Dasatinib (Sprycel) for Previously Untreated Early Chronic Myelogenous Leukemia

- Jorge Cortes, MD, MD Anderson Cancer Center, Houston, Tex.

In patients with chronic myelogenous leukemia in the early chronic phase (CP–CML), their initial responses to therapy correlated with improved long-term outcomes. Among previously untreated patients receiving first-line dasatinib (Sprycel, Bristol-Myers Squibb), nearly all patients had complete cytogenetic responses (CCyRs). Although CCyRs are induced in 82% of early CP–CML patients treated with standard therapy, imatinib (Gleevec, Novartis), molecular complete remissions are infrequent. Dasatinib induced CCyRs in 45% of patients with resistance to imatinib and in 78% of patients with intolerance to imatinib.

In a clinical trial that assessed major molecular responses (MMRs) after 12 months of treatment as a primary endpoint, 72 participants (median age, 49 years) who had no prior therapy (or less than one month of interferon-alpha or imatinib) were randomly assigned to receive daily or twice-daily dasatinib. The total daily dose was 100 mg. Patients were observed for a median of 25 months. All participants had Philadelphia chromosome–positive (Ph+) early CP–CML. After 66 patients were enrolled, the twice-daily arm was suspended and all patients received once-daily dasatinib.

Among patients with at least three months of follow-up, CCyRs were reported in 67 of 70 subjects (96%), and MMRs were reported in 55 of 70 subjects (79%). Complete molecular responses (CMRs) were documented in 8 of 70 patients (11%). Responses occurred early, and by three months, 80% of patients had already achieved CCyRs. By six months, that rate improved to 95%. MMRs were achieved by 64% of patients at six months and by 89% of patients at 24 months. Event-free survival was 90% at three years.

Myelosuppression was the most common adverse event. Approximately 25% of patients experienced grade 3 or 4 thrombocytopenia or neutropenia. Myelosuppression tended to be transient, occurring most often within the first two to three months of therapy. Thirty-eight patients required dose interruptions (median, 10 days). These interruptions were more common with twice-daily dosing in 16 of 33 patients (48%) than with once-daily dosing in 13 of 39 patients (33%).

Responses to dasatinib compared favorably with imatinib responses in other trials at MD Anderson Cancer Center (Table 1).

Dr. Cortes commented, “The results so far suggest that there seems to be a benefit compared to historical data over imatinib at the standard dose and possibly at the higher dose.”

He noted further that all patients were alive and none had progressed to the accelerated or blast phase. He concluded that dasatinib induced rapid CCyRs in most patients and had a favorable toxicity profile. Efficacy was similar for both doses, although tolerance was better with once-daily dosing. Cytogenetic responses (CyRs) occurred faster than with the standard dose of imatinib, and MMR rates were higher than those for imatinib.

Nilotinib (Tasigna) Superior to Imatinib (Gleevec) in Patients with Newly Diagnosed Early Chronic Myelogenous Leukemia: Phase 3 ENEST-nd Results

- Giuseppe Saglio, MD, University of Turin, Turin, Italy
- Hagop Kantarjian, MD, MD Anderson Cancer Center, Houston, Tex.

At twice-daily doses of 300 mg and 400 mg, nilotinib (Tasigna, Novartis) was superior to imatinib and led to signif-
icantly higher rates of MMRs and CCyRs in patients with newly diagnosed CML.

Imatinib is the current standard of care for CML. Disease progression in patients receiving imatinib usually occurs in the first three years of treatment. Molecular monitoring, the most sensitive measure of CML disease burden, shows that rates of disease progression are extremely low in patients achieving MMRs.

ENEST-nd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials in Newly Diagnosed Patients) is a phase 3, randomized, open-label, multicenter study comparing the efficacy and safety of twice-daily nilotinib 300 mg or 400 mg with once-daily imatinib 400 mg in patients with newly diagnosed (within six months) Ph+ chronic-phase CML (CP-CML). This study has completed patient recruitment. In this active study, 846 patients (median age, 47 years), were randomly assigned, in a 1:1:1 ratio, to the three treatment arms. The primary endpoint was rate of MMRs at 12 months. For 45 patients (16%) in the imatinib arm, the dose was escalated to 400 mg twice daily according to the protocol.

Rates of MMRs at 12 months were superior for nilotinib 300 mg twice daily, compared with imatinib 400 mg once daily (44% vs. 22%; \( P < 0.0001 \)), and for nilotinib 400 mg twice daily, compared with imatinib 400 mg once daily (43% vs. 22%; \( P < 0.0001 \)). The median time among patients who achieved MMRs was faster with nilotinib 300 mg twice daily (5.7 months) and nilotinib 400 mg twice daily (5.8 months) compared with imatinib 400 mg once daily (8.3 months).

At 12 months, CCyR rates also favored nilotinib: 80% for 300 mg twice daily, 78% for 400 mg twice daily, and 65% for imatinib (\( P < 0.0001 \) for nilotinib, \( P < 0.0005 \) for imatinib).

Overall, progression to advanced disease (the accelerated phase/blast crisis) was lower with nilotinib 300 mg twice daily (in two patients, 0.7%) and nilotinib 400 mg twice daily (in one patient, 0.4%) compared with imatinib 400 mg once daily (in 11 patients, 3.9%). At a press conference, Dr. Saglio also pointed out that it was important for his team just to see that no patients who had achieved MMRs had disease progression.

Overall, both drugs were well tolerated. Rates of discontinuation attributed to adverse events or laboratory abnormalities were 7% for nilotinib 300 mg twice daily, 11% for nilotinib 400 mg twice daily, and 9% for imatinib 400 mg once daily. Cardiac events and toxicities were not increased in the nilotinib groups.

Dr. Saglio concluded, “Nilotinib is superior to imatinib with significantly higher rates of major molecular and complete cytogenetic responses at both 300 mg twice daily and 400 mg twice daily.”

At the press conference, which was sponsored by Novartis Oncology, Dr. Kantarjian agreed:

I think the most important thing is the transformation rate—which has been reduced from 3.9% in the first year to less than 1%. Patients with CML still have significant risk of transformation in the first three to four years. So if we have a new drug that can reduce that risk by 80%, then you are going to have an improvement in outcomes of at least 15% to 20% of CML patients.

Deferasirox (Exjade) in Beta-Thalassemia Patients with Myocardial Siderosis: Two-Year Results for the EPIC Cardiac Substudy

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The frequent blood transfusions required by patients with beta-thalassemia major often lead to iron overload. Seventy percent of deaths from beta-thalassemia major are attributed to heart failure caused by cardiac iron deposition. Magnetic resonance imaging (MRI) T2* values measured at the heart’s intraventricular septum are indirectly related to myocardial iron levels. Higher iron levels (and shorter T2* values) are associated with reduced left ventricular function and an increased likelihood of heart failure and arrhythmia. Myocardial T2* values of less than 20 milliseconds (msec) indicate iron overload, and levels below 10 msec are considered severe.

In a substudy of the one-year multicenter prospective EPIC (Evaluation of Patients’ Iron Chelation) trial with deferasirox (Exjade, Novartis), patients experienced significant decreases in myocardial iron content. The EPIC cardiac substudy evaluated deferasirox in 114 patients with beta-thalassemia major (54 men, 60 women). Patients (mean age, 21 years) had myocardial siderosis, defined by an MRI assessment of the relaxation parameter T2*.

This report of the one-year extension phase results included patients 10 years of age or older with a myocardial T2* between 5 and 20 msec who received up to two years of deferasirox therapy. EPIC included patients with mild, moderate, and severe cardiac siderosis. Patients also had a left ventricular ejection fraction (LVEF) of 56% or more, serum ferritin levels of 2,500 ng/mL or higher, an MRI R2 liver iron concentration above 10 mg of iron/g (dry weight), and a lifetime minimum of 50 transfused blood units. (R2 is the inverse of T2*.)

Deferasirox was initiated at 30 mg/kg per day and was increased to 40 mg/kg per day by the time patients had entered the one-year extension. Dose decreases were allowed for safety reasons. The primary endpoint was the change in myocardial T2* from baseline to two years.

Two-year data are available for 81 of the 100 patients who entered the one-year extension phase. Mean age was 20.6 ± 7.3 years. Baseline cardiac T2* was below 10 msec (severe cardiac siderosis) in 39 patients (39%) and 10 to 20 msec (mild-to-moderate cardiac siderosis) in 61 patients (61%). The mean actual deferasirox dose was increased from 33.1 ± 3.7 mg/kg per day in the core one-year phase to 36.1 ± 7.4 mg/kg per day during the extension. After two years of deferasirox therapy, improvement in myocardial T2* continued; T2* values were increased significantly by 40.8% from a baseline geometric mean of 11.2 to 15.3 msec (\( P < 0.001 \)). Significant increases from 7.3 to 9.3 msec (\( P < 0.001 \)) and from 14.6 to 19.9 msec (\( P < 0.001 \)), respectively, were noted in patients with a baseline T2* below 10 and 10 to 20 msec. LVEF remained stable in both subgroups throughout the two-year follow-up period, and right ventricular function improved.

Dr. Pennell speculated: “The improvement in right ventricular function is best explained by improved left and right ventricular compliance associated with reduced cardiac iron and...
may be an early marker of functional improvement.”

Overall, deferasirox treatment was well tolerated, and there was no evidence of progressive impairment of renal or liver function. Both mean hepatic iron and median serum ferritin levels were significantly reduced from baseline by 10.7 ± 12.8 mg of iron/g (dry weight) and by 2.343 ng/mL (range, 12,795–25,127), respectively, based on the last-observation-carried-forward analysis (P < 0.001).

Dr. Pennell concluded that in this first large prospective study to report two-year data on cardiac iron removal for any iron chelator, continued therapy with deferasirox for up to two years at doses of 30 to 40 mg/kg per day was effective in removing iron from the heart in beta-thalassemia major patients with mild, moderate, and severe cardiac siderosis.

Eculizumab (Soliris) Improves Platelet Consumption and Thrombocytopenia in Patients With Paroxysmal Nocturnal Hemoglobinuria

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In patients with paroxysmal nocturnal hemoglobinuria (PNH), life-threatening thromboembolic events are more common if platelet counts are low (thrombocytopenia). Treatment with the terminal complement inhibitor eculizumab (Soliris, Alexion), an anti-C5 monoclonal antibody, has been found to increase platelet counts.

In PNH, a debilitating hematopoietic stem-cell disorder, complement system activation leads to significant morbidities and a shortened life span. Thromboembolism, the most untoward complication of PNH, causes 45% of deaths in these patients. It is thought that platelet activation and consumption contribute to the chronic thrombocytopenia of PNH. Dr. Muus and colleagues tested whether chronic inhibition of terminal complement activation with eculizumab would reverse the thrombocytopenia seen in PNH.

In an analysis of results from SHEPHERD (Safety in Hemo- lytic PNH Patients Treated with Eculizumab: A Multicenter Open-Label, Research Design), TRIUMPH, phase 2 eculizumab trials, and the extension trial, 49 patients were identified as having thrombocytopenia and 145 did not have it. Mean patient age was approximately 41 years. Platelet counts were measured at the baseline and after 26 and 52 weeks of eculizumab treatment. Results confirmed that patients with thrombocytopenia were more likely to have a history of thromboembolism (45%) than those with normal platelet counts of 100 × 10^9/L or higher (27%) (P = 0.02).

Median platelet counts in thrombocytopenic patients were significantly increased (P < 0.03 vs. baseline) by eculizumab’s ability to inhibit C5 activity. One third of patients were no longer thrombocytopenic at 26 weeks, and 35.6% were no longer thrombocytopenic at 52 weeks (P < 0.05 for both).

Median platelet counts significantly increased in thrombo cytopenic patients from 68 × 10^9/L at baseline to 80 and 85 × 10^9/L (P < 0.001) at 26 and 52 weeks, respectively. Platelet counts increased regardless of prior bone marrow failure. There were no changes in absolute neutrophil counts, indicating that the improvements in platelet counts had not resulted from a general improvement in bone marrow function.

During an interview, Dr. Muus explained: “We knew before that platelets were affected by PNH, but this confirms that there must be some consumption of platelets in at least quite a few patients. We didn’t really know that before. We know now also that eculizumab reverses it.”

Especially for patients with very low platelet counts (e.g., 20 × 10^9/L), the boost in the count with eculizumab could be clinically important, she added.

Romiplostim (Nplate) Benefits Patients With Myelodysplastic Syndromes Who Receive Lenalidomide (Revlimid)

- Roger M. Lyons, MD, Cancer Care Centers of South Texas, US Oncology, San Antonio, Tx.

Thrombocytopenia, which occurs in 40% to 65% of patients with myelodysplastic syndromes (MDS) over their disease course, can cause hemorrhagic complications, including death. Thrombocytopenia has been reported in 62% of patients treated with lenalidomide (Revlimid, Celgene), an approved therapy for MDS patients with a chromosome 5q deletion.

Romiplostim is a peptibody protein designed to increase platelet production by binding to and activating the thrombopoietin receptor. It is indicated for chronic immune thrombocytopenia in adults with insufficient responses to corticosteroids, immunoglobulins, or splenectomy.

The effect of romiplostim on the incidence of clinically significant thrombocytopenic events (grade 3 or 4) in patients requiring platelet transfusions and on safety in patients with low- or intermediate-risk MDS was tested in a phase 2 multicenter, randomized, placebo-controlled trial. Enrolled patients were assigned, in a 1:1:1 fashion, to receive placebo, 500 mcg of romiplostim, or 750 mcg of romiplostim by weekly subcutaneous injections plus lenalidomide. The lenalidomide dose was one oral capsule daily for each of four 28-day cycles.

Among 39 enrolled patients, the median age was 74 years (range, 39–90 years). Platelet counts were below 50 × 10^9/L in 15 patients (39%), and seven patients (18%) had 5q deletions. Throughout 17 weeks of follow-up evaluations, a clear dose response was apparent in higher platelet counts for romi plostim than for placebo.

Responses to MDS treatment, based on modified MDS International Working Group guidelines, were noted in one of 12 placebo patients (8%), in 5 of 14 patients (36%) receiving romiplostim 500 mcg, and in two of 13 patients (15%) receiving romiplostim 750 mcg. There was one complete response in the placebo group (8%) and two complete responses for romiplostim 500 mcg (14%) and for romiplostim 750 mcg (15%).

Among patients with the 5q deletion, response rates were 0/1 (0%) with placebo, 2/3 (67%) with romiplostim 500 mcg, and 1/2 (50%) with romiplostim 750 mcg. The romiplostim patients had higher median cumulative exposure to lenalidomide (placebo = 420 mcg; romiplostim 500 mcg = 1,040 mcg; and romiplostim 750 mcg = 750 mcg). Clinically significant thrombocytopenic events occurred in eight patients in the placebo group (67%), in four of the romiplostim 500-mcg patients (29%) and in seven of the romiplostim 750-mcg patients (54%). Platelet transfusions were required for two patients receiving placebo (25%), one patient receiving continued on page 112
romiplostim 500 mcg (7%), and four patients receiving romiplostim 750 mcg (31%). Only one treatment-related serious adverse event was reported in the romiplostim 500-mcg group of patients (8%).

Dr. Lyons concluded, “This preliminary analysis suggests that romiplostim may reduce the rate of clinically significant thrombocytopenic events while increasing platelet counts in lower-risk MDS patients receiving lenalidomide.”

**Panobinostat Holds Promise for Hodgkin’s Lymphoma after High-Dose Chemotherapy And Stem-Cell Transplantation**

- Anas Younes, MD, MD Anderson Cancer Center, Houston, Tx.

  In heavily pretreated patients with post-transplant, refractory, or relapsed classical Hodgkin’s lymphoma, panobinostat (LBH589, Novartis) has shown encouraging activity. The finding comes from a trial that was launched to confirm a 40% response rate in a phase 1 trial. *In vitro*, panobinostat decreased proliferation and induced apoptosis in Hodgkin’s lymphoma cell lines.

  The ongoing trial is being conducted among 129 patients with refractory or relapsed Hodgkin’s lymphoma following high-dose chemotherapy and autologous hematopoietic stem-cell transplantation. Oral panobinostat is administered at a dose of 40 mg three times per week every week in 21-day cycles and is continued until disease progression or intolerance. Computed tomography and MRI scans are conducted after every two cycles.

  The median age in the 67 patients who have completed at least two cycles of treatment is about 31 years. The response rate after 16 responses is 22.5%.

  In an interview, however, Dr. Younes pointed out that responses can still occur after four or six months of therapy. He said that 80% of patients have had reductions in tumor measurements and 88% achieve disease control (defined as stable disease plus partial remission plus complete remission).

  “We’ve taken a snapshot. Many have received only two to three months of therapy and may be close to a partial remission,” he said.

  Panobinostat is well tolerated, with the class effect of thrombocytopenia grade 3 or 4 reported at 45%. However, as soon as the drug is stopped, platelets rebound in a few days.

  Dose modification or interruptions are determined by platelet counts. Dr. Younes commented that an alternate dosing approach would be to administer panobinostat every other week. He also observed that if the panobinostat response rate exceeds 30%, the FDA benchmark, it would be tested further as a monotherapy. Otherwise, it will be tested in combination with other agents.

  In an educational session at the ASH meeting, Dr. Younes said that drug development for Hodgkin’s lymphoma has been neglected for more than three decades; although many agents demonstrate clinical activity, that activity is modest in both Hodgkin’s and non-Hodgkin’s lymphomas. The most promising agents for relapsed classical Hodgkin’s lymphoma, he said, are SGN-35 (Seattle Genetics), panobinostat, and everolimus (Afinitor, Novartis), a derivative of sirolimus (rapamycin).