A diagnosis of chronic myeloid leukemia (CML) remains unwelcome news. Thanks to imatinib, however, the majority of newly diagnosed patients with chronic phase CML achieve a complete cytogenetic response (CCyR) and can expect long-term survival, often without major side effects (1). Unfortunately, these responses are not equivalent to a cure because residual leukemia cells persist even in patients who become negative by reverse transcription-PCR, and recurrence of active leukemia is common upon imatinib cessation. The mechanisms that allow CML stem cells to survive in the presence of drug are largely unknown, and it is currently unclear how these cells can be specifically targeted to achieve disease eradication (reviewed in ref. 2). For patients with advanced phase CML or Philadelphia chromosome–positive acute lymphoblastic leukemia, the agenda is different: imatinib responses are mostly transient, and eligible patients are advised to proceed to allograft, using imatinib as a bridge. For those without a transplant option, the long-term outlook remains grim.

We begin with an update on second-generation inhibitors for patients with resistance or intolerance to imatinib, including challenges such as pan-resistant BCR-ABL mutations and BCR-ABL–independent progression in advanced disease. We then examine current strategies for achieving disease eradication by targeting CML stem cells.

Second Generation Inhibitors: Concept to Clinic in Record Time

It is estimated that ~30% of patients receiving imatinib as frontline therapy will switch to an alternative therapy within 5 years due to side effects or onset of imatinib resistance (1, 3, 4). At the time of imatinib resistance, restoration of BCR-ABL tyrosine kinase activity is frequently demonstrable by assessing the phosphorylation status of the adaptor protein CrkL, a BCR-ABL substrate. Feeding information gained from pharmacodynamic studies with this biomarker back into the laboratory led to the discovery that BCR-ABL kinase domain mutations are a major mechanism of imatinib resistance and treatment failure (5). Once the molecular basis for imatinib resistance and for imatinib binding to the ABL kinase were delineated (6), the search for BCR-ABL inhibitors that retain efficacy against imatinib-resistant mutants was on. The two main approaches taken involved structural modifications to imatinib (Fig. 1A) and exploiting the anti-ABL activity of compounds developed as SRC kinase inhibitors (Fig. 1B). Among clinical inhibitors emerging from this laboratory work, nilotinib (7, 8) and dasatinib (9, 10) have been approved by the Food and Drug Administration for patients with imatinib-refractory CML (Fig. 1). Neither of these inhibitors is active against the T315I mutant.

The inhibition of imatinib-resistant BCR-ABL mutants by dasatinib (9, 11) has been tied to its ability to bind to ABL with fewer conformational constraints than imatinib (9, 12), although the issue of whether dasatinib binds the inactive conformation of ABL is controversial (13). Nilotinib binds ABL much like imatinib, “freezing” the kinase in an inactive conformation (7) but with an improved topological fit and substantially lower IC50 values for kinase inhibition (7, 11).

Nearly half of resistant patients treated with dasatinib or nilotinib while in chronic phase reached a CCyR within 1 year (8, 10). It has been suggested that failure to reach this benchmark and/or to exhibit any cytogenetic response by 3 to 6 months be invoked as one criterion defining failure of second-line therapy (14). In comparison to chronic phase, primary resistance is common in blastic phase disease and durable responses are the exception (15, 16). This raises several questions. What can we offer patients who fail second-line inhibitors? Should we use these drugs as frontline therapy rather than salvage therapy? Will the more potent ABL inhibitors eradicate the disease and cure patients?

Resistance to Second-Line ABL Kinase Inhibitors

Among patients with advanced disease who exhibit primary resistance to imatinib, some cases are explained by the presence of any of a small set of kinase domain mutations that have been predicted by in vitro resistance screens with a high level of reliability (reviewed in ref. 17). A characteristic spectrum of resistance mutations is regularly observed in patients who relapse after a transient response to second-line tyrosine kinase inhibitors (TKI), the T315I mutation being the most notorious (17).

In the clinic, sequential ABL inhibitor therapy has been linked to selection of rare CML subclones with two or more mutations in a single BCR-ABL molecule (18). These compound mutants are potentially resistant to all clinical BCR-ABL inhibitors. The eventual clinical effect of compound mutants is not yet known and will depend in part on how many mutations the kinase can tolerate without losing catalytic competency. Relatively little is known about resistance mechanisms in patients who fail TKI therapy without kinase domain mutations. We have previously suggested that exposure to a potent BCR-ABL inhibitor such as dasatinib amounts to a test for BCR-ABL dependence, implying that primary resistance in the absence of a highly resistant kinase domain mutation probably reflects BCR-ABL–independent disease (17). However, this has not yet been verified experimentally. Also, the SRC family...
member LYN may play a role in some cases of treatment-refractory CML in which imatinib resistance is not attributable to a BCR-ABL mutation (19).

The BCR-ABL T315I Mutant: Clinical Candidates on the Horizon

Several compounds targeting T315I are in preclinical or early clinical development (Fig. 1C and D). Most of these inhibitors are ATP competitive, the exception being DCC-2036 (20), which is reported to be an allosteric “switch pocket” inhibitor. Among compounds with potent Aurora kinase activity, the clinical development of MK-0457 (18, 21) has been discontinued due to toxicity, whereas PHA-739358 (22) and XL228 (23) are currently in phase 1 trials (Fig. 1C and D).

T315I inhibitor candidates without potent Aurora kinase activity include SGX393 (24) and AP24534 (ref. 25; Fig. 1D). Results from a validated in vitro resistance screen indicate that SGX393 has significant “gaps” in coverage, including prevalent mutants such as E255K. Thus, although SGX393 completely suppresses outgrowth of resistant subclones when combined with nilotinib or dasatinib (24), escape mutants emerge in experiments with single-agent SGX393, limiting prospects for use of SGX393 as a stand-alone agent in imatinib-resistant disease.

AP24534 is an oral, multitargeted kinase inhibitor developed by ARIAD Pharmaceuticals (25). In cell proliferation assays, the IC\textsubscript{50} was <15 nmol/L for Ba/F3 cells expressing native or any of 13 BCR-ABL kinase domain mutants. The only mutant slightly outside this range was E255V (IC\textsubscript{50}, 35.7 nmol/L) within the P-loop of ABL. Also, preliminary results from a mutagenesis assay indicate that in vitro resistance is completely suppressed at 40 nmol/L AP24534.\textsuperscript{3} Together, these results suggest that single-agent AP24534 therapy may be sufficient to suppress all known escape routes due to kinase domain mutations. However, it is virtually impossible to predict in vivo toxicity. The safety of AP24534 is currently being evaluated in a phase 1 trial for hematologic malignancies including CML.

Will Second-Line Agents Become Frontline Therapy?

Preliminary results from phase 1 studies show that ∼100% of newly diagnosed patients treated with nilotinib (26) or

\textsuperscript{3} T.O’Hare, unpublished observation.
Second-generation inhibitors currently dominate clinical trials, but the focus is already shifting toward the new frontier of cure. At the heart of this endeavor is the question of whether or not CML stem cells are addicted to BCR-ABL. Ex vivo assays have consistently shown that phenotypically primitive BCR-ABL–positive cells survive exposure to TKIs, including the potent second-line inhibitors. However, the results have been controversial with respect to the crucial question of whether BCR-ABL is active under these conditions. If not, or if survival of these cells is not strictly dependent on BCR-ABL activity, then disease eradication by biochemically targeting BCR-ABL will be impossible, and a fundamentally different approach to targeting CML stem cells will be required.

Because we do not have a clear understanding as to why CML stem cells survive in the presence BCR-ABL inhibitors, approaches to target these cells are empirical by necessity. Ironically, IFN-α, the standard drug therapy ousted by imatinib (1, 4), may see a revival in the setting of residual leukemia. In a small series of patients who discontinued imatinib after achieving a complete molecular response, relapse was inevitable in patients treated with frontline imatinib, whereas several patients previously exposed to IFN-α maintained their response (30, 31). There is evidence that this effect may be mediated by cytotoxic T cells directed against leukemia-specific antigens, such as peptides derived from myeloperoxidase (MPO; ref. 32). Intriguingly, MPO itself is transcriptionally regulated by BCR-ABL kinase activity, implying that the timing of IFN-α and imatinib therapies may be critical to allow for recognition of the leukemia clone by the patient’s T-cells.

Conclusions

We are still learning how best to use imatinib and other TKIs for maximum clinical benefit and to reduce the incidence of resistance below the current 20% to 25% (1, 3). Another key positive development is that a clinical T315I inhibitor may soon be available. Whether the capability to contain all kinase domain escape mutants will induce lasting responses in patients with advanced disease or whether we will see a surge of BCR-ABL–independent resistance is an open question.

Must cure equal disease eradication? Probably not. There may be room for functional cure, i.e., long-term and stable responses despite persistence of residual leukemia. Here, financial considerations will become important. Due to the success of imatinib, it is projected that there will be 250,000 CML patients in the United States alone by the year 2040. Finding ways to either eradicate the disease or maintain responses by less expensive measures than continuing TKIs indefinitely will be of critical health-economic importance. Depending on what we discover in the realm of CML stem cell-targeted therapies, the ideal outcome would be that treatment paradigms for moving from minimal residual disease to cure could also be tailored toward advanced disease. Until then, continuing to refine the use of TKIs for maximum disease control truly is the next best thing to a cure.
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