

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Second Generation Tyrosine Kinase Inhibitors for the Treatment of Chronic Myelogenous Leukemia

Hagop Kantarjian, MD
Professor and Chairman
Leukemia Department
The University of Texas
M. D. Anderson Cancer Center
Houston, Texas

H&O What is the current standard of care for chronic myelogenous leukemia (CML), and what are the shortcomings?

HK The current frontline standard of care of CML is with imatinib (Gleevec, Novartis) at the standard dose of 400 mg/day. With this treatment we now have long term results which are very favorable. Approximately 85% of patients achieve complete cytogenetic response; at 5 years, approximately 70% of patients are in continuous complete cytogenetic response—the estimated 7-year survival in these patients exceeds 85–90%. So the treatment is very effective.

We have a problem with the emergence of resistance in approximately 4% of patients every year on imatinib therapy. Among those patients who develop imatinib resistance, half of the cases have resistance related to mutations in the BCR-ABL kinase domain, and the cause of resistance in the other half is unknown. Because of this problem, investigators have developed more potent second generation tyrosine kinase inhibitors (TKIs). There are 2 such main categories. The first one is the selective BCR-ABL—more potent inhibitors like nilotinib (Tasigna, Novartis); the second category is dual Src-ABL inhibitors like dasatinib (Sprycel, Bristol-Myers Squibb) and bosutinib (SKI606). There is a particular mutation involving T315I which is not covered by any of these second generation TKIs, and this is where we are

developing T315I selective inhibitors as well as testing agents like homoharringtonine and decitabine (Dacogen, MGI Pharma) in that setting.

I think the role of allogeneic transplant is now easily second or third line therapy in patients on imatinib who fail imatinib therapy. While they are in chronic phase we can try second generation TKIs as a second line strategy and not consider the transplant unless they progress on that. However patients who fail imatinib therapy while they are in accelerated or blastic phase should go for allogeneic transplant; we can use the second generation TKIs only as a temporary measure to reduce the amount of disease and improve the results of transplant.

The problems with the transplant are essentially 2-fold. The first one is early mortality in the first year, which can be anywhere from 5–50% depending on the age of the patient, whether the transplant is from a related donor or an unrelated donor, and whether the matching is a perfect matching or a mismatch. Also, there are chronic toxicities related to quality of life such as infertility, development of cataracts, development of secondary cancer, problems with osteonecrosis of the hips, etc.

H&O What is the mechanism of action for second generation TKIs?

HK Nilotinib is a selective BCR-ABL inhibitor. Its about 30 times more potent than imatinib. It binds to the BCR-ABL kinase domain, and it can overcome resistance in the BCR-ABL kinase domain related to mutations. Therefore, the mechanism of action is similar to imatinib in terms of its binding site, but it is a more potent BCR-ABL inhibitor.

What makes it more potent are the changes in the structure outside the mandatory binding site. The structure of nilotinib is very similar to imatinib at the site of the kinase domain binding; however there are nonmandatory binding sites outside the kinase domain which restrict the entry of imatinib at the adenosine triphosphate (ATP) binding site. By modifying that part of the structure, nilotinib was rendered more potent.

Dasatinib is a dual Src-ABL inhibitor. It was developed originally as a Src inhibitor but was found also to be a very potent inhibitor of BCR-ABL, about 300 times more potent than imatinib. It also binds to the BCR-ABL kinase domain and can overcome resistance related to mutations at those sites.

There are downstream events of the BCR-ABL that contribute to the CML pathogenesis. For example, some investigators believe that the JAK2 kinase pathway is involved in the pathogenesis of resistance in CML; this is the basis, for example, for using dual Src-ABL inhibitors as well as potentially using JAK2 inhibitors. There are other pathways that investigators discuss as being involved, including the mammalian target of rapamycin (mTOR) pathway and the Src kinase pathways. Therefore, there are multiple pathways downstream of BCR-ABL or independent of BCR-ABL that could contribute to the pathogenesis or the resistance in CML.

H&O What is the difference between these agents?

HK The difference is mostly in terms of the mechanism of action. They appear to have similar degrees of efficacy, and we are waiting for long term results to see how long this is maintained.

Nilotinib is approved for the treatment of CML post imatinib failure, for chronic phase patients either intolerant or resistant, and for the chronic and accelerated phases. It is not approved for treatment of blastic phase CML or for Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL). In term of toxicities, because it is known to rarely induce pancreatitis, patients who have had a history of pancreatitis should probably not be treated with nilotinib. Also, patients with prolongation of QT interval or patients who are on medications that prolong the QT interval should probably not be exposed to nilotinib.

Dasatinib is associated with 2 particular toxicities: one of them is myelosuppression which occurs in about 50% of patients at the dose of 70 mg twice a day. There are now studies that show that giving a dose of 100 mg as a single daily dose reduces the incidence of myelosuppression, as well as the incidence of the second problem which is pleural effusion. The 100 mg dose was also more efficacious in terms of PFS and is now the FDA approved

dose for chronic phase; 70 mg bid remains the dose for advanced phases.

So in terms of side effects, these agents have different toxicity profiles. In terms of efficacy in chronic and accelerated phases, they may have equivalent efficacy. We know that dasatinib is effective in the blastic phase as well as Ph+ ALL; the data on nilotinib in those settings is emerging.

H&O How does a clinician choose between the agents?

HK Essentially, when evaluating patients who have imatinib failure, if they fail in the chronic phase, the first thing to do is a mutational analysis. If we identify a T315I mutation, we do not choose either of the 2nd generation TKIs, but you opt for a transplant or some of the other T315I inhibitors. For patients who have no T315I mutations, sometimes we can select the drug based on the particular mutations.

Dasatinib is known to be more active against mutations affecting the P loop, whereas nilotinib is known to be more active against particular mutations involving 248, 299, and 317. So we can look at the IC50 of the mutation for the particular drug and make a choice on the second generation TKI. If the above does not help with the selection, we look at the history of the patients for pancreatitis, severe diabetes, QT prolongation on the EKG, or whether they are taking drugs that prolong QT interval—then avoid nilotinib. For patients who have a previous history of pleural effusions or pulmonary problems, we may want to avoid dasatinib.

H&O Can regimens include a combination of imatinib and one of these second generation TKIs from the start?

HK Given that the main toxicity of all TKIs is myelosuppression, it will be necessary to dose reduce both agents in order to combine them. This brings up the question of whether a possible synergy between the 2 would override the fact that lower doses of each would be given. So the combinations of TKIs are being considered, but the data are too early to decide whether or not they will be useful.

H&O In your opinion, should these agents also be administered after transplantation?

HK I think if patients who undergo a transplant have persistent polymerase chain reaction positivity, they could receive one of these agents. Also, if the transplant is done in a patient who is at a high risk of relapse (eg, a patient in accelerated or blastic phase) it might be useful to give them maintenance therapy with TKIs.

H&O What would be an important avenue of research in the future with these agents?

HK In terms of the research in CML, the main issue is not to develop more TKIs but perhaps to address the issue of minimal residual disease and whether we can discontinue therapy with the TKIs if we can stimulate the immune system or kill the persistent dormant stem cells.

For this, investigations are ongoing on the use of vaccines as well as the use of some chemotherapeutic agents like homoharringtonine and decitabine, in addition to possibly using pegylated forms of interferon, like pegasys, at the time of minimal residual disease.

Another area of important research is developing inhibitors against T315I mutations.

The third area of research is what to do with women who want to get pregnant on TKIs because so far they don't appear to be safe during pregnancy, and there are genetic malformations that have been reported. There has been a review of approximately 180 pregnancies on imatinib therapy and a report of maybe 3 or 4 babies that have consistent syndromic malformations involving abnormalities in the eyes, the skeletal system, and the kidneys. So at this stage, for women with CML on imatinib, we advise them not to get pregnant. If they do get pregnant, we advise them to stop imatinib immediately and be monitored in a setting of high-risk obstetric care. The same goes for dasatinib and nilotinib; in fact there is even less information with these agents than with imatinib.