

ADVANCES IN LLM

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

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Advances in CML

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H&O Could you discuss the clinical background of imatinib from its introduction to the present day?

JG Imatinib (Gleevec, Novartis) was introduced into clinical practice in June 1998, initially in Portland, Ore., and then at two other centers in the United States, in Los Angeles, Calif., and Houston, Tex. By July 1999, it was apparent that the drug, then known as STI571, could induce Philadelphia chromosome (Ph) negativity in some patients with chronic myelogenous leukemia (CML), which already was an exciting development. The only agent capable of inducing such a complete cytogenetic remission until then was interferon alfa, which was toxic and had a complete cytogenetic response of approximately 10%—not too unimpressive but better than no response. By the end of 1999, it was clear that imatinib was inducing a substantial degree of Ph negativity in patients who had previously failed interferon, which made the agent appear very exciting. By 2000, the manufacturer had designed a prospective study, International Randomized Study of IFN versus STI571 (IRIS), of imatinib versus the combination of interferon plus cytarabine. Over a period of 8 months, 1,106 patients were recruited in many countries, 553 to the interferon-plus-cytarabine arm and 553 to the imatinib arm. Imatinib was given at a single, standard oral dose of 400 mg daily to adults. There were analyses at 2 years and, recently published, at 5 years.

The IRIS study was meant to be a prospective study, but as a prospective study, it collapsed for one very important reason, which was that patients crossed over from interferon plus cytarabine to imatinib with high frequency, although only a few patients crossed over in the opposite direction. The reason for the one-way crossover was that many patients could simply not tolerate the toxicity of the

combination regimen; also the positive results already seen with imatinib led researchers to want patients to receive the new agent. Nevertheless, it was still possible to analyze clinical results in patients who started treatment with imatinib as well as in those who were allocated to receive interferon plus cytarabine but subsequently received treatment with imatinib. The 5-year data published by Druker and colleagues in December 2006 suggested that the survival of patients who received imatinib as first-line therapy was 89%. There is no contemporary comparator, but historical controls suggest that the comparable figure for survival on interferon would be approximately 70–80%. Thus, it appears that imatinib is significantly prolonging survival compared with any previous drug treatment. The rate of progression to advanced-phase disease seems to be much lower than it would be with interferon alone or interferon plus cytarabine. The toxicity is not trivial, but it is manageable. Therefore, as of March 2007, most hematologists worldwide would start a newly diagnosed chronic-phase CML patient on imatinib at 400 mg daily and then wait and see what happens. The exception is pediatricians, who might think that allogeneic stem cell transplantation is appropriate to a 10-year-old CML patient, for example, but these young patients with CML are rare.

H&O Could you discuss resistance to imatinib therapy?

JG Not all patients respond to imatinib as well as might be hoped. The criteria of response exist at three levels—hematologic, chromosomal, and molecular. Most clinicians would regard the minimum desirable response as a durable complete chromosomal response, which takes a variable amount of time to be reached. As long as a patient is heading in that direction, most clinicians would be happy. A better response is a so-called major molecular response, which corresponds to a 3-log reduction in *BCR-ABL* transcripts compared with a theoretical baseline value. The best response of all is molecular negativity, which is achieved when a patient has a reduction in transcript numbers of at least 4.5- to 5-logs.

Speaking predominantly about chronic-phase disease, resistance occurs in two distinct forms. Either a patient does not respond well initially, which is called

primary resistance, or a patient does respond reasonably well initially but loses the response in time, which is called secondary resistance. If primary and secondary resistance are put together, the two forms comprise 25–30% of patients. Estimates of rates of each resistance are approximately 10% with primary resistance and perhaps 15% with secondary resistance. A very small number of patients do not achieve a good hematologic response, some do not achieve a good chromosomal response, and others achieve a complete chromosomal response but do not achieve the major molecular response level. The first two categories should definitely be regarded as primary failures, and the third category also might be regarded as a failure. The criteria used to define failures are somewhat flexible. Baccarani and colleagues for European LeukemiaNet published recommendations defining these landmarks in *Blood* in September 2006.

Secondary resistance describes patients who responded reasonably well at the hematologic and chromosomal levels and possibly at the molecular level and then lost their response in the subsequent year or two. They can be treated by increasing the dose of imatinib, which is not always successful, but patients with confirmed resistance to imatinib, be it primary or secondary, do unquestionably need alternative therapy.

Approximately half the patients in chronic phase who develop secondary resistance are associated with an interesting phenomenon, namely they have point, or single nucleotide, mutations in the kinase domain of the *ABL* component of the *BCR-ABL* gene. These mutations code for alternative amino acids, so the leukemia is now caused by a mutant clone of the original Ph-positive cells, which has one single amino-acid substitution. Some of these amino-acid substitutions are undoubtedly the cause of the resistance, whereas others are not so obviously the direct cause. This observation is very fascinating but poorly understood. Why do these point mutations occur in the kinase domain and how exactly do they cause resistance in some cases but not in others? It is difficult to know what proportion of patients with secondary resistance have definable kinase-domain mutations, but it is probably between 35% and 65%. We do not know the mechanism of resistance in other patients who become secondarily resistant and do not have mutations in the kinase domain.

Secondary resistance can also be divided into two categories; in some patients the imatinib ceases to block the excessive kinase activity but in other patients its inhibitory effect is retained. Obviously most of those with significant point mutations come in the former category—those in whom imatinib loses its effect. In those in whom imatinib is still effective there must be other mechanisms underlying the leukemia because *BCR-ABL* is still inhibited by

the imatinib. One of the most interesting clinical observations is that as the years pass, the incidence of progression to advanced-phase or resistance to imatinib seems to be diminishing, partly because those likely to develop resistance early on have been selected out of the population, but this observation also means that the pessimistic prediction that all patients receiving imatinib would do well for 5 years and then relapse has proved to be false.

H&O Is research ongoing into the cause and characterization of these point mutations?

JG Presently, there is a good deal of research going on in various laboratories to characterize the point mutations and define the way in which they interact with imatinib and the second-generation tyrosine kinase inhibitors. Most researchers believe the mutations do exist before the administration of imatinib, meaning imatinib does not cause them but rather the mutated subclone is selected for by imatinib. This belief does not, however, entirely exclude the possibility that some mutations might be caused by imatinib. These mutations pose a fascinating series of questions that no one can answer currently: for example, why do the mutations occur and do they occur in the kinase domain only in *BCR-ABL* or also in other genes within the Ph-positive clone?

H&O How does the assessment of minimal residual disease in CML play into the understanding of resistance?

JG I prefer the terms “low-level residual disease” or “minimal measurable disease” because the term “minimal residual disease” assumes totally reliable technology. In practice the lowest level of measurable leukemia which a patient can achieve is an important prognostic factor. One patient with newly diagnosed CML given 400 mg of imatinib will have the overall volume of his or her disease reduced at 6 months to a considerable degree but another patient may experience a substantially lesser reduction under similar conditions. Many clinicians believe that the speed at which the amount of leukemia is reduced is a prognostic factor—the faster the reduction, the better the prognosis. According to results from the IRIS study, approximately two thirds of patients are alive and well on imatinib, in complete chromosomal remission, at 5 years, which is a very good result. If one then subdivides the patients in complete chromosomal remission, which is roughly equivalent to a 2-log reduction in *BCR-ABL* transcripts, from those who achieve a 3-log reduction or better, it appears that those with a 3-log reduction or better have more favorable outcome overall. The patients who achieve only a 2-log reduction are slightly more

likely to progress than those who achieve a 3-log reduction. Furthermore, the patients who achieve a 3-log reduction at 1 or 2 years may have diminishing levels of residual disease over the next 3 years, which is another interesting observation. A good response at 1 year seems to correlate with a still better response at 3 or 4 years. Levels of molecular disease are currently measured by a molecular technique that still requires standardization, namely reverse transcriptase-polymerase chain reaction. This technique measures the number of *BCR-ABL* transcripts, the mRNA produced by leukemia cells, though its sensitivity is limited (approximately 1 leukemia cell in 100,000 or possibly better). This technology relies on the level to which a leukemia cell is producing transcripts, but eventually a more sensitive technology should be developed.

H&O How has the diagnostic definition of CML been modified in recent years?

JG For the past 40 years, Ph positivity was used as the criteria of diagnosis for CML. In the last 5 years or so, this criterion has been refined and the presence of the *BCR-ABL* fusion gene is used for diagnosis. One hundred percent of patients who are Ph-positive have the *BCR-ABL* fusion, but there are 5% of patients with the fusion gene and a clinically identical disease who are negative.

H&O Could you discuss prognostic factors in CML?

JG The first really valuable approach to prognosis was published by Dr. Joseph Sokal and colleagues in 1984. It was widely used and subsequently it was updated by Dr. Jorg Hasford and colleagues in 1998. Sokal's research was in patients receiving busulphan or hydroxyurea and Hasford's was in patients receiving interferon. What is interesting is that the Sokal prognostic classification, based on age, spleen size, blast cell numbers, and platelet numbers, is still valid up to a point in terms of a patient's likelihood of responding well to imatinib. This classification does thus seem to measure something intrinsic to the disease or characteristic of the general response to therapy rather than the response to one particular agent. In the last few years, clinicians have attempted to estimate response to imatinib based on in vitro characteristics of leukemic cell populations. Two examples are the measurement of response in vitro of cells to a given dose of imatinib, so-called IC_{50} , and the capacity of cells collected at the time of diagnosis to phosphorylate a target molecule, called Crkl, which is heavily phosphorylated in CML. It is possible to estimate the rate by which Crkl phosphorylation

is reduced by imatinib in vitro (and in vivo from samples). There are other approaches too.

It has recently been recognized that a particular drug transporter called OCT1 is low in patients who do not respond well and 'normal' or high in patients who do respond well. Moreover pharmacokinetic data are emerging that suggest that people who do not respond well may have relatively low levels of imatinib in their blood at different timepoints. Based on imatinib metabolism, there are a number of ways to predict response to the agent, which is linked to but different from overall prognosis.

H&O What is the current status of research into the use of allogeneic stem cell transplantation in CML?

JG Recently, German researchers have published data suggesting that in the long term, drugs and interferon may be better than allogeneic stem cell transplantation. This is still controversial. Looking at the results of transplantation in CML in the chronic phase in the 1990s, it does appear that survival of 60–70% is possible with sibling donors and perhaps somewhat lower with unrelated donors. Most of those survivors are free of disease, but conversely there is a rate of mortality associated with the procedure of 30–40%, which is substantial. Insofar as the projected median survival of people on imatinib is now of the order of 15 or 20 years, the use of allogeneic stem cell transplantation as primary therapy for CML is not indicated unless the patient is a child with a matched sibling donor, typically, such a patient has a chance of survival after an allograft of 85% or higher. Transplantation is the only treatment method that definitely cures CML, but we simply do not know whether a tyrosine kinase inhibitor or something that follows a tyrosine kinase inhibitor may also be found to cure CML. At the moment, transplantation is usually reserved for patients who fail imatinib or fail both imatinib and a second-line tyrosine kinase inhibitor (and who have donors).

H&O What is the status of other novel agents in CML?

JG There are four drugs now competing with imatinib for treating patients with CML. Each of the manufacturers would probably like their drug to be used in the first-line setting. The drugs are dasatinib (Sprycel, Bristol-Myers Squibb), nilotinib (Novartis), bosutinib (SKI-606, Wyeth), and INNO-406 (Innovive). Those four drugs are all in clinical use, particularly at the University of Texas M. D. Anderson Cancer Center. In different ways, they

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all look quite good, and if imatinib did not exist, any one of them would be very exciting in its own right. In fact, I believe all four are potentially very valuable, but a fundamental question for clinicians and regulatory agencies is, do you approve the formal use of any of these these agents as upfront treatment for CML, which would require displacing imatinib's 9-year record of success as frontline therapy in chronic-phase CML? This question is not readily answerable at the moment.

The single *BCR-ABL* kinase domain mutation that seems most resistant to all four drugs I mentioned is the threonine to isoleucine mutation at position 315, colloquially known as T315I. Merck has developed a compound that successfully attacks this mutation, called Merck 0547, which is also in clinical use currently.

Suggested Readings

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