ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Chronic Myelogenous Leukemia Therapy Beyond Imatinib

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H&O What are the treatment options for patients who do not respond to or respond poorly to imatinib?

MD The second-line tyrosine kinase inhibitors (TKIs) approved by the US Food and Drug Administration to treat imatinib (Gleevec, Novartis)-resistant chronic myelogenous leukemia (CML) are nilotinib (Tasigna, Novartis) and dasatinib (Sprycel, Bristol Myers-Squibb); allogeneic stem cell transplant is another option. There are other agents available that are nonspecific and can be used in a palliative manner like hydroxyurea, cytarabine, or decitabine (Dacogen, Eisai); however, they are not first-class agents used to treat patients with imatinib resistance.

H&O Are there different options for newly diagnosed patients as opposed to refractory patients?

MD The standard of care in newly diagnosed patients with chronic phase CML is imatinib. There are ongoing clinical trials evaluating the second-line inhibitors nilotinib and dasatinib, and another TKI, bosutinib (Wyeth), in newly diagnosed patients. Presently, none of these second-line drugs have been approved for first-line treatment. Therefore, if you go by the book, imatinib remains the treatment of choice for newly diagnosed patients.

H&O In what circumstances can second-line agents be used to treat newly diagnosed patients?

MD Patients have received dasatinib or nilotinib as front-line therapy in clinical trials and in cases where a patient is diagnosed with advanced disease, where we know that imatinib response is not durable. One can assume that this practice happens frequently in the community. What is not clear, however, is whether chronic phase patients are started on second-line agents right away; outside of clinical trials, I suspect that this does not happen frequently. Conversely, I think the threshold of switching a patient because of an unsatisfactory response or intolerance is quite low because these agents are well-tolerated.

Studies presented at the 2009 ASH meeting showed that nilotinib and dasatinib were effective in newly diagnosed, previously untreated Ph+ CML in early chronic phase. A phase II study reported by Cortes and colleagues evaluated the efficacy and safety of frontline dasatinib and found that a significant number of patients achieved major molecular response at 12 months, the study's primary endpoint. In a phase II trial of frontline nilotinib presented by Rosti and colleagues, a similar trend in molecular response was seen.

H&O What kind of response do we see with second-generation TKIs? How durable are these responses?

MD In patients who are refractory or resistant to imatinib, looking at the different disease phases, response rates range from approximately 50% complete chromosomal response in chronic phase CML to 20–25% in blast crisis CML. Responses in chronic phase CML patients tend to be quite durable, perhaps somewhat more with dasatinib, but also with nilotinib, whereas responses in accelerated/blast crisis CML phases are much less durable. Currently, only dasatinib is approved for use in blast crisis CML, and in these patients, there is a very high relapse rate over the first 12 months.

In newly diagnosed patients, limited phase I trials have examined both nilotinib and dasatinib, and have found very high rates of complete chromosomal responses of up to approximately 90–100%, which were mostly durable, although follow-up is limited. The response appears durable, but there have been relapses with progression to accelerated/blast crisis CML. These data come from phase I studies and therefore should be

interpreted with a great deal of caution. There are concerns that the proportion of low-risk patients in these phase I trials may be somewhat high, so more follow-up time is required. Some of the data, reported by Dr. Cortes and colleagues, now have been published in the *Journal of Clinical Oncology.*

The more important trial that was presented at the 2009 American Society of Hematology (ASH) meeting was a trial of nilotinib in newly diagnosed patients that compared 2 doses of nilotinib versus imatinib. In this study, the 2 nilotinib regimens were superior to imatinib in terms of complete chromosomal responses and major molecular responses. Also noteworthy was the reduced rate of progression to accelerated phase or blast crisis seen in patients receiving nilotinib; this indicates that beyond improving surrogate endpoints, the second-line agent might be superior in terms of progression-free survival (PFS). Though these results are very encouraging, further follow-up is required. What we would like to see is whether or not the conventional arm will catch up over time, and whether nilotinib will prevent progression or merely delay it.

In regard to endpoints, PFS has always been a critical endpoint but it is difficult to assess in these studies, due to the long survival and relatively low progression rates seen even with standard care, meaning that most patients on imatinib, as long as they are treated during the chronic phase, do pretty well. Thus, to improve on this, large studies and long follow-up are needed.

H&O How are the newer second-generation TKIs different from imatinib?

MD There are 2 important differences: the potency and the binding mode. Second-line TKIs are more potent than imatinib to begin with, therefore the concentrations required to inhibit the native BCR-ABL protein kinase are lower, and as such there is a greater therapeutic window in the patient. Secondly, dasatinib binds to the BCR-ABL kinase in a different fashion than imatinib. As a result, it is not liable to being pushed out by certain point mutations that abrogate, or at least impair, imatinib binding to its target. Nilotinib on the other hand binds in a similar fashion as imatinib, but with greater avidity. Thus, it can overcome a number of mutations that confer resistance to imatinib.

H&O What are some of the third-generation drugs that are being studied?

MD There are 2 groups of agents. The first and more important group is the TKIs that are essentially the same class as the available agents (imatinib, nilotinib, dasatinib), with the main kinase target of BCR-ABL. There are several of these compounds in clinical development. Provisional classification groups these agents into those with and without aurora kinase inhibitory activity. In the first group of agents, there are several compounds currently in clinical trials. One such compound is XL228 (Exelixis), a protein kinase inhibitor that has shown some activity in patients with imatinib- and dasatinib-resistant CML. PHA-739358 (Nerviano) is another compound in this class. It is currently in phase I/II trials and has also shown some activity. Because these are early phase studies, we will have to see how these agents do clinically. These compounds have a disadvantage because they are not oral agents (they are given intravenously).

The second group of agents are oral kinase inhibitors that primarily target ABL. One agent, DCC-2036 (Deciphera) is undergoing phase I trials that will evaluate the safety and tolerability of once a day continuous oral dosing of the drug in patients with treatment-resistant or -intolerant Philadelphia chromosome positive (Ph+) CML or acute lymphoblastic leukemia (ALL), including patients with the T315I mutation. One other inhibitor, AP24534 (Ariad), is a multi-targeted kinase inhibitor. There has been a report of the preliminary data from the phase I trial of this agent at the 2009 ASH meeting. It appears promising in terms of cytogenetic responses in patients who failed imatinib and second-line inhibitors. These kinase inhibitors are based on the premise that BCR-ABL remains a good target at the time of resistance.

In addition, there are other compounds that are not kinase inhibitors that are used to treat patients who failed second-line agents, the most advanced of which is omacetaxine (Omapro, ChemGenex), which is an inhibitor of protein synthesis that has specific activity against BCR-ABL, including the T315I mutant. Several studies have been conducted with this agent, including phase I and phase II trials that have been published and showed a considerable degree of activity in patients with refractory CML.

There is also interest in exploiting other agents for this purpose that are broadly anti-leukemic agents, such as demethylating agents, histone deacetylase inhibitors, and PI3 kinase inhibitors. Exploration of these agents shifts the focus away from BCR-ABL as the critical target. I think the most interesting approach is to develop third-line BCR-ABL kinase inhibitors that have complete coverage of all the BCR-ABL mutants that confer resistance to imatinib and second-line agents.

H&O What role does resistance play in directing drug development?

MD Resistance is frequently, but not exclusively, associated with certain BCR-ABL mutations. In the case

of imatinib, there is a very broad smattering of mutant genotypes that can cause resistance, and because of this resistance, second-line agents were developed. With these agents, the spectrum is much narrower and related to a handful of mutations that are still able to escape the effects of nilotinib and dasatinib. T315I is a mutation in ABL seen in approximately 15% of patients with CML. Because T315I mutation confers resistance to imatinib as well as other BCR-ABL targeted agents, there is a great drive to develop inhibitors that are able to cover this particular mutant, which is quite challenging to do because of its specific localization in the BCR-ABL enzyme. Omacetaxine, AP24534, and DCC-2036 have activity against T315I and appear to be very interesting agents.

H&O Is the treatment paradigm in CML moving away from imatinib?

MD This is a complicated situation because there are numerous factors that may influence the outcome of this shift. The available data suggest that second-line inhibitors are more active than imatinib in newly diagnosed patients, at least in terms of the surrogate markers that we have. Perhaps, emerging evidence will also suggest that second-line agents may reduce progression of disease, in which case the initial treatment of chronic phase patients may change.

The second factor of importance is cost. At present, imatinib is patent protected, but it is going to run out in 2015, at which time generic replacements will come on the market. With the high cost of treatment and the discussion about healthcare expenses, it would be surprising if cost did not have a major impact on how the market behaves. In 5 years, someone with a high co-pay may decide to get treated with generic imatinib and wait to see what kind of response is obtained, rather than paying for a more expensive drug from the start that he or she may not need.

The third factor is the anticipation of developing better biomarkers that will predict response to imatinib. With the identification of biomarkers, we will be able to administer imatinib to those patients who are likely to do well on the drug and reserve a more aggressive approach for patients with more advanced disease.

Another consideration is that it is not yet clear whether any of the second-line agents will be able to eliminate all leukemia cells in a significant number of patients. I believe that this is unlikely, but if it did turn out to be the case, this would have a major impact on how patients would get treated. For example, if one-third of patients are able to eliminate their leukemic cells with either dasatinib or nilotinib, there would be a great push to use these agents as early as possible. In that case, CML treatment would become a transient exercise, similar to treating an infection, and this would greatly impact which agents are used as frontline therapy.

The fifth, less important point is that there are a number of clinical trial options that are theoretically very appealing that could change our approach to treatment. For example, investigators can treat patients with nilotinib or dasatinib initially and then switch to imatinib if a certain response milestone is achieved in a certain time, or patients can be started on imatinib but switched to a second-line agent early on if the response is not as strong as predicted.

Because of all the factors that may affect a shift in treatment, we see a very complex interplay between a changing therapeutic landscape in terms of the endpoints and biomarkers, and a changing landscape in terms of costs and what people are willing to invest in this expensive drug therapy.

It is important to emphasize that imatinib is a very good drug that is easy to use, but to exploit its full benefit, patients need to be continuously monitored. Monitoring is necessary in order to diagnose resistance as early as possible, because once resistance is observed, the biology of the disease has changed. Our goal is to increase community awareness of the need to use appropriate tests and instruments to monitor patients and to stress the importance of providing patients with optimal treatment by obtaining consultation from a medical center if resistance is observed.

Suggested Readings

Cortes JE, Jones D, O'Brien S, et al. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. *J Clin Oncol.* 2010;28:392-397.

Cortes JE, Jones D, O'Brien S, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol.* 2010;28:398-404.

Cortes JE, Borthakur G, O'Brien S, et al. Efficacy of Dasatinib in Patients (pts) with Previously Untreated Chronic Myelogenous Leukemia (CML) in Early Chronic Phase (CML-CP). *Blood* (ASH Annual Meeting Abstracts). 2010;114: Abstract 338.

Rosti G, Castagnetti F, Palandri F, et al. Nilotinib 800 Mg Daily as Frontline Therapy of Ph + Chronic Myeloid Leukemia: Dose Delivered and Safety Profile for the GIMEMA CML Working Party. *Blood* (ASH Annual Meeting Abstracts). 2010;114:Abstract 2205.