Medical Management of CML

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Management strategies of patients with chronic-phase chronic myeloid leukemia (CML) have been revolutionized by the BCR-ABL–selective kinase inhibitor imatinib, which is substantially improving median survival. However, a proportion of patients suffer progressive disease on imatinib therapy. Importantly, patients who are particularly at risk for developing progressive disease can be identified with appropriate monitoring of disease burden. Many of these patients may benefit from alternative treatment strategies, including second-generation kinase inhibitors such as dasatinib. As a result of improvements in medical therapy, allogeneic stem cell transplantation is increasingly deferred despite its known curative potential. It is anticipated that outcomes with medical therapy will continue to improve with the availability of effective second- and third-generation kinase inhibitors, and the percentage of patients progressing to the advanced phase of the disease is projected to decline. The future of kinase inhibitor therapy for CML may involve combinations of ABL kinase inhibitors.

The past decade has seen a remarkable shift in the management of chronic-phase chronic myeloid leukemia (CML). While allogeneic stem cell transplantation was historically pursued aggressively whenever possible, inability to offer the procedure to most CML patients limited its practical utility. Additionally, treatment-related morbidity and mortality can be substantial. Although targeted therapy with imatinib was initially investigated in patients with no transplantation option who had also exhausted meaningful medical therapies, its impressive response rates and good tolerability quickly led to its adoption as frontline therapy for all patients with chronic-phase CML.

Imatinib in 2007—Where Do We Stand?
The long-term effectiveness of imatinib in patients with newly diagnosed chronic-phase CML has been studied in the IRIS trial (International Randomized Study of Interferon vs STI571) that completed enrollment in 2001. With 5 years of follow-up, Druker and colleagues recently reported a risk of progression to accelerated- and blast-phase CML of 7%. Additionally, only 5% of patients had died due to CML-related causes. These figures compare quite favorably with historical expectations in this patient population. Complete cytogenetic responses have been observed in fully 82% of patients, and after 5 years, 67% of patients were in complete cytogenetic remission and continuing imatinib on study.

Imatinib 400 mg daily is therefore considered to be the medical standard of care for patients with newly diagnosed chronic-phase CML.

Clinical Resistance to Imatinib: Definitions and Proportion of Cases
Failure to achieve a desired response is considered primary resistance. It has become clear that the risk of developing progressive disease is related to the depth of clinical response achieved. As a result, the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net have established milestones of response. Hematologic resistance (failure to achieve a complete hematologic response within 3 to 6 months after initiating imatinib) is quite rare (2% to 4% of cases). There is consensus that failure to achieve any level of metaphase cytogenetic response (“cytogenetic resistance”) at 6 months, lack of a major cytogenetic response at 12 months (less than or equal to 35% Philadelphia chromosome–positive [Ph+] metaphases), and absence of a complete cytogenetic response at 18 months are all considered to be evidence of imatinib failure, and other treatment strategies are warranted under these circumstances. The proportion of patients that meet these criteria within 6 to 18 months after initiating imatinib is between 15% to 25%, and detection of these cases requires routine monitoring with...
metaphase analysis by bone marrow biopsy and aspiration. Not entirely exclusive of these cases of primary resistance is a proportion of patients who achieve some or all of the desired milestones but nonetheless subsequently lose response to imatinib. It has been estimated that approximately 4% of patients per year suffer loss of response/progression on imatinib. Loss of response is defined as secondary resistance.

Resistance Mechanisms

Primary resistance

As stated previously, primary hematologic resistance (failure to achieve a hematologic response) to imatinib is rare and remains poorly understood, whereas primary cytogenetic resistance affects 15% to 25% of patients. It is important to consider that the achievement of a cytogenetic response requires two distinct processes: (1) successful BCR-ABL inhibition, and (2) a bone marrow environment with adequate hematopoietic reserve (i.e., adequate numbers of normal hematopoietic progenitors). Mechanisms of primary cytogenetic resistance are therefore likely to involve deficiencies in one or both of these processes. Because at the present time there are no medical interventions for patients with inadequate hematopoietic reserve, this topic will not be discussed further.

Evidence for the role of insufficient BCR-ABL inhibition comes from both clinical and correlative studies. A small number of phase 2 studies assessed the ability of dose escalation to effect deeper remissions in patients with primary resistance, and in several instances this maneuver appears to be successful, although the durability of responses has been questioned. Additionally, single-arm studies of high-dose imatinib have shown high rates of cytogenetic response. An evolving body of evidence supports multifactorial causes of insufficient BCR-ABL inhibition. There is evidence that low trough plasma levels of imatinib correlate with failure to achieve a complete cytogenetic response. Imatinib plasma concentrations likely depend upon diverse factors such as drug absorption, metabolism, and compliance. Additionally, the ability of imatinib to successfully enter cells may be hampered by differences in the expression and activity of drug transporters such as hOCT1. These studies suggest that more potent inhibitors of BCR-ABL may be effective for a subset of patients with primary cytogenetic resistance.

Secondary resistance

It should be noted that primary and secondary clinical resistance are not mutually exclusive; secondary resistance frequently evolves out of primary resistance. Primary resistance should therefore be considered an important risk factor for the development of secondary resistance. The molecular mechanisms responsible for secondary resistance are well-understood. Most of these cases involve escape of BCR-ABL inhibition, either through kinase domain mutation within BCR-ABL and resultant impairment in the ability of imatinib to efficiently bind, or presumed overproduction of BCR-ABL via genomic amplification or the acquisition of additional Ph chromosomes in the resistant clone. A subset of loss of responses may be due to BCR-ABL-independent mechanisms. These studies clearly identified the need for second-generation ABL kinase inhibitors that were not only more potent than imatinib, but also capable of binding and inhibiting the activity of imatinib-resistant BCR-ABL kinase domain mutants.

Second-Generation ABL Inhibitors for Patients with Resistance or Intolerance to Imatinib

By implicating poorly controlled BCR-ABL kinase activity, knowledge of the molecular mechanisms of imatinib resistance led directly to the hypothesis that alternative ABL inhibitors with increased potency relative to imatinib, as well as activity against imatinib-resistant BCR-ABL kinase domain mutants, would be therapeutically promising. A number of “second-generation” ABL kinase inhibitors that share these characteristics have entered clinical trial evaluation (Figure 1), see Color Figures, page 512), and at the time of this writing, one (dasatinib) has been approved by the U.S. Food and Drug Administration (FDA) for patients with CML with resistance or intolerance to imatinib. Notably, all second-generation agents are completely ineffective against the BCR-ABL/T315I mutation in vitro.

Dasatinib

Dasatinib harbors the greatest potency in vitro against ABL kinase activity of all the second-generation ABL kinase inhibitors. Its activity against nearly all imatinib-resistant BCR-ABL mutations has been confirmed clinically. Notable exceptions are the highly resistant T315I mutation, which fails to respond objectively to dasatinib, and the moderately resistant F317L mutation, which is frequently associated with hematologic response, rarely with cytogenetic response, and occasionally with secondary resistance to dasatinib. The experience of 387 patients with chronic-phase CML participating in the phase 2 study has been recently updated. With a median follow-up of 15.2 months, the complete cytogenetic response rate was 49%. It should be noted that only 19% of these patients had achieved a prior complete cytogenetic response on imatinib, despite a median treatment duration with imatinib of greater than 36 months. Seven percent of patients had discontinued due to disease progression. Enthusiasm for the efficacy of dasatinib at the FDA-approved dose of 70 mg twice daily has been somewhat tempered by a toxicity-related discontinuation rate in chronic-phase CML of 13% after a median follow-up of 15.2 months, primarily as a result of cytopenias (grade 3/4 neutropenia and grade 3/4 thrombocytopenia in approximately 50% of cases) and pleural effusion (grade 3/4 in 6% of cases). The toxicity-related discontinuation rate is higher than that observed with imatinib 400 mg daily in newly diagnosed chronic-phase
CML, which is approximately 4%. Encouragingly, a recent dose-optimization randomized study of dasatinib (100 mg daily vs 50 mg twice daily vs 140 mg daily vs 70 mg twice daily) suggests that the dose schedule of 100 mg daily is equally as effective as 70 mg twice daily, and associated with a lower incidence of pleural effusion, thrombocytopenia, and importantly, toxicity-related discontinuation (6% vs 15%) in imatinib-resistant or -intolerant cases of chronic-phase CML with nearly 1 year of follow-up.

**Nilotinib**

Nilotinib is an investigational structural derivative of imatinib that has undergone extensive clinical trial evaluation. The phase 2 experience of nilotinib in 320 patients with chronic-phase CML with resistance or intolerance to imatinib has revealed that 40% of patients have achieved a complete cytogenetic remission with a median follow-up of 1 year. As with dasatinib 70 mg twice daily, a substantial proportion of patients had discontinued due to treatment-related toxicity (15%). An additional 16% of patients had discontinued nilotinib due to disease progression. In contrast to dasatinib, pleural effusions with nilotinib were rarely encountered, but grade 3/4 elevations in total bilirubin, lipase, and glucose have been observed in 9% to 15% of patients. Cytopenias were a relatively common occurrence, with more than 30% of patients developing grade 3/4 neutropenia or thrombocytopenia.

**Bosutinib**

Bosutinib (SKI-606) is an investigational SRC/ABL kinase inhibitor that has undergone relatively limited phase 1/2 clinical testing to date. The experience of 76 patients with chronic-phase CML with resistance or intolerance to imatinib was recently presented. With a median follow-up of less than 3 months, fewer than half of the patients have been evaluated for a cytogenetic response. Of 31 evaluable patients, 32% have achieved a complete cytogenetic remission. The incidence of grade 3/4 nonhematologic toxicity was quite low, with 9% of patients suffering a grade 3/4 rash and 5% of patients suffering grade 3/4 diarrhea. Despite the limited follow-up, grade 1/2 diarrhea and nausea were reported in more than 50% of patients. Grade 3/4 neutropenia and thrombocytopenia were encouragingly reported in 1% and 9% of patients, respectively, but longer follow-up is necessary to obtain a more accurate assessment of this agent’s toxicity and efficacy profiles.

**Third-Generation ABL Kinase Inhibitors**

**Aurora kinase inhibitors**

The failure of the second-generation agents to affect disease associated with the highly resistant BCR-ABL/T315I mutation has led to strategies to identify novel agents. Using a high-throughput screen of compounds undergoing clinical development, Ambit Biosciences described the ability of the Aurora kinase inhibitor VX-680 (currently known as MK-0457) to bind to the ABL/T315I mutant. A phase 1 study has confirmed the activity of this compound in this setting, with a small number of T315I-harboring patients presented thus far having achieved complete cytogenetic remissions. At least two other Aurora kinase inhibitors with activity against the BCR-ABL/T315I mutation are currently undergoing clinical development: PHA-739358 (phase 2) and XL-228 (phase 1). As a result of Aurora kinase inhibition, all these agents are expected to result in myelosuppression, whereas the cytopenias observed with second-generation ABL kinase inhibitors are most likely not due to suppression of normal hematopoiesis, but rather to increased potency of BCR-ABL inhibition in patients with limited Ph− bone marrow reserve.

**Resistance to Second-Generation Agents and the Promise of ABL Kinase Inhibitor Combinations**

Evolving data suggest that secondary resistance to second-generation kinase inhibitors is most frequently the result of selection for evolving BCR-ABL kinase domain mutations. Encouragingly, the available data from patients treated with dasatinib or nilotinib suggest that a limited repertoire of resistant mutations will confer the majority of secondary resistance to each of these agents. The ability to complement these resistant mutations with a third-generation agent is therefore particularly appealing, particularly for patients with advanced-phase disease, in whom the durability of response to second-generation agents is markedly shorter than for patients with chronic-phase disease. To this end, a combination study of dasatinib with MK-0457 has been designed. If such combination strategies are safe, it is hoped that progression-free survival in the advanced phase will improve significantly. Whether such a combination approach will ever be applied to chronic-phase CML, which is currently associated with excellent outcomes, is presently unclear.

**Novel Agents in the Frontline Setting**

As stated previously, 400 mg imatinib daily should be considered standard-of-care for patients with newly diagnosed chronic-phase CML. The increased in vitro potency of second-generation agents, coupled with the relatively limited number of mutations that can apparently confer resistance to these agents, has generated considerable enthusiasm for their investigation in imatinib-naïve chronic-phase CML. Randomized clinical trials have been designed to compare the efficacy and tolerability of these agents with 400 mg imatinib daily in patients with newly diagnosed chronic-phase CML.

Recently, results from a pilot study of dasatinib in imatinib-naïve chronic-phase CML that was performed at M.D. Anderson Cancer Center (MDACC) was reported. Of 34 patients randomized to receive dasatinib either 100 mg daily or 50 mg twice daily, 21 had been followed for at least 12 months. Of these 21, 20 (95%) had achieved a complete cytogenetic response (CCyR) by the 12-month
timepoint. Based upon the historic experience with 400 mg imatinib daily, approximately 70% of patients are expected to have achieved this level of response after 12 months. Molecular analyses of disease burden were also assessed, and 32% of patients achieved a 3-log reduction in BCR-ABL transcript level (“major molecular response [MMR]”) after 12 months. While the percentage of patients with CCyR compared favorably with historic experience at MDACC of 400 mg imatinib daily and 400 mg imatinib twice daily, the MMR rate at 12 months was less than had been previously observed in patients treated with 400 mg imatinib twice daily. A more comprehensive dataset is required before definitive conclusions can be made about the relative efficacies of these agents in this setting.

A similar MDACC pilot study assessing 400 mg nilotinib twice daily in patients with newly diagnosed chronic-phase CML has also been reported. Of 13 patients treated, 7 were evaluable for cytogenetic evaluation after 6 months, and all of these patients (100%) had achieved a CCyR. Two of 7 (28%) had achieved a MMR after 6 months. While the small number of patients and short follow-up limit interpretation of the data, comparison studies of nilotinib versus 400 mg imatinib daily appear to be warranted in this setting.

Conclusions
Imatinib arguably represents the single most important oncologic advance in the past 25 years and should be considered frontline therapy for CML. Despite its successes, issues of resistance and intolerance provide opportunities for further improving outcomes. It is predicted that the relatively low percentage of imatinib-treated patients with chronic-phase disease suffering progression to advanced-phase CML (approximately 7%) or CML-related death (approximately 5%) after 5 years will further decline with the availability of effective second-line therapies such as dasatinib. Dasatinib is a currently approved ABL inhibitor with substantial preclinical potency and limited susceptibility to BCR-ABL kinase domain mutation as a mechanism of resistance. To properly identify patients with resistance to imatinib, careful cytogenetic monitoring is essential. At the present time, treatment options for patients with imatinib resistance include dasatinib, dose escalation of imatinib, allogeneic stem cell transplantation, interferon, or investigational agents. A notable common weakness of all second-generation kinase inhibitors is the BCR-ABL/T315I mutation, which confers a high degree of resistance to dasatinib, nilotinib, and bosutinib. Currently, there are investigational third-generation kinase inhibitors with activity against the BCR-ABL/T315I mutation. Combinations of kinase inhibitors such as dasatinib and MK-0457 may collectively suppress the emergence of resistant BCR-ABL kinase domain mutants, and clinical studies assessing the safety of combining ABL kinase inhibitors are ongoing. Participation of patients with newly diagnosed chronic-phase CML in randomized studies comparing imatinib 400 mg/d with second-generation agents should be strongly encouraged.

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