Inhibidores de Tirosinkinasas

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TREATMENT OF CML IN 2007: WHAT HAVE WE LEARNED?

Results with imatinib in CML have been excellent with most patients achieving a rapid complete hematologic remission and over 80% achieving a complete cytogenetic remission. Long-term results after 5 years of follow-up has confirmed the efficacy of imatinib, with a decreasing rate of events in the later years of follow-up.1 In addition, molecular responses have continued to improve over time. However, there is growing evidence of the relevance of early responses (cytogenetic and molecular), as these translate into the most durable responses over time and improved long-term outcome. The safety of imatinib has also been maintained long-term, with a decreasing rate of adverse events and no major new events appearing after long-term use.

In an attempt to improve the results obtained with imatinib, higher doses of imatinib have been used as frontline therapy. An analysis of 3 consecutive studies in newly diagnosed early chronic phase CML (≤6 months since diagnosis) demonstrated improved response rates (cytogenetic and molecular) in CML patients treated with high-dose imatinib therapy.2,3 Responses occur significantly earlier with the higher doses and molecular responses have been more sustained. This is translating into a significant improvement in event-free survival and transformation-free survival. A randomized trial of standard versus high-dose imatinib has been completed.

RESISTANCE TO IMATINIB

Multiple mechanisms of resistance to imatinib have been identified. Some mechanisms of resistance involve changes to Bcr-Abl. These include increased expression of Bcr-Abl kinase or BCR-ABL gene amplification, and mutations in BCR-ABL fusion gene affecting drug binding or kinase activity. The latter is a dominant and well-understood mechanism of acquired resistance. Mutations disrupt critical contact points between imatinib and Bcr-Abl or induce a transition from the inactive to the active configuration, to which imatinib is unable to bind. Thus the trend towards increasing imatinib resistance in late-phase CML is consistent with the higher rates of BCR-ABL point mutations in these patients. Over 50 different BCR-ABL mutations have been detected in patients with resistant CML. Not all mutations have the same biochemical and clinical properties: some BCR-ABL mutations result in a highly resistant phenotype in vitro; others are relatively sensitive and resistance may be overcome with higher concentrations of imatinib that might be achieved through dose increase. The T315I mutation and some mutations affecting the so-called P-loop of Bcr-Abl confer a greater level of resistance to imatinib and to the novel tyrosine kinase inhibitors.

Other mechanisms of resistance do not involve any changes to Bcr-Abl. For example, it is known that imatinib requires a transporter to be carried inside the leukemic cells where it can bind and inhibit Bcr-Abl. This transporter may be less active thus decreasing the ability of imatinib to find its target. In addition, imatinib is a substrate for the multi-drug resistance-associated proteins such as ABCB1 and ABCG2. Increased expression of these proteins has been associated with resistance to imatinib. It has also been suggested that overexpression of other pathways, such as Src, may be associated with imatinib resistance even when the kinase activity of Bcr-Abl has been effectively inhibited.

This has been described in individual patients, but the actual incidence of this phenomenon as a mechanism of resistance to imatinib is not known.

In addition to resistance, there is an important mechanism that may cause persistence of the disease. This is represented by the fact that imatinib as well as dasatinib and nilotinib do not inhibit the leukemic stem cell. This stem cell appears to be in a quiescent state and carries increased copies of BCR-ABL, as well as decreased activity of hOCT1 and increased activity of ABCB1 and ABCG2. Persistence of these cells may be responsible for the relatively rapid recurrence of the disease in patients in whom imatinib is discontinued even after having undetectable disease by PCR.

NEW TROSINE KINASE INHIBITORS

Nilotinib (AMN107)

Nilotinib is a phenylamino-pyrimidine derivative with 20 to 30-fold increased potency compared to imatinib against Bcr-Abl. Crystallographic models suggest that this increased potency is a result of nilotinib representing a better topographical fit for the Abl kinase pocket. However, nilotinib, like imatinib, only binds the Abl protein in its inactive conformation. Nilotinib inhibits the tyrosine kinase activity of the majority of clinically significant Bcr-Abl mutants, with the exception of T315I.4 A phase I/II of nilotinib included 106 patients with imatinib-resistant CML in all phases and 13 patients with Ph- positive acute ALL.5 Patients received nilotinib at doses ranging from 50 mg to 1200 mg daily. In CML, hematologic response rates ranged from 44% to 89% and cytogenetic responses ranged from 22% in lymphoid and myeloid BP to 29% in AP and 50% in CP. Among patients with Bcr-Abl mutations prior to nilotinib therapy, 60% had a hematologic response and 41% a cytogenetic response. Nilotinib dosage was escalated up to 1200 mg daily with good tolerance and the MTD was estimated at 600 mg twice daily. The most common drug-related adverse events were gastrointestinal, rash, and hematologic. Importantly, greater exposure to the drug and inhibition of Bcr-Abl phosphorylation was observed with twice daily dosing schedules compared to equivalent total doses administered on a once-daily schedule. Phase II studies have further demonstrated the efficacy and safety of this agent that is expected to be approved by the regulatory authorities this year. Studies of nilotinib as first line of therapy have been initiated.

Dasatinib (BMS-354825)

Since it is possible that inhibition of Bcr-Abl alone may not be sufficient to eradicate all CML cells, particularly the leukemic imatinib-insensitive quiescent stem cells, agents with additional inhibitory capacity against other kinases have been investigated. Since Src kinases have been implicated in CML pathogenesis and progression, dual Abl/Src inhibitors may have enhanced activity as compared with imatinib. Among this new class of compounds, dasatinib has reached the furthest level of clinical development. Dasatinib is an ATP-competitive, dual-specific Src- and Abl-kinase inhibitor with 100- to 300-fold higher potency against Bcr-Abl compared to imatinib, and significant activity against c-kit (IC50 5 nM), PDGFRβ (IC50 28 nM), and Hck, Fyn, Src, and Lck kinases (IC50 ~0.5 nM).6 However, dasatinib does not inhibit the T315I mutant even in the presence of μM concentrations.4 In phase II studies, dasatinib was administered at 70 mg twice daily to patients with CML in all phases after imatinib failure. A CHR was achieved by 87%, 66%, 55%, and 46% of patients in CP, AP, myeloid BP and lymphoid BP/Ph chromosome positive ALL, respectively. Among patients in CP, 44% had a CCGR, whereas major cytogenetic responses ranged from 46% to 66% of patients with advanced phase CML.7-10 Dasatinib is overall well tolerated, with myelosuppression and gastrointestinal toxicity seen in some patients. Pleural effusions have also been reported in a 20% to 30% of patients, particularly those in blast phase and it is usually grade 1 or 2. Ongoing studies are testing dasatinib as first line of therapy.

Two other dual Abl/Src kinase inhibitors are currently also being tested in phase I or II trials: bosutinib (SKI-606)11,12 and NS-187 (INNO406)13. In addition, there are multiple other inhibitors that are being developed with properties that may distinguish them from the existing one.14

Inhibitors directed at T315I

Imatinib, nilotinib, and dasatinib are ATP-competitive inhibitors, and therefore amenable of being affected in their ability to bind to the Bcr-Abl kinase by the T315I mutation, which is considered the "gatekeeper" of the kinase domain. Compounds targeting binding-sites unrelated to the ATP-kinase domain may overcome this problem. ON012380 targets the substrate-binding site of Bcr-Abl, competing with natural substrates like Crkl, but not with ATP.15 In fact, ON012380 causes regression of leukemia induced by intravenous injection of 32DcI3 cells expressing the Bcr-Abl mutant T315I.15 BIRB796, a p38 MAP kinase inhibitor, binds with excellent affinity to the Bcr-Abl T315I mutant (Kd 40nM) although high concentrations of this compound are necessary to inhibit autophosphorylation of this mutant in Ba/F3 cells (IC50 1-2 μM).16 In this regard, VX680 (MK-0457), a multi kinase inhibitor that inhibits, among others, aurora A and B kinase, seems to have a more favorable profile against T315I although remarkably less affinity for wildtype Bcr-Abl (IC50

>10 μM).16 MK-0457 has entered into clinical trials with very promising early results. Another approach is to inhibit the synthesis of Bcr-Abl. Homoharringtonine is an old drug that has significant activity in CML and has shown potential both in vitro17 and in vivo18,19 for patients with T315I and/or who have failed tyrosine kinase inhibitors.

Other therapeutic options

Immune-mediated events play an important role in the suppression of the CML clone as evidenced by a subset of patients who maintained a durable CHR after discontinuation of IFN-α therapy20 and after allo-SCT due to a graft-versus-leukemia effect.21 These observations have sparked the interest in developing immunologic approaches in CML. One such approach is the use of vaccines to elicit specific immune responses directed towards CML-restricted tumor antigens. Several vaccines are being currently developed in clinical studies, which encompass the use of BCR-ABL1 junction-spanning sequences,22,23 24 the nonapeptide PR1 derived from proteinase 3,25 leukocyte-derived HSP70-peptide complexes,26 and GM-CSF secreting vaccines.27 The Bcr-Abl breakpoint fusion peptide vaccine has been already tested in phase II clinical studies.23,24 Bocchia et al have reported on 16 patients with stable residual disease after more than 12 months on imatinib therapy (n=10) or 24 months of IFN-α therapy (n=6) who received 6 vaccinations with a peptide vaccine derived from the sequence p210-b3a2.24 Five of 9 patients on imatinib with obtained a CCGR after vaccination, and 3 had undetectable levels of b3a2 transcripts by RT-PCR. Among the patients treated with IFN-α, 2 achieved a CCGR and 3 had improvement in the percentage of Ph-positive metaphases. Overall, these data suggest that this peptide vaccine may have a role in the management of patients with CML and minimal residual disease.

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