Tyrosine Kinase Inhibitors for the Treatment of Philadelphia Chromosome-Positive Adult Acute Lymphoblastic Leukemia

Pier Paolo Piccaluga, MD, PhD
Stefania Paolini, MD
Giovanni Martinelli, MD

Institute of Hematology and Medical Oncology L and A Seràgnoli S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.

Acute lymphoblastic leukemia (ALL) is a heterogeneous disorder, with the greatest prevalence in children, but it also affects adults, and has an increasing incidence with age. Chromosomal abnormalities in ALL have been frequently described, the most common is the Philadelphia chromosome (Ph). The resulting fusion gene, \( BCR-ABL1 \), encodes for a chimerical oncoprotein (BCR-ABL) with constitutive tyrosine kinase activity, which leads to uncontrolled cell proliferation, reduced apoptosis, and impaired cell adhesion. Treating Philadelphia chromosome-positive (Ph\(^+\)) ALL patients with conventional chemotherapy has not substantially improved their long-term outcomes. Recently, however, BCR-ABL–targeted strategies have been successfully adopted. Imatinib is an oral competitive inhibitor of ABL with demonstrated phase 2 efficacy in patients with treatment-naïve and pretreated ALL. Despite its efficacy, imatinib may induce specific resistance in a large proportion of patients, mainly because of the occurrence of \( ABL1 \) mutations. Therefore, novel inhibitors have been developed. Dasatinib is a multitargeted kinase inhibitor of BCR-ABL, SRC, C-KIT, PDGFRs, and ephrin A receptor kinases. Unlike imatinib, it binds both the active and inactive BCR-ABL as well as the majority of ABL mutants. Dasatinib is approved for treatment of imatinib-pretreated Ph\(^+\) ALL, and chronic myeloid leukemia (CML) on the basis of phase 2 trials that demonstrated impressive efficacy and favorable tolerability profiles. Nilotinib is another BCR-ABL targeted agent that is similar in structure to imatinib but has significantly greater binding affinity. It also has demonstrated promising efficacy in Ph\(^+\) ALL but is still being evaluated in phase 2 trials. In this article, the authors reviewed current knowledge on novel tyrosine-kinase inhibitors in adult Ph\(^+\) ALL patients.

KEYWORDS: acute lymphoid leukemia, Philadelphia chromosome-positive acute lymphoblastic leukemia, Ph\(^+\) ALL, dasatinib, imatinib, nilotinib, \( BCR/ABL1 \), targeted therapy, tyrosine kinase inhibitors.

Pathophysiology of Philadelphia Chromosome-Positive Acute Lymphoid Leukemia (ALL)

ALL is a heterogeneous disorder deriving from transformation of hematopoietic stem cells and, possibly, from lymphoid-committed progenitor cells.\(^1,3\) In particular, ALL is the most common type of malignancy diagnosed in children, with an annual occurrence of approximately 30 cases per million and a peak incidence occurring between the ages of 3–4 years.\(^4,5\) In adults, ALL is less common, with approximately 7–18 cases per million diagnosed each year, although a second peak incidence occurs after the age of 70 years.\(^5,6\) Chromosomal abnormalities have been frequently described in this
disease; the most common in adult ALL is the Philadelphia chromosome (Ph), a truncated derivative of chromosome 22 that arises from the translocation of genetic material between this chromosome and chromosome 9 (t(9;22)(q34;q11)).6 The resulting fusion gene, BCR-ABL1 (Breakpoint Cluster Region-Abelson murine leukemia viral proto-oncogene), encodes for an abnormal, nonmembrane-bound oncoprotein. The oncoprotein is a constitutively active tyrosine kinase that perturbs numerous signal transduction pathways resulting in uncontrolled cell proliferation, reduced apoptosis, and impaired cell adhesion, and it has been shown to transform cells in culture by producing chronic myeloid leukemia (CML) and ALL-like syndromes in mice.7 Two fusion proteins of different sizes may be produced – p190 and p210. The p190 protein is found in approximately two-thirds of adults and in >90% of pediatric cases of Philadelphia chromosome-positive (Ph+) ALL, whereas p210 is typically found in patients with CML.8 Although p190 and p210 are provided with different transforming properties, the exact biochemical differences in their signaling are largely unknown. In addition, it is not established whether the 2 proteins behave differently concerning their response to different inhibitors. BCR-ABL is associated with deregulated and increased ABL tyrosine kinase activity,9 demonstrating activation in multiple signal transduction pathways, including Ras/Raf/mitogen-activated protein kinase (MAPK); phosphatidylinositol 3 kinase; STAT5/Janus kinase; and Myc.7,10,11 Many of these pathways are used by cytokines to regulate hematopoiesis, thereby allowing BCR-ABL to prolong survival and to increase proliferation of cells in early leukemogenesis. BCR-ABL has also been shown to associate directly with some of the SRC family tyrosine kinases, including Lyn and Hck, which facilitate BCR-ABL coupling to pathways related to transformation.7

Approximately 20%–30% of adult ALL patients present with Ph abnormality; notably, the prevalence of (t9;22)(q34;q11) increases with age, being greater in elderly rather than in young adults and children.12 Despite age, both adult and pediatric patients with Ph+ ALL typically have a poorer prognosis than patients without this chromosomal abnormality.13 Disease-free survival (DFS) rates at 2 years have been estimated to be only 10%–15% in Ph+ ALL patients

### TABLE 1
Clinical Results of Chemotherapy Regimens in Adult Ph+ ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy regimens</th>
<th>No. (% total)</th>
<th>CR, %</th>
<th>Median CRD, mo</th>
<th>CCR/DFS</th>
<th>Survival/EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloomfield16</td>
<td>Low-risk or standard-risk induction chemotherapy</td>
<td>29 (17)</td>
<td>46</td>
<td>7</td>
<td>NA</td>
<td>11-mo median survival</td>
</tr>
<tr>
<td>Secker-Walker17</td>
<td>UKALLa protocol</td>
<td>23 (20)</td>
<td>64</td>
<td>NA</td>
<td>NA</td>
<td>8-mo median survival</td>
</tr>
<tr>
<td>Gotz26</td>
<td>Daunorubicin, vincristine, prednisone, and L-asparaginase (phase 1); cyclophosphamide, Ara-C, and 6-mercaptopurine (phase 2)</td>
<td>25 (76)</td>
<td>76</td>
<td>9</td>
<td>NA</td>
<td>13-mo median survival; 6% 3-y EFS</td>
</tr>
<tr>
<td>Westbrook19</td>
<td>Daunorubicin-containing induction regimens</td>
<td>12 (23)</td>
<td>71</td>
<td>10</td>
<td>NA</td>
<td>11.2-mo median survival</td>
</tr>
<tr>
<td>Larson20</td>
<td>Cyclophosphamide; daunorubicin, vincristine, prednisone, and L-asparaginase</td>
<td>25 (29)</td>
<td>70</td>
<td>7</td>
<td>11% 3y CCR</td>
<td>16% 3-y survival</td>
</tr>
<tr>
<td>GFCH21</td>
<td>Anthracycline, prednisone, and vincristine as induction; Some received cyclophosphamide or L-asparaginase</td>
<td>127 (29)</td>
<td>59</td>
<td>NA</td>
<td>NA</td>
<td>5-mo median EFS; 5% 3-y EFS</td>
</tr>
<tr>
<td>Chir22</td>
<td>Daunorubicin, vincristine, prednisone, L-asparaginase (phase 1); cyclophosphamide, Ara-C, 6-mercaptopurine, methotrexate (phase 2), followed by consolidation, reinduction, and maintenance regimens</td>
<td>6 (38)</td>
<td>83</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Secker-Walker23</td>
<td>Daunorubicin, vincristine, L-asparaginase, prednisone, methotrexate as induction</td>
<td>40 (11)</td>
<td>83</td>
<td>NA</td>
<td>11 mo median</td>
<td>DFS 13% 3 y DFS</td>
</tr>
<tr>
<td>Thomas24</td>
<td>Anthracycline, prednisone, vincristine, and cyclophosphamide</td>
<td>43 (64)</td>
<td>64</td>
<td>NA</td>
<td>6-mo median DFS</td>
<td>9-mo median survival</td>
</tr>
<tr>
<td>Wetzler25</td>
<td>Daunorubicin, prednisone, vincristine, L-asparaginase, methotrexate as induction</td>
<td>67 (29)</td>
<td>82</td>
<td>NA</td>
<td>11 mo median DFS; 8% 5 y DFS</td>
<td>16-mo median survival; 11% 5-y survival</td>
</tr>
<tr>
<td>Fader26</td>
<td>Vincristine, Adriamycin, dexamethasone (VAD), or hyper-CVAD</td>
<td>67 (13)</td>
<td>90</td>
<td>10.2</td>
<td>10 mo (median DFS)</td>
<td>15.7-mo median survival</td>
</tr>
<tr>
<td>Ko27</td>
<td>Anthracycline, vincristine and prednisone (±cyclophosphamide, L-asparaginase) or vincristine and prednisone alone</td>
<td>26 (23)</td>
<td>64</td>
<td>NA</td>
<td>0% 5 y CCR</td>
<td>7% 5-y survival</td>
</tr>
<tr>
<td>Thomas28</td>
<td>Corticosteroid, vincristine; cyclophosphamide±anthracycline:bleomycin</td>
<td>10 (24)*</td>
<td>69</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Thomas29</td>
<td>Corticosteroid, vincristine; cyclophosphamide±anthracycline:bleomycin</td>
<td>51 (13)</td>
<td>NA</td>
<td>13% 5 y DFS</td>
<td>NA</td>
<td>10% 5-y survival</td>
</tr>
<tr>
<td>Amino30</td>
<td>Cyclophosphamide, vincristine, daunorubicin, asparaginase, and prednisone or same without Cy</td>
<td>47 (22)</td>
<td>83</td>
<td>9</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Adapted from Faderl 2002.

CR indicates complete remission; CCR, continuous complete remission; CRD, complete remission duration; EFS, event-free survival; NA, data not available; CVAD, cyclophosphamide, vincristine, adriamycin, and dexamethasone; Cy, cyclophosphamide.

*Patients aged >60 years.
who were treated with nonimatinib-based chemotherapy regimens.\textsuperscript{14}

Until recently, the only treatment options for patients with Ph\textsuperscript{1} ALL were conventional chemotherapy and, for a minority of cases, allogeneic stem-cell transplantation. Clinical results in adults before the availability of imatinib are summarized in Table 1 and were recently reviewed by Piccaluga et al.\textsuperscript{15–30}

**BCR-ABL\textsubscript{1} as a Therapeutic Target in Ph\textsuperscript{1} ALL**

Because the role of tyrosine kinases in the molecular pathogenesis of ALL has been well described, they make logical anticancer therapeutic targets. As shown in Figure 1, tyrosine kinases bind adenosine triphosphate (ATP) and catalyze the transfer of a phosphate group to the hydroxy group of a tyrosine residue on a protein participating in a signal transduction cascade.\textsuperscript{9,31}

Inhibition of tyrosine kinases by ATP competitive inhibitors has been a recent focus for new drug design. In this article, we review the evidence for tyrosine kinase inhibitors in adult Ph\textsuperscript{1} ALL.

**Imatinib for Relapsed Ph\textsuperscript{1} ALL**

Imatinib mesylate (formerly STI571 and Gleevec; Novartis Pharma, Basel, Switzerland) is an oral potent competitive inhibitor of ABL that has the ability to induce hematologic and cytogenic remissions (CyRs) in CML. Several phase 1 and 2 studies have evaluated the role of imatinib for the treatment of patients with relapsed or refractory Ph\textsuperscript{1} ALL (Table 2).\textsuperscript{32–35} These studies have reported a complete remission rate of approximately 20%, with 60% of patients achieving remission or clearance of peripheral blood blasts. Notably, molecular response was achieved in some cases. Unfortunately, these results

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**TABLE 2**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study description</th>
<th>No. (total)</th>
<th>Response (%)</th>
<th>Median CRD</th>
<th>TTP</th>
<th>Survival/EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Druker\textsuperscript{32}</td>
<td>Phase 1</td>
<td>20 (34) Ph\textsuperscript{1} ALL or lymphoid blast</td>
<td>14 (70); 4 CR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ottmann\textsuperscript{33}</td>
<td>Phase 2</td>
<td>48 (86)</td>
<td>19% CHR; 10% CMR</td>
<td>4 wk in 6% pts</td>
<td>2.2 mo TTP</td>
<td>4.9 mo survival</td>
</tr>
<tr>
<td>Wassmann\textsuperscript{34}</td>
<td>Phase 2</td>
<td>68</td>
<td>70% CHR; 29% CMR; CCyR 89% of CHR</td>
<td>NA</td>
<td>0.9 to 5.2 mo TTP</td>
<td>NA</td>
</tr>
</tbody>
</table>

TTP indicates; CCyR, complete cytogenic response; CHR, complete hematologic response; CMR, complete marrow response; CR, complete remission; CC, continuous complete remission; CRD, complete remission duration; EFS event-free survival; MCyR, major cytogenic response; MaHR, major hematologic response; NA data not available.
are not long lasting, with median times to disease progression and overall survival rates of 2.2 and 4.9 months, respectively. Interestingly, favorable outcomes of 51% disease-free survival after 1 year have been reported in subsets of patients that underwent allogeneic stem cell transplantation during remission.36 Interestingly, our group and others have shown that imatinib alone is able to induce molecular complete remission in patients with advanced Ph+ ALL and minimal residual disease after 2, 4, and 8 weeks of treatment was predictive of outcome.34,35

**Imatinib as Frontline Therapy for Ph+ ALL**

Several clinical studies have explored the role of imatinib as frontline therapy for Ph+ ALL disease by using various strategies as follows: in combination with induction and consolidation chemotherapy; as a single agent; and before stem cell transplantation (Table 3). The combination of imatinib has been evaluated with a variety of chemotherapy regimens including hyper-CVAD,37 and high-dose methotrexate/cytarabine.38 These studies report high complete remission of approximately 95% with encouraging overall survival rates of 88% at 1 year and acceptable toxicities.

Debate remains over whether concurrent or sequential regimens are most appropriate for Ph+ ALL, with a recent study by Wassmann et al. providing some clarity.39 In a study of 92 patients with newly diagnosed Ph+ ALL, 2 treatment schedules with imatinib administered concurrent to or alternating with a uniform induction and consolidation regimen were evaluated. Concurrent administration of imatinib and chemotherapy resulted in a complete remission rate of 95% and polymerase chain reaction (PCR) negativity for BCR-ABL in 52% of patients, compared with 19% in patients in the alternating treatment cohort ($P = .01$).

Additional studies that used imatinib as single-agent induction in elderly patients with newly diagnosed Ph+ ALL disease suggest that imatinib alone may be superior to chemotherapy in elderly patients (100% overall response vs 46% failures).40,41 Overall, the addition of imatinib to induction and consolidation regimens has almost certainly increased their antileukemic efficacy and will possibly influence achievement of improved long-term outcomes.42 Notably, the addition of imatinib to chemotherapy may also improve the curative potential of stem cell transplantation. In 1 study with 29 patients who had completed induction chemotherapy followed by allogeneic stem cell transplantation, a significantly greater number of patients treated with imatinib were transplanted, with sustained complete remission creating lower relapses and greater disease-free survival compared with historical controls (78% vs 39%, $P = .001$).43

**Development of Resistance During Imatinib Therapy**

Tumor cells can develop various mechanisms of resistance during therapy. Some of these mechanisms include up-regulation of alternative signaling pathways, drug-resistant variants of targeted proteins, and increased expression of drug efflux proteins.44 Despite initial hematologic or cytologic responses, many patients with Ph+ ALL become refractory to imatinib, or they relapse within several months. Primary or innate resistance is defined as a failure to achieve a complete remission despite therapeutic levels of imatinib. Secondary or acquired resistance to imatinib arises in the form of a relapse after an initial complete remission has been obtained. Several mechanisms of drug resistance in Ph+ leukemias have been postulated including 1) expression of a rapid drug efflux protein, or extracellular binding of drug molecules44; 2) Non–BCR-ABL–dependent transforming events involving SRC family; and 3) BCR-ABL–dependent events involving genetic changes in the ATP binding site that lead to decreased imatinib binding affinity.42 Genetic mutations in BCR-ABL

### TABLE 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Study description</th>
<th>No. % total</th>
<th>Response, %</th>
<th>Median CR</th>
<th>CCR/DFS/TTP</th>
<th>Survival/EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas37</td>
<td>Imatinib + CVAD</td>
<td>20</td>
<td>100% CR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yanada38</td>
<td>Phase 2, Imatinib + intensive chemo</td>
<td>80</td>
<td>71% PCR negative; 96% CR</td>
<td>5.2 mo</td>
<td>NA</td>
<td>OS 1 y: 73.3% allogeneic HSCT; 84.8% no HSCT</td>
</tr>
<tr>
<td>Wassmann39</td>
<td>Phase 2, concurrent or alternating imatinib with chemo</td>
<td>92</td>
<td>Concurrent: 95% CR, 52% PCR negative.</td>
<td>NA</td>
<td>NA</td>
<td>OS 1 y: 72%; Alternating: 72%; Concurrent: 61%</td>
</tr>
<tr>
<td>Lee52</td>
<td>Imatinib + Allo SCT</td>
<td>29</td>
<td>23% CR, 86.2% received SCT after 1st CR</td>
<td>NA</td>
<td>78.1% DFS</td>
<td>78.1% OS</td>
</tr>
</tbody>
</table>

CCR/HR indicates complete cytogenic response, CHR, complete hematologic response, CMR, complete marrow response, CR, complete remission; CCR continuous complete remission; CTD complete remission during; EFS event free survival; MCyR major cytogenic response, MaHR major hematological response, NA, data not available; CCR/DFS/TTP Survival/EFS
result in several possible changes as follows: the overexpression of BCR-ABL; disruption of contact points between imatinib and BCR-ABL and/or structural changes that activate BCR-ABL preventing the inhibitor from binding. Interestingly, the effect of additional cytogenetic abnormalities has not yet been well established.

Recently, Pfeifer et al. analyzed the ABL1 mutational status in 94 patients with relapsed Ph+ ALL or lymphoid blast crisis CML. They showed that tyrosine kinase domain mutations emerged in 54% and 83% of patients treated with imatinib alone or in combination with chemotherapy, respectively. In contrast, mutations were detected in only 18% of patients who had relapsed after stem cell transplantation and who had not been treated with imatinib. The vast majority (74%) of the mutations were found in the P-loop domain, whereas the T315I was the second most common (17%) location for mutations. This is noteworthy, because the latter mutation appears to confer resistance to imatinib as well as to novel tyrosine kinase inhibitors. Interestingly, in many cases, it was possible to detect the same mutation both before imatinib administration and again at relapse, thus suggesting that effective treatment of Ph+ ALL will require the up-front use of agents effective against mutant BCR-ABL. Finally, it should be underlined that resistance to TKI may reflect their inability to suppress leukemic stem cells, even though this phenomenon is still largely obscure.

Figure 2 summarizes potential mechanisms of resistance to imatinib postulated to occur in patients with Ph+ leukemias.

In summary, the use of imatinib has most likely improved clinical outcomes in patients with Ph+ leukemias. However, patients do relapse, and other therapeutic options are required. Patients who have failed or relapsed on imatinib-based therapy will typically follow a rapid and aggressive course of disease. Disappointing results observed in cases of imatinib resistance have led to the development and testing of novel noncross-resistant inhibitors, as described in the section below.

**Rational Design of Novel Kinase Inhibitors for Ph+ ALL**

Two novel therapies designed to inhibit wild-type and mutant forms of BCR-ABL and/or other molecular targets have been tested in clinical settings: dasatinib (formerly BMS 354825 and Sprycel; Bristol-Myers Squibb, New York, New York) and nilotinib (formerly AMN107; Novartis Pharma, Basel, Switzerland).

Dasatinib is a novel, oral, potent, multitargeted kinase inhibitor of BCR-ABL and SRC kinases (so-called dual inhibitor) that has been approved by the US Food and Drug Administration for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy. It has also been approved for the treatment of adults with chronic phase, acute phase, or myeloid or lymphoid blast phase CML with resistance to or intolerance of prior therapy, including imatinib. Its wide range of oncogenic targets include BCR-ABL, SRC kinases (including LYN, HCK, and C-KIT), PDGFRs, and ephrin A receptor kinase. Dasatinib has a 325-fold greater affinity for BCR-ABL than imatinib. Unlike nilotinib and imatinib, it can bind both inactive and active conformations of BCR-ABL (Fig. 3).

Because of its less stringent binding requirements, dasatinib has demonstrated inhibitory activity against imatinib-resistant mutations with the exception of T315I.

**Dasatinib for Ph+ ALL Refractory to, or Intolerant of, Imatinib**

A phase 1 dose-escalation study evaluated the safety and efficacy of dasatinib in 84 patients with imatinib-intolerant or resistant leukemias, including patients with Ph+ ALL as follows: 10 patients with lymphoid blast-phase CML or Ph+ ALL; 40 patients with chronic-phase CML; 11 patients with accelerated-phase CML; and, 23 patients with myeloid blast-phase CML. Dasatinib was administered at a dose of 15–240 mg either as 1 dose or twice a day. The main toxicity was grade 3 or 4 myelosup-
pression, which was effectively managed by dose modification. After a median follow-up of 5 to 12 months, clinical hematologic responses were maintained in 82% of accelerated-phase CML patients and 95% of chronic-phase CML patients, respectively. The major cytogenetic response (MCyR) rates were 25% and 45%, respectively. Although most patients with Ph

ALL or myeloid blast-phase CML relapsed in 6 months, responses occurred across all mutant BCR-ABL genotypes except for the T315I. Because of these promising phase 1 results, phase 2 studies were initiated.

The START program (SRC-ABL Tyrosine kinase inhibition Activity Research Trials) included 5 studies, ongoing at the time of approval, and investigating the safety and efficacy of dasatinib in patients with imatinib-resistant or imatinib-intolerant CML or Ph

1

ALL diseases as follows: chronic-phase CML57; accelerated-phase CML58; myeloid blast phase59, lymphoid blast-phase CML or Ph+ ALL59,60; and, chronic-phase CML compared with high-dose imatinib.61

The registration study demonstrated the effectiveness of dasatinib in patients with Ph+ ALL or lymphoid blast-phase CML on hematologic and cytogenetic response endpoints. This was an open-label study (CA180015 START-L) conducted in 42 centers worldwide, which enrolled 94 patients with imatinib-resistant or imatinib-intolerant lymphoid blast CML (n = 48) or Ph+ ALL (n = 46). Dasatinib was administered twice daily at a dose of 70 mg orally with escalation to 100 mg in patients with poor response or dose reductions to 40 mg twice daily in patients experiencing toxicity. Among patients with Ph+ ALL disease, 44 patients were resistant to imatinib with 78% (of 40 patients with baseline mutation data) expressing BCR-ABL mutations. The dasatinib dose was reduced in 30% of ALL patients and temporarily interrupted in 43%. At minimum 9 months of follow-up, the results yielded efficacy in the trial’s primary endpoint. Major hematologic response (MaHR) was 45%, including 35% complete hematologic response, and a high rate of cytogenetic complete remissions. The median duration of MaHR was 11 months, and progression-free survival was 3.7 months. Among all patients, the most frequent hematologic adverse events were grade 3–4 thrombocytopenia and neutropenia, with diarrhea, nausea, pyrexia, and pleural effusion as major nonhematologic toxicities. Dasatinib demonstrated significant and clinically meaningful activity in heavily pretreated patients with Ph+ ALL.60,62,63 Results of the study are summarized in Table 4.60

### TABLE 4

<table>
<thead>
<tr>
<th>Characteristic/Parameter</th>
<th>Ph+ ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled patients</td>
<td>46</td>
</tr>
<tr>
<td>Median age, y</td>
<td>48</td>
</tr>
<tr>
<td>Major hematologic response, ≥4 wk, %</td>
<td>45</td>
</tr>
<tr>
<td>Complete hematologic response, %</td>
<td>35</td>
</tr>
<tr>
<td>Major cytogenetic response, %</td>
<td>57</td>
</tr>
<tr>
<td>Complete cytogenetic response, %</td>
<td>54</td>
</tr>
<tr>
<td>Duration of response, mo</td>
<td>11</td>
</tr>
<tr>
<td>ABL1 mutation occurrence, %</td>
<td>78</td>
</tr>
<tr>
<td>Dose reduction, %</td>
<td>30</td>
</tr>
<tr>
<td>Dose interruption, %</td>
<td>43</td>
</tr>
<tr>
<td>Main cause of discontinuation</td>
<td>Nonhematologic AEs</td>
</tr>
<tr>
<td>Progression-free survival, mo</td>
<td>3.7</td>
</tr>
</tbody>
</table>

AEs indicate adverse events.

Nilotinib for Ph+ ALL Refractory to, or Intolerant of, Imatinib

Nilotinib is an oral ATP-competitive inhibitor of BCR-ABL in clinical development with a modified aminopyrimidine backbone comparable to imatinib.

Similar to imatinib, nilotinib can bind only the inactive conformation of the ABL kinase domain but with a 25-fold greater affinity than imatinib. Nilotinib has demonstrated activity in imatinib-resistant mutations, with the exception of T315I. In a phase 1 study that included patients with either imatinib-resistant CML or Ph+ ALL, 10% of Ph+ ALL patients enrolled (n = 10) achieved complete hematologic responses with no cytogenetic responses following treatment with nilotinib. Grade 3–4 adverse events reported with nilotinib. Grade 3–4 adverse events reported with no mutations at baseline. Results of this phase 1 study are summarized in Table 5.

CONCLUSIONS
The use of targeted therapies such as imatinib against BCR-ABL tyrosine kinase has led to significant improvements in the treatment of patients with Ph+ ALL. Unfortunately, relapses do occur. With a growing understanding of the molecular basis for imatinib resistance, including BCR-ABL1 gene mutations and the development of BCR-ABL independent pathways, novel drugs are being evaluated. The second generation small tyrosine kinase inhibitor, dasatinib, has demonstrated robust clinical activity in patients with Ph+ ALL resistant to or intolerant of imatinib. Combined with a favorable tolerability profile, the recent approval of dasatinib provides a new option for patients with Ph+ ALL and heralds a significant breakthrough in this difficult-to-treat patient population (Tables 2 and 3). Nilotinib, which is still under evaluation in phase 2 trials, may represent another interesting option, while further strategies for treating patients with imatinib-resistant leukemia are also currently under investigation. Some compounds have been designed for combination with imatinib, such as Raf kinase inhibitors, the farnesyl transferase inhibitors lonafarnib (SCH66336), and tipifarnib (R115777), mTOR, cyclin-dependent kinase inhibitors, and histone deacetylase inhibitors. Aurora kinase inhibitors (eg, MK-0547) in Ph-negative ALL with T315I mutations are also in development. Clinical data from studies that are investigating the use of these compounds are awaited with interest.

REFERENCES

TABLE 5
Nilotinib in Imatinib-Resistant Ph+ ALL Patients: Summary of a Phase 1 Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Study description</th>
<th>No., % total</th>
<th>Response, %</th>
<th>Median CRD</th>
<th>CCR/DFS/ EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantarjian</td>
<td>Phase 1, AMN107 (Ph+ ALL or CML (imatinib-resistant))</td>
<td>119 (Ph+ ALL)</td>
<td>69% response in pts w/baseline mutations; 55% no mutations</td>
<td>15 CRD 160 d</td>
<td>NA NA</td>
</tr>
</tbody>
</table>


