New Developments in Tyrosine Kinase Inhibitor Therapy for Newly Diagnosed Chronic Myeloid Leukemia

Philipp le Coutre, Michaela Schwarz, and Theo D. Kim

Abstract

The biology of chronic myeloid leukemia (CML) has enabled pioneering studies with targeted therapies. BCR-ABL inhibition with imatinib results in high levels of efficacy in patients with newly diagnosed CML in chronic phase (CP), but an estimated 35% of patients could benefit from more effective treatment. Several novel treatment strategies are being investigated in newly diagnosed CML-CP. These strategies include upfront treatment with next-generation tyrosine kinase inhibitors, such as dasatinib, nilotinib, or bosutinib, which also target BCR-ABL but with increased in vitro potency compared with imatinib, and possibly a reduced potential for resistance. Recent in vitro studies have shown that short-term exposure to dasatinib or continuous exposure to imatinib result in equivalent levels of apoptosis, indicating that potent intermittent inhibition is a successful strategy for improving dasatinib tolerability. Modified imatinib regimens are also being investigated in newly diagnosed CML-CP, including higher doses and combination with alternative classes of agents, such as interferon. Existing data suggest that both newer agents and combination approaches can improve treatment responses compared with standard imatinib treatment, although further data are needed, particularly from ongoing phase 3 trials, before the standard of care is revised. Clin Cancer Res; 16(6); 1771–80. ©2010 AACR.

The development of chronic myeloid leukemia (CML) in chronic phase (CP) seems to result entirely from the activity of a single oncogenic fusion gene, BCR-ABL, formed during the creation of the Philadelphia (Ph) chromosome (1). Therapies that block BCR-ABL tyrosine kinase activity have the potential to substantially delay or arrest disease progression from CP disease. In advanced-phase disease, additional genetic changes, potentially induced by BCR-ABL activity, limit the effectiveness of targeted therapy (2, 3). The current article focuses on CML-CP.

Following the diagnosis of CML-CP, patients are currently treated with 400 mg/d of imatinib, a tyrosine kinase inhibitor (TKI) of BCR-ABL. The approval of imatinib for treating newly diagnosed CML followed unprecedented efficacy observed during the IRIS [International Randomized Study of Interferon (IFN) versus STI-571] trial (4). After 19 months of follow-up, rates of major cytogenetic response (85% versus 22%, P < 0.001) and complete cytogenetic response (CCyR; 74% versus 9%, P < 0.001) were significantly higher with imatinib than with IFN plus cytarabine, the previous standard of care (5). Estimated rates of major molecular response (MMR; i.e., BCR-ABL transcript reduction to 0.1% of the standardized baseline) at 12 months were 39% versus 2%, respectively (based on available data from patients in CCyR), indicating substantial reductions in residual disease (6). Imatinib also had superior tolerability to IFN. With follow-up now at 8 years, imatinib’s efficacy has been maintained, with the cumulative CCyR rate reaching 83%, overall survival (OS) of 85%, and 55% of patients initially randomized to imatinib remaining on study and in CCyR (7). A recent single-center analysis of imatinib-treated patients with newly diagnosed CML-CP (N = 204) reported similar efficacy to IRIS, and found that after 5 years, the probability of maintaining at least a partial cytogenetic response (PCyR) was 63% (8). These data indicate that although response and survival rates are high, approximately 35% of patients have intolerance or some form of intrinsic or acquired resistance to imatinib and could benefit from more effective treatment. Potential mechanisms associated with inadequate response include: BCR-ABL kinase domain mutations; BCR-ABL or Ph chromosome amplification; clonal evolution; inadequate plasma concentrations due to pharmacokinetic variability or noncompliance; variations in expression of drug transport proteins; and loss of BCR-ABL dependence through the overexpression of downstream signaling molecules, particularly SRC-family kinases (9–16).

Strategies to optimize front-line therapy in newly diagnosed CML-CP include: upfront treatment with next-generation TKIs or upfront treatment with modified imatinib regimens.
Translational Relevance

Developments in therapy for chronic myeloid leukemia (CML) continue to be driven by in vitro studies, and lessons learned from this disease have potential application to other cancers. Recent studies in patients with newly diagnosed CML with novel tyrosine kinase inhibitors or modified imatinib regimens suggest that it may be possible to improve on the already impressive efficacy of standard imatinib monotherapy. These studies show that even if an established targeted therapy exists, agents with altered chemistry and increased target potency and/or specificity, or combination treatment using different classes of therapy, have the potential to increase responses to front-line therapy. Recent developments in therapy have been built on a detailed molecular and cellular understanding of the biology of CML.

Distinctive Characteristics of Next-Generation TKIs

Like imatinib, dasatinib, nilotinib, and bosutinib are orally administered and bind at overlapping sites within the ATP-binding site of BCR-ABL. Dasatinib has more than 300-fold higher in vitro potency (lower in vitro IC50) than imatinib against BCR-ABL and a completely different chemical structure (17–19). Whereas imatinib binds only the closed conformation of ABL, dasatinib binds to the open (active) conformation. X-ray modeling suggested that dasatinib could also bind the closed ABL conformation, although nuclear magnetic resonance (NMR)-based studies have detected dasatinib complex in open conformation only (19, 20).Dasatinib has a shorter half-life than imatinib (3.6 to 15 to 27 hours) and no highly active metabolites, whereas imatinib has an active primary metabolite (N-desmethyl imatinib) with a half-life of 40 to 70 hours (21–23). Whereas imatinib inhibits few kinases other than BCR-ABL [including c-KIT and platelet-derived growth factor receptor (PDGFR)], dasatinib inhibits additional kinases, including the SFKs (24, 25). It has not been elucidated which attribute(s) contributes to the improved activity of dasatinib.

Nilotinib was developed through chemical modification of imatinib and has a similar structure, with 30-fold higher in vitro potency against BCR-ABL (26). Compared with imatinib, nilotinib has a near-identical binding site within ABL, but requires fewer hydrogen bonds (four versus six), enabling binding to numerous imatinib-resistant BCR-ABL mutants (17, 18, 26). In NMR studies, nilotinib bound the closed ABL conformation only (20). Nilotinib has a similar half-life (approximately 17 hours) and kinase target profile to imatinib, albeit with increased specificity for BCR-ABL (25–27). Among approved BCR-ABL inhibitors, nilotinib has the highest IC50 for c-KIT and PDGFR, limiting potential toxicity caused by off-target inhibition of these molecules.

Bosutinib inhibits BCR-ABL with 10- to 20-fold higher in vitro potency than imatinib, and binds to an intermediate conformation of ABL (18, 28). Bosutinib has a half-life of 22 to 27 hours and inhibits a broader range of kinase targets than imatinib or nilotinib, including SFKs, but with low activity against c-KIT and PDGFR (25, 28, 29).

In addition to the agents discussed above, INNO-406 (NS-187) and AP24534 are novel ATP-competitive TKIs in early clinical development (30–32). Encouraging phase 1 data have been reported for both agents, including CCyRs to AP24534 in patients with a T315I mutation (33, 34).

Clinical Development of Next-Generation TKIs for Newly Diagnosed CML-CP

Dasatinib, nilotinib, and bosutinib were initially evaluated in patients with imatinib-resistant or -intolerant CML or Ph+ acute lymphoblastic leukemia (Ph+ ALL; refs. 35–44). In clinical studies with 2 years of follow-up, both dasatinib and nilotinib have shown efficacy in CML-CP (Table 1; refs. 44–46). Follow-up in the bosutinib trial is currently too short to draw full conclusions, although data are encouraging. No studies have been initiated to compare different next-generation TKIs or determine the optimal time point for switching to second-line treatment. Currently, dasatinib is approved for all phases of CML or Ph+ ALL following imatinib resistance or intolerance, and nilotinib is approved for patients with CP or accelerated-phase CML following imatinib resistance or intolerance.

Dasatinib and nilotinib have been assessed in small single-arm phase 2 studies in newly diagnosed CML-CP. In the dasatinib study, 50 patients received either dasatinib 100 mg once daily or 50 mg twice daily, and responses were similar for both dosing groups. At 3, 6, and 12 months, 82%, 94%, and 98% of evaluable patients were in CCyR, and at 12 and 18 months, 71% and 79% of patients were in MMR (47). Two studies of nilotinib 400 mg twice daily in newly diagnosed CML have been done (N = 51 and N = 73; refs. 48, 49). Following nilotinib treatment, CCyR at 3, 6, and 12 months was 78 to 90%, 96%, and 96 to 97%, respectively. MMR rates at 12 to 18 months were 79 to 85%. With both dasatinib and nilotinib, 12-month response rates compare favorably with historical imatinib data (Fig. 1).

Across multiple studies, BCR-ABL inhibitors have been well tolerated, with few adverse event (AE)-related discontinuations. With imatinib, dasatinib, and nilotinib, cytopenias are the most common grade 3–4 AEs (Table 2), although this normally occurs during initial therapy and probably represents antileukemic activity. The most common nonhematologic AEs are gastrointestinal symptoms (diarrhea, vomiting, nausea), skin complaints (rash, pruritus), and nonspecific AEs (headache, fatigue, musculoskeletal pain), with few grade 3–4 AEs. However,
differences exist in AE profiles between agents. Fluid retention has been noted with dasatinib, including pleural effusion of any grade in 14% of patients treated with 100 mg once daily during 2 years of follow-up (grade 3 in 2%). Bleeding was recorded in 11% of patients treated with dasatinib 100 mg once daily (grade 3/4 in 1%; ref. 50). With nilotinib, changes in biochemical markers were notable, with grade 3–4 hyperglycemia or elevated lipase occurring in 12 and 18% of patients, respectively (46). QT interval prolongation has been observed with both dasatinib and nilotinib, although fewer than 1% of study populations experienced a QTcF > 500 msec (51, 52). Nilotinib US product labeling contains a warning related to QT prolongation and sudden deaths, on the basis of sudden death occurring in five patients (0.6%) during the nilotinib study program. With both drugs, AEs are manageable with appropriate monitoring and temporary dose interruption and/or reduction, and comorbidities should be considered prior to treatment. Whether the toxicities of both agents result from inhibition of alternative targets remains unclear. Current data for bosutinib suggest favorable safety, although few patients have been treated compared with approved agents.

Phase 3 trials are now comparing the efficacy and safety of imatinib with dasatinib, nilotinib, or bosutinib in first-line treatment of newly diagnosed CML-CP. Although standard endpoints will be assessed in each trial, different primary endpoints have been selected (Table 3). The ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients) trial compares two twice daily doses of nilotinib (300 mg and 400 mg) to a standard imatinib arm (400 mg once daily) in a randomized design (1:1:1) in 846 patients with newly diagnosed CML-CP. Initial results have shown that both nilotinib doses are associated with significantly higher 12-month rates of CCyR (300 mg: 80%; 400 mg: 78%) and MMR (300 mg: 44%; 400 mg: 43%) compared with imatinib (CCyR: 65%; MMR: 22%; Fig. 1). Furthermore, progression to accelerated phase (AP) or blast crisis (BC) occurred in 11 patients (3.9%) in the imatinib arm, compared with only 2 (0.7%) in the nilotinib 300-mg arm, and 1 (0.4%) in the nilotinib 400-mg arm (53). In addition, in the GiMENA CMLD048 single-arm study, 114 patients will receive alternating 3-month treatment with imatinib followed by nilotinib, with a primary endpoint of CCyR at 12 months (NCT00769327). In the Irish Clinical Oncology Research Group study, approximately 40 patients will be treated with nilotinib 300 mg twice daily (NCT00809211).

**Table 1.** Response rates in phase 2 studies of next-generation TKIs in patients with CML-CP after imatinib resistance or intolerance

<table>
<thead>
<tr>
<th>Response</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Bosutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Minimum</td>
<td>Minimum</td>
<td>Resistant: 5 mo</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>387</td>
<td>321</td>
<td>201</td>
</tr>
<tr>
<td>Resistant (%)</td>
<td>74</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>Intolerant (%)*</td>
<td>26</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>CHR (%)</td>
<td>Overall</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>No baseline</td>
<td>87</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>CHR</td>
<td>MCR (%)</td>
<td>62</td>
<td>59</td>
</tr>
<tr>
<td>CCyR (%)</td>
<td>53</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>PFS (%)¹</td>
<td>12 mo</td>
<td>91</td>
<td>73</td>
</tr>
<tr>
<td>24 mo</td>
<td>80</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>OS (%)</td>
<td>12 mo</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>24 mo</td>
<td>92</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHR, complete hematologic response; NA, not available; NR, not reported; MCR, major cytogenetic response.

*In the nilotinib trial, intolerance to imatinib was defined as having intolerance with no MCR. In the dasatinib trial, imatinib-intolerant patients included patients who had achieved a MCR.

¹In the dasatinib study, progression was defined as increasing white blood cell count, loss of complete hematologic response or MCR, development of accelerated- or blast-phase disease, or death. In the nilotinib study, progression was defined as development of accelerated- or blast-phase disease, or death (44–46).

**TKIs and BCR-ABL Mutations**

Mutations of the BCR-ABL kinase domain are the most common mechanism of imatinib resistance. More than 50 imatinib-resistant BCR-ABL mutations have been described, and *in vitro* studies have shown that T315I and certain mutations within the P-loop region (Y253F/H, E255K/V) have the highest levels of imatinib resistance (15, 17, 18). However, unlike advanced-phase CML, T315I is relatively uncommon in CML-CP (Fig. 2; refs. 15, 54). Although T315I is also highly resistant to dasatinib, nilotinib, and bosutinib, each agent has a distinct *in vitro* IC₅₀ profile against other mutations (17, 18). Clinical activity also depends partly on *in vivo* parameters such as maximum serum concentrations. Because compound resistance can occur, i.e., the combination of two or more mechanisms of imatinib resistance, caution is advised when selecting TKI treatment purely on the basis of kinase domain mutations, although correlation has been observed in clinical studies between mutation type and frequency of response to dasatinib or nilotinib (54–56).

During *in vitro* mutagenesis studies, both dasatinib and nilotinib showed a substantially decreased potential for mutational resistance than did imatinib, which may reflect the higher potency of newer agents. Using
intermediate drug concentrations, dasatinib-selected mutations occurred in residues T315 and F317, whereas commonly selected mutations with nilotinib occurred in residues Y253, E255, T315, and F359 (57–59). Subsequent clinical data have confirmed in vitro observations, with the same mutations being associated with insensitivity and/or resistance to dasatinib or nilotinib (55, 60–63). Mutations affecting residue V299 have also been associated with dasatinib resistance (60–62).

In vitro studies suggest that the modified chemistry of next-generation TKIs compared with imatinib could decrease the potential for resistance caused by mechanisms other than BCR-ABL mutation, e.g., reduced OCT-1 expression (64, 65), or SFK-mediated resistance (66, 67). However, the frequency and clinical relevance of SFK-mediated resistance is unclear.

**Potent Intermittent BCR-ABL Inhibition With Dasatinib**

Dasatinib was investigated in initial registration studies using twice daily dosing. However, retrospective analysis...
of phase 1 data suggested that once daily treatment had similar efficacy to twice daily treatment, but with improved tolerability (68). In a subsequent phase 3 dose-optimization trial, dasatinib 100 mg once daily was confirmed to have similar efficacy to other dosing regimens, including the previously approved 70 mg twice daily dose, but with significantly fewer AEs, particularly pleural effusion (6-month data: all grades, 7% versus 11–16%; *P* = 0.024; ref. 69). As a result, 100 mg twice daily became the approved dasatinib dose in CML-CP. Indeed, pharmacokinetic analysis showed that dasatinib 100 mg once daily treatment resulted in a lower steady-state trough concentration (Cmin) than other dosing arms, and lower Cmin correlated with less frequent AEs (70).

In vitro studies have shown that transient dasatinib treatment of CML cells results in equivalent cytotoxic effects to prolonged treatment, potentially explaining clinical findings (71, 72).

### Evolution of Imatinib-Based Therapy for Newly Diagnosed CML-CP

In addition to next-generation TKIs, modified imatinib-based treatment is also being evaluated. One early hypothesis was that high-dose imatinib might improve on responses. In two single-arm phase 2 studies of imatinib 800 mg/d (400 mg twice daily), response rates after 12 to 18 months (CCyR in 83–90%, MMR in 54–63%) were higher than historical data for imatinib 400 mg once daily, with no tolerability issues reported (73, 74). Similarly, a single-arm phase 2 trial of imatinib 800 mg/d in patients with intermediate Sokal risk scores (*n* = 78) reported higher rates of CCyR (88% at 12 months) and MMR (69% overall) than in equivalent patients from IRIS, although AE rates were slightly increased (75).

To more rigorously assess the efficacy of high-dose imatinib, randomized studies have been done. In the phase 3 TOPS (Tyrosine kinase inhibitor Optimization and Selectivity) trial, 476 patients with newly diagnosed CML-CP were randomized 2:1 to imatinib 800 or 400 mg/d. Response rates were higher for 800 versus 400 mg/d at 6 months (CCyR in 57% versus 45%, *P* = 0.0146; MMR in 34% versus 17%, *P* = 0.0002), but not at 12 months (CCyR in 70% versus 66%, *P* = 0.3470; MMR in 46% versus 40%, *P* = 0.2035; ref. 76). At 24 months, rates of event-free survival, progression-free survival (PFS), and OS were almost identical (77). A randomized phase 2 study of imatinib 800 versus 400 mg/d has also been done in patients with high Sokal-risk CML-CP, which found similar response rates at all time points (78). Across several studies, post hoc analyses suggested that patients able to tolerate and maintain an imatinib dose of 800 mg/d achieved the highest response rates. Overall, available data have not provided a rationale for high-dose imatinib treatment in newly diagnosed CML-CP.

Following suboptimal response, imatinib dose escalation from 400 to 600 and/or 800 mg/d is often done.

### Table 2. Grade 3–4 AEs (regardless of causality) following treatment of patients with newly diagnosed CML-CP during phase 3 (imatinib) or phase 2 (dasatinib-nilotinib) trials

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8%</td>
<td>11%,</td>
<td>3–11%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14%</td>
<td>21%</td>
<td>4–12%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3%</td>
<td>9%</td>
<td>0–5%</td>
</tr>
<tr>
<td>Nonhematologic (≥3%)</td>
<td>Musculoskeletal pain: 3%</td>
<td>Fatigue: 6%</td>
<td>Rash: 2–5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Musculoskeletal pain: 6%</td>
<td>Fever: 0–5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspnea: 5%</td>
<td>Musculoskeletal pain: 2–4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Memory impairment: 5%</td>
<td>Pruritis: 0–4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuropathy: 5%</td>
<td>Fatigue: 0–3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac: 3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache: 3%</td>
<td></td>
</tr>
<tr>
<td>Elevated biochemical markers</td>
<td>ALT/AST: 5%</td>
<td>Hyperglycemia: 2%</td>
<td>Bilirubin: 7–16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypophosphatemia: 2%</td>
<td>Lipase: 5–8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyponatremia: 2%</td>
<td>ALT: 0–8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>yGT: 0–7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperglycemia: 3–5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amylase: 2–4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AST: 0–3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypophosphatemia: 0–3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperkalemia: 0–2%</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase (5, 47–49).
Studies have shown that nonresponding patients can achieve a durable response following dose escalation (79–81), although no evidence exists to show that the rate of response is higher than would have been achieved with no escalation. The single-arm phase 2 TIDEL (Therapeutic Intensification in DE-novo Leukemia) study (N = 103) investigated treatment with an imatinib starting dose of 600 mg/d, with escalation to 800 mg/d done if aggressive criteria for suboptimal response were met. At 12 months, response rates were 88% for CCyR and 47% for MMR, which were higher than reported during IRIS for standard imatinib dosing at the equivalent time point (Fig. 1).

Table 3. Ongoing randomized trials of next-generation TKIs versus imatinib in patients with newly diagnosed CML-CP

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arms</th>
<th>Estimated enrollment</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA180-056</td>
<td>Dasatinib 100 mg once daily</td>
<td>518 (Complete)</td>
<td>CCyR at 12 mo</td>
</tr>
<tr>
<td>(DASISION)</td>
<td>Imatinib 400 mg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(NCT00481247)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPIRIT2</td>
<td>Dasatinib 100 mg once daily</td>
<td>810</td>
<td>Event-free survival at 5 y</td>
</tr>
<tr>
<td>(ISRCTN54923521)</td>
<td>Imatinib 400 mg once daily</td>
<td></td>
<td>MMR at 12 mo</td>
</tr>
<tr>
<td>S0325</td>
<td>Dasatinib 70 mg twice daily</td>
<td>400 (Complete)</td>
<td></td>
</tr>
<tr>
<td>(NCT0070499)</td>
<td>Imatinib 400 mg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAMN107A2303</td>
<td>Dasatinib 300 mg twice daily</td>
<td>846 (Complete)</td>
<td>MMR at 12 mo</td>
</tr>
<tr>
<td>(ENESTnd)</td>
<td>Imatinib 400 mg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAMN107A2405</td>
<td>Dasatinib 400 mg twice daily</td>
<td>192 (patients with persistently detectable BCR-ABL after CCyR on imatinib)</td>
<td>CMR at 12 mo</td>
</tr>
<tr>
<td>(ENESTcmr)</td>
<td>Imatinib 400 mg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3160A4-3000</td>
<td>Dasatinib 500 mg once daily</td>
<td>412 (Complete)</td>
<td>CCyR at 12 mo</td>
</tr>
<tr>
<td>(NCT00574873)</td>
<td>Imatinib 400 mg once daily</td>
<td></td>
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</tr>
</tbody>
</table>

Fig. 2. Bar chart showing the 11 most commonly mutated residues of BCR-ABL after imatinib treatment of patients with CML-CP, as observed in pooled analyses by Apperley (15) and Müller et al. (54). For each residue, the range of potential amino acid changes reported in either analysis is shown. The Apperley analysis reported the affected residue only for patients with CML-CP, and hence the range of potential changes may include some detected only in patients with advanced phases of CML. Of amino acid changes listed above, those observed in patients with CML-CP in the analysis by Müller et al. were: M244V, L248V, G250A/E/V, Y253F/H, E255D/K/R/V, T315I, F317C/L/V, M351T, E355A/G/K, F359C/I/L/V, and H396P/R.
However, the authors noted that similar rates were achieved later in the IRIS trial, suggesting that responses might be more rapid rather than increased overall (82). In recent retrospective studies, lower response rates have been correlated with low C\textsubscript{min} (13, 14). Preliminary prospective data suggest that dose escalation in patients with low C\textsubscript{min} (<1,000 ng/mL) at day 22 can increase C\textsubscript{min} and restore molecular responses at 6 months to levels similar to patients with higher C\textsubscript{min} at day 22 (83). Further data are needed to confirm these findings.

Imatinib-based combination treatment is being evaluated in large clinical trials. In the French SPIRIT trial, patients were randomized 1:1:1:1 to receive imatinib 400 mg/d, 600 mg/d, 400 mg/d plus cytarabine, or 400 mg/d plus pegylated IFN (N = 636). CCyR rates at 12 months were 55% versus 62% versus 63% versus 65%, respectively (P = NS; Fig. 1). After 18 months, MMR rates were 41% versus 52% versus 53% versus 62% (P = 0.0001). PFS was similar across all arms. Grade 3–4 cytopenia occurred more frequently in combination arms versus imatinib monotherapy (~40% versus ~10%), and almost half of patients in the imatinib plus IFN arm discontinued IFN within 12 months (84, 85). The German CML Study Group has done a similar trial (study IV) of imatinib 400 mg/d versus 800 mg/d versus 400 mg/d plus pegylated IFN. Response rates were higher in the imatinib 800-mg/d arm (CCyR 65%, MMR 54%) than in imatinib 400-mg/d arms with or without IFN (CCyR 52% and 51%; MMR 30% and 35%, respectively). PFS or OS were similar during 5 years of follow-up (86).

Even with extended treatment, TKI monotherapy is unlikely to eradicate quiescent leukemic stem cells and cure patients with CML. However, BCR-ABL transcripts become undetectable in a small proportion of imatinib-treated patients (8% in one study; ref. 8). Two small studies have examined outcomes after imatinib discontinuation in patients with undetectable BCR-ABL transcripts on imatinib after previous stem-cell transplant or IFN-chemotherapy (87, 88). In both studies, approximately half of patients maintained molecular remission after imatinib was discontinued, including several patients who maintained molecular remission throughout 37 months of median follow-up (89). Importantly, relapsing patients responded to further imatinib treatment. Two prospective studies are now investigating imatinib discontinuation in patients with at least 2 years of undetectable BCR-ABL transcripts. In the STIM (STop IMatinib) study (N = 69), the probability of maintaining molecular remission at 12 months was similar in patients with or without IFN pretreatment (45% and 44%, respectively). Most relapses (39 out of 41) occurred within 7 months of imatinib discontinuation (89). In an Australian study, molecular remission was maintained in 3 out of 5 patients who had received imatinib only and 10 out of 13 who received prior IFN (90). These data suggest that in selected patients, molecular remission might be maintained without imatinib treatment, although discontinuation should not be done outside of a clinical trial and longer follow-up in larger study populations is needed.

Conclusions

The specific molecular characteristics of BCR-ABL-positive CML resulted in studies with targeted therapies. These studies have shown that even if an effective inhibitor of a molecular target exists, i.e., imatinib, alternative agents with increased potency and altered chemistry can induce responses after failure of the initial therapy or potentially improve on response rates during front-line therapy. Compared with imatinib, next-generation TKIs have an increased potential to avoid or overcome mutations and other causes of resistance. In addition, in one trial, combination treatment with a TKI (imatinib) and a different class of therapy (pegylated IFN) was found to reduce levels of residual disease, although it is not clear if this will translate into improved long-term outcomes. In all ongoing trials in newly diagnosed CML, meaningful clinical benefits must be shown before any change is made to the standard of care. In the future, novel therapies, e.g., CML vaccines or stem cell-targeted agents, could provide additional benefits. However, it is likely that any novel treatment for CML will be administered either following or in combination with a BCR-ABL inhibitor, and that TKI therapies will provide the foundation for treating newly diagnosed CML-CP for the foreseeable future.

Disclosure of Potential Conflicts of Interest

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References

6. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly published OnlineFirst March 2, 2010; DOI: 10.1158/11078-0432.CCR-09-2760


(CML-CP) with resistance or intolerance to imatinib: a 2-year update of the START-C study, Haematologica 2008;93:0934.


58. van Bubnoff N, Manley PW, Mestan J, Sanger J, Peschel C, Duyster J. Bcr-Abl resistance screening predicts a limited spectrum of point mutations to be associated with clinical resistance to the Abi kinase inhibitor nilotinib (AMN107). Blood 2006;108: 1328–33.


64. White DL, Saunders VA, Dang P, et al. OCT-1 mediated influx is a key determinant of the intracellular uptake of imatinib but not nilotinib (AMN107); reduced OCT-1 activity is the cause of low in vitro sensitivity to imatinib. Blood 2006;108:697–704.


83. Osborn MP, White DL, Saunders VA, et al. Early dose-escalation in chronic myeloid leukemia patients with low plasma imatinib levels leads to equivalent BCR-ABL values and drug levels at 6 months to
those with optimal drug levels: first analysis from the TIDEL II trial of de-novo patients treated with 600 mg imatinib. Blood 2009;114: 1131.


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