed AML. In a randomized trial of single-agent midostaurin, 95 patients were randomized to therapy with 50 mg or 100 mg orally twice daily on a continuous basis. Most patients had relapsed or refractory disease. No CRs were achieved, but a substantial reduction in blast percentage was noted for mutated and wild-type patients at both doses. The median OS for the entire cohort was about 2 months.

Sorafenib, a multikinase inhibitor approved for renal cell and hepatocellular carcinomas, is also a potent FLT3 inhibitor. Other kinase targets of sorafenib include NRAS and c-KIT. Sorafenib was active in refractory AML in small studies. Because of data indicating that intensive chemotherapy can induce FL elevations, which may confer resistance to FLT3 inhibitors, Ravandi and colleagues evaluated sorafenib in combination with azacitidine, (less intense than traditional AML chemotherapy). Patients received azacitidine 75 mg/m² daily for 7 days every 28 days.
and sorafenib 400 mg orally twice daily, given continuously. Forty of 43 were positive for FLT3 ITD; most patients had relapsed or refractory disease and had received a median of two previous therapies. Among 37 patients evaluable, the overall response rate was 46% (16% CR, 27% CR with incomplete hematologic recovery, and 3% partial response). The toxicity profile was manageable (rash and fatigue). The regimen bridged 16% of patients to alloASCT. FLT3 target inhibition was attained in 64% of patients, and FL levels did not increase significantly following azacitidine therapy.

More selective FLT3 inhibitors may improve AML results. Quizartinib (formerly AC220) is more potent and selective for FLT3 than most other kinase inhibitors under development. Results from a phase II, open-label, multicenter study evaluating quizartinib as a single agent were recently presented. The study enrolled two distinct groups of patients. The first cohort included 134 elderly patients with primary refractory AML or a short duration of first CR, who had FLT3 ITD (69%) or a point mutation (31%). Quizartinib was given orally daily at a dose of 135 mg/d to male patients, and 90 mg/d to female patients. The investigators used an endpoint known as composite remission (CRc = CR + CR without hematologic recovery + CR without platelet recovery). Patients with FLT3 ITD achieved a CRc rate of 54%, most being CR without hematologic recovery (51%). The median OS was 23.3 weeks. Grades 3/4 QT prolongation occurred in 13% of the patients. There was one episode of torsade de pointes, which was not fatal.

The second cohort included 137 patients in salvage 2 or worse and patients post alloASCT. Among FLT ITD patients, the CRc rate was 44% (nine patients met the definition of CR). Interestingly, patients with wild type FLT3 also responded to quizartinib (CRc rate of 34%). Median OS was 23.1 weeks. Approximately one third of the patients were able to be bridged to an alloASCT.

As with imatinib in CML, identifying mechanisms and patterns of resistance post FLT3 inhibitors therapy is critical. An important observation is the emergence of FLT3 point mutations at the time of relapse or progression on FLT3-directed therapy. Crenolanib is a potent FLT3 inhibitor that was molecularly designed to retain activity in the presence of most known mutations. Investigators from the University of California San Francisco and the University of Pennsylvania have presented data indicating that crenolanib maintains potency in cases of quizartinib resistance.

Strategies to optimize the use of FLT3 inhibitors are ongoing. The most attractive strategy maybe using these agents as part of frontline AML therapy and at the time of minimal residual disease in high-risk patients. Trials are underway evaluating quizartinib in this regard and as post-transplant maintenance.

Monoclonal Antibodies

**Gemtuzumab Ozogamicin**

Gemtuzumab ozogamicin (GO) is an antibody-drug conjugate that was previously approved for salvage therapy in elderly patients with AML. The monoclonal antibody portion is directed against CD33, a cell surface marker expressed on myeloid cells. Once GO binds to CD33, it is internalized, where it releases a potent cytotoxin, calicheamicin, which causes cell death. This offered one of the first targeted approaches in AML. GO was withdrawn from the market in 2010 after preliminary results of a randomized trial evaluating the drug as a component of frontline AML therapy showed that GO did not improve the outcome. There were also some concerns regarding toxicity, including early death. This study is flawed in several ways: (1) the GO dose of 6 mg/m² might have been too high in combination; (2) the daunorubicin dose in the chemotherapy + GO arm was lower than in the chemotherapy arm alone (45 mg/m² vs. 60 mg/m²), which might have overcome the additional GO benefit; and (3) the 4-week mortality of 1% in the chemotherapy arm (V 5% with chemotherapy + GO) is unprecedently low, since all previous and later Southwest Oncology Group (SWOG) trials using the same chemotherapy regimen have shown mortality of 5% or more. Several large studies internationally were already underway, and their results have reopened the debate about the efficacy and toxicity of GO.

The Acute Leukemia French Association (ALFA) conducted a randomized trial evaluating the addition of GO to standard chemotherapy in newly diagnosed AML patients aged 50 to 70. All patients received the 7+3 regimen (daunorubicin 60 mg/m²) with or without fractionated doses of GO (3 mg/m² [capped at 5 mg] intravenously [IV] on days 1, 4, and 7 with induction). For patients not achieving CR after one course, a second cycle of daunorubicin 60 mg/m² combined with moderate doses of cytarabine was given (1,000 mg/m² over 2 hours IV every 12 hours for 6 doses) was given. The second induction course did not contain GO. While the CR rate between the two groups was similar (72% for the control arm vs. 73% for the GO arm), patients in the GO group had superior estimated 2-year EFS (41% vs. 17%; P = .0003) and OS (53% vs. 41%; P = .0368). Induction-related mortality was similar between the two groups. Grades 3 to 4 thrombocytopenia was more frequent in the GO arm. Hepatic veno-occlusive disease has been associated with the use of GO. In this study, there were two fatal cases in the GO group (none reported in the control arm).

The results of the French study are supported by two reports from the British Medical Research Council (MRC). First, a subgroup analysis of a large, randomized trial in younger adults with AML identified patients who significantly benefited from the addition of GO to induction chemotherapy. In the study, patients were randomized to receive one dose of GO (3 mg/m²) added to one of three chemotherapy regimens. Patients also received one additional dose of GO during consolidation. There was a survival benefit detected for patients with favorable risk cytogenetics, a trend for benefit in patients with intermediate-risk cytogenetics but no benefit for
patients in the high-risk group. The same group also studied whether the addition of GO to induction chemotherapy benefited elderly AML patients (the majority of the patients were > 60 years old). Patients received one of two chemotherapy regimens, and were subsequently randomized to one dose of GO (3 mg/m²) or chemotherapy alone. With a 3-year follow-up, GO therapy was associated with higher relapse-free survival rates (21% vs 16%; P = .04) and OS rates (25% vs 20%; P = .05) Unlike the results of the trial in younger adults, patients in all age and cytogenetic categories appeared to benefit in this study.

The combination of all-trans retinoic acid (ATRA) and GO can be a substitute for ATRA plus anthracyclines in curing newly diagnosed acute promyelocytic leukemia (APL), producing a response rate of 84%, plausibly with less acute toxicity, less early and delayed cardiotoxicity, and a lower risk of therapy-related myelodysplastic syndrome or AML. In a study conducted at the M.D. Anderson Cancer Center, the CR rate was 81% in high-risk patients who received GO. The combination of ATRA and arsenic trioxide plus GO is now being evaluated in a North American Intergroup APL trial for high-risk APL. Furthermore, Italian investigators noted that early treatment of molecular relapse of APL with single-agent GO resulted in longer survival than was seen when treatment began at hematologic relapse.

There is a need for reappraisal of the role of GO in AML, particularly in the subsets of APL, core binding factors (CBF), and diploid karyotype. Optimization of the dose schedules of GO is needed.

Other Monoclonal Antibodies

Lintuzumab (HuM195; SGN-33), an unconjugated, humanized anti-CD33 monoclonal antibody, was constructed by grafting the complementarity-determining regions of murine M195 into a human IgG1 framework and backbone. Lintuzumab has modest single-agent activity against AML but failed to improve patient outcomes in two randomized trials when combined with conventional chemotherapy. Based on the results of these two large trials, further clinical development of lintuzumab was halted because of lack of efficacy. To increase the potency of the antibody without the nonspecific cytotoxicity associated with β-emitters, the α-particle-emitting radionuclide bismuth-213 was conjugated to lintuzumab. Sequential administration of cytarabine and ²¹³Bi-lintuzumab was assessed in a phase I/II trial in 31 patients with newly diagnosed (n = 13) or relapsed/refractory (n = 18) AML. The combination was found to be safe and effective.

A novel biologic targeted therapy, comprised of human interleukin (IL)-3 coupled to a truncated diphtheria toxin

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<td><strong>Agent</strong></td>
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Future Directions

Considerable efforts are elucidating the genetic and molecular abnormalities in AML. The “3+7” regimen is a poor standard of care; better regimens using FLAG-Ida (fludarabine, cytarabine, GM-CSF, and idarubicin) or adding cladribine or omacetaxine or GO already exist. The development of monoclonal antibody therapy for AML is lagging behind other malignancies, such as lymphomas, acute lymphocytic leukemia, and solid tumors. Convincing evidence suggests many AML patients benefit from GO and we strongly advocate that GO be made available again in the United States for AML therapy. Additional improved monoclonal antibodies should be tested expeditiously. Important research is ongoing to clarify the optimal use of FLT3 inhibitors. A large number of mutations have been identified in AML, and it will be important to establish which of these are “druggable” or amenable to disruption of the pathway they influence (Table 4).

REFERENCES


