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The Best Frontline Therapy for CML: Imatinib?

Giuseppe Saglio, MD
Professor of Internal Medicine and Hematology
Department of Clinical and Biological Sciences
University of Turin
San Luigi Gonzaga Hospital
Orbassano, Italy

H&O What do we know of imatinib's efficacy as frontline therapy in chronic myeloid leukemia (CML) patients?

GS Imatinib (Gleevec, Novartis) is the most important drug discovered in recent years. After the studies of Brian Druker, there was a revolution in the therapy of CML. For this disease, before the "imatinib era," the only really curative option was represented by allogeneic stem cell transplantation (SCT). This procedure, however is associated with a high degree of toxicity, which may also lead to a procedure-related mortality whose incidence is dependent on several factors, including the age, the disease phase, and the comorbidities of the recipient patient. For those who could not undergo SCT, before imatinib the only possibility for a cure was represented by interferon therapy, but only a small percentage of patients (around 15–20% of the total) could really benefit from this treatment in a long-term setting.

Imatinib has caused a revolution because the drug is able to "functionally" cure most patients. In the first and most famous trial—the IRIS (International Randomized Study of Interferon and STI571) trial—which examined imatinib 400 mg once a day as first-line therapy for CML, 85% of the enrolled patients are still alive after 8–9 years of follow-up; of note, more than half of the deaths that had occurred in this trial were due to causes unrelated to CML. Therefore, we can say that the life expectancy of CML patients is now very good, almost similar to that of a control population matched for age.

H&O What new drugs are candidates for frontline therapy?

GS Following imatinib, new drugs called *tyrosine kinase inhibitors* (TKIs) were developed for the therapy of CML patients. These drugs were originally tested as second-line therapy in patients who had to stop imatinib therapy because of problems with tolerance or resistance to this drug. These new drugs, often referred to as *second-generation TKIs*, such as dasatinib (Sprycel, Bristol-Myers Squibb), nilotinib (Tasigna, Novartis), or bosutinib, are more potent in inhibiting the BCR-ABL tyrosine kinase activity and have been shown to be able to induce good and durable responses in approximately 50% of the patients who develop resistance to imatinib. Since then, the idea is to move these second-generation TKIs that are approved for second-line therapy to first-line therapy, as even better results are expected at this initial stage of the disease. This approach has initiated several investigational trials, and the results of some of these phase II and phase III trials are now available.

First of all, however, it is important to point out the way in which, from the time of interferon therapy, we evaluate the effective response in CML patients. In fact, we know that hematologic response (when all the hematologic parameters again become apparently normal) are

not sufficient in these patients, as it does not prevent the progression of the disease. A clinical advantage in terms of progression-free survival (PFS) and overall survival can be seen in those patients who achieve at least a major or a complete cytogenetic response (MCyR or CCyR respectively, which means Ph-positive [Ph+] metaphases <35% or 0%). In more recent years, as most of the patients achieve CCyR, we have also started to consider molecular responses as important endpoints because major molecular response (MMR), which corresponds to a residual leukemic burden 1 log lower than that observed in CCyR, is associated with an extremely good clinical outcome and with an almost nonexistent risk of disease progression. Therefore, we now consider this MMR as a real safe haven for patients and a goal to be reached in the evaluation of the response in our patients

Dr. Jorge Cortes presented at the 2009 American Society of Hematology (ASH) meeting 2 phase II studies, respectively using dasatinib and nilotinib as first-line therapy, which showed an extremely good efficacy and tolerability of these second-generation TKIs in CML patients when treated at diagnosis. In one study that evaluated the effect of nilotinib in patients with newly diagnosed, previously untreated Ph+ CML, 98% achieved a CCyR, and rates at different time points were favorable compared with historical controls treated with 400 mg or 800 mg of imatinib. MMR was achieved in 63% of the patients, including 24% with complete molecular response (CMR), which is the apparent absence of residual disease as judged by the absence of the typical BCR-ABL transcript at the polymerase chain reaction analysis.[1]

Another study by Dr. Cortes and colleagues investigated the efficacy and safety of dasatinib as initial therapy for patients with chronic phase CML. In this trial, 98% achieved CCyR, and again, rates at different time points were favorable compared with historical controls treated with 400 mg or 800 mg of imatinib. MMR was achieved in 70% of the patients, including 10% with CMR.[2]

With these encouraging data, we started a phase III trial to compare nilotinib to standard care currently represented by imatinib 400 mg. This trial, called ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients), compares imatinib 400 mg versus nilotinib 400 mg twice a day versus nilotinib 300 mg twice a day. The initial results of this study were presented at the 2009 ASH meeting, and the data will soon be published.

In this study, nilotinib demonstrated greater efficacy than imatinib and was equally well tolerated. More patients who received nilotinib therapy at both doses achieved MMR and CCyR at 12 months than those who received imatinib therapy. Also important was that less disease progression to a more advanced stage was observed in both nilotinib arms.[3] The results of a study using dasatinib 100 mg once a day versus imatinib 400 mg once a day as first-line therapy will be presented at the 2010 annual meetings of the American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA), and we are also waiting in the near future for the results of the phase III study comparing bosutinib 500 mg once daily versus imatinib 400 mg once daily.

H&O How does high-dose imatinib compare to new drugs that are being investigated for frontline therapy?

GS There are a number of studies looking into imatinib 800 mg, and in some cases, imatinib 600 mg. One company-sponsored study by Novartis called the TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity)study showed that there was a faster achievement of MMR after 12 months of therapy with high-dose imatinib. However, the percentage of MMR between the 2 study arms was not statistically significant. In the study, there was no advantage in terms of PFS and event-free survival.[4]

There was another study, done by the GIMEMA (Gruppo Italiano Malattie Ematologiche Maligne Dell'Adulto) group, in high-risk patients—those patients with a higher risk of progression. This study also showed that there was no advantage in imatinib 800 mg versus imatinib 400 mg in intent-to-treat analysis. However, the problem is that only approximately 60% of patients could tolerate the high dose of 800 mg imatinib; most were more tolerant of the lower dose. Thus, the problem of 800 mg imatinib may be represented by intent-to-treat analysis and also by tolerability.[5]

There is a third study—the German CML-IV study—presented by Dr. Rüdiger Hehlmann at the ASH 2009 meeting. In this study, after 12 months, a higher percentage of MMR was observed in patients in the 800 mg arm compared to those in the 400 mg arm. However, in terms of event-free survival and PFS, no difference was observed.[6]

Therefore, the major difference in what has been observed in studies of nilotinib and those of high-dose imatinib is not only the higher percentage of MMR in the nilotinib arm, but also a lower rate of progression—something that we do not see with high-dose imatinib. Why this occurs is difficult to explain, but we believe that it is due to the ability of nilotinib to suppress possible clones with mutation as well as clones that are more prone to develop resistance and undergo progression. This difference is attributed to these second-generation TKIs—nilotinib in particular, for the moment—than to imatinib. It is a rather drug-specific effect.

H&O What can we expect in the future research of CML?

GS CML is a disease that is attracting much attention. What is most feared in CML is the risk of disease progression to a more advanced stage—the blast phase—which is, in most cases, still incurable even now.

On the flip side, however, the prevalence of the disease means that it is a disease that can also teach us many ways to cure leukemia, and we ought to apply the concepts that we are extrapolating from CML treatment to treating similar patients with other leukemias. Second-generation TKIs will most certainly be eventually registered as first-line therapy. However, the correct strategies (ie, when and how to use these drugs and whether or not to start with second-generation TKIs) are yet to be established. Unquestionably, more clinical trials are necessary.

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