**Meeting Highlights**

**American Society of Hematology, 50th Annual Meeting and Exposition**

Walter Alexander

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**ASH 2008 Overview**

The 2008 meeting of the American Society of Hematology hosted a record 24,000 attendees in San Francisco from December 6 to 9, 2008. Sessions covered almost 4,000 abstracts on a wide variety of hematologic disorders. Key topics included leukemias, myelodysplastic disorder, multiple myeloma, paroxysmal nocturnal hemoglobinuria, and idiopathic thrombocytopenic purpura.

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**Imatinib (Gleevec) versus Imatinib Combination Therapies for Newly Diagnosed Chronic Myeloid Leukemia (Chronic Phase)**

- Francois Guilhot, MD, Centre Hospitalier Universitaire, La Miletrie, Poitiers, France

The most powerful treatment for patients with chronic myeloid leukemia (CML) in chronic phase, according to the results of the SPIRIT (STI571 Prospective Randomized Trial), is the combination of imatinib mesylate (Gleevec, Novartis) and pegylated interferon (PEG-IFN). The prospective, four-arm phase 3 trial explored higher doses of imatinib and combination therapies. Earlier phase 2 trials had evaluated imatinib plus either cytarabine arabinoside (Ara-C) or PEG-IFN. In the four treatment arms, chronic-phase 636 CML patients (median age, 51 years, with 62% men) were randomly assigned, in a 1:1:1:1 fashion, to receive 14 days of imatinib 400 mg or 600 mg, or imatinib 400 mg/day plus cytarabine 20 mg/m² for 14 days per month or imatinib 400 mg/day plus PEG-IFN alfa 2a 90 mcg/week. The primary endpoint was overall survival.

SPIRIT investigators enrolled patients who received a diagnosis of chronic-phase CML within the previous three months and who had no prior CML therapy except hydroxyurea or aagrelide (Agrylin, Shire) for three months. The median follow-up period was 36 months. Complete hematological responses at three months were achieved by 88% of patients. At six months, complete cytogenetic responses (CCyRs) were attained by more patients in the imatinib 600-mg/day arm. At 12 months, CCyRs were achieved by 55% of patients receiving imatinib 400 mg, by 62% receiving imatinib 600 mg, by 63% receiving imatinib/Ara-C, and by 65%, receiving imatinib/PEG-IFN.

The major molecular response rate (bcr-abl/abl ≤ 0.01%) was significantly higher with imatinib/PEG-IFN than with imatinib 400 mg at both six months (39%/20%, P = 0.0005) and at 12 months (57%/38%, P = 0.005). The cumulative incidence of achieving bcr-abl/abl levels of 0.01% or below within 12 months was significantly higher in the imatinib/PEG-IFN group (36%) than in the other groups: imatinib 600 mg, 21%; imatinib/Ara-C, 20%; and imatinib 400 mg, 16% (P = 0.002).

Optimal molecular deep and complete responses at 12 months also occurred more often in the imatinib/IFN arm (30%) than in the others: 15% with imatinib 400 mg, 18% with 600 mg, and 15% with 600 mg of imatinib + Ara-C (P = 0.0019).

Higher rates of grade 3 and 4 toxicities, especially neutropenia and thrombocytopenia, were recorded with higher doses of imatinib and with the combination. Discontinuation of therapy was most frequent in the IFN arm (45%) at one year.

The SPIRIT trial, Dr. Guilhot concluded, established the imatinib/PEG-IFN combination as the most efficacious therapy for chronic-phase CML.

**Reduction of bcr-abl Transcript Levels With Imatinib (Gleevec) in Chronic Myeloid Leukemia (Chronic Phase)**

- Timothy P. Hughes, MD, Department of Haematology, Institute of Medical and Veterinary Science, Adelaide, Australia

A second imatinib-related session examined polymerase chain reaction (PCR) data from IRIS (International Randomized Study of Interferon) to determine the event-free survival (EFS) implications of bcr-abl reductions in bone marrow to the level of a major molecular response (MMR). MMR was defined as a response such that the ratio of the abnormal bcr-abl gene to a control gene is 0.1% or less.

Adverse events included within the definition of “event-free survival” were death during study treatment, loss of complete hematological response, loss of major cytogenetic response, progression to the accelerated phase or blast crisis, and an increasing white blood cell count to exceed 20 x 10⁹/L.

The depth of molecular responses did increase between four and seven years of treatment; approximately 70% of patients achieved MMRs by 24 months, and 80% achieved MMRs by 84 months. The correlation between achieving an MMR and event-free survival was positive, with 18-month event-free survival at 98.5% for those achieving a level of 0.1% or below and 14% for those achieving the 0.1 to 1% level or above (P = 0.01). It is noteworthy that the length of time it took to achieve an MMR did not significantly affect event-free survival.

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Mr. Alexander is a freelance medical writer living in New York City.
Nilotinib (Tasigna) versus Imatinib (Gleevec) For Newly Diagnosed, Previously Untreated Chronic Myelogenous Leukemia (Early Chronic Phase)

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

Patients with early-chronic-phase, Philadelphia-positive (Ph+) CML achieved cytogenetic responses faster with nilotinib (Tasigna, Novartis) than with imatinib, and more nilotinib-treated patients achieved MMRs and undetectable transcript levels.

Although imatinib induces CCyRs in 80% of patients with chronic-phase CML, molecular complete remissions are infrequent at standard doses. Earlier complete remissions are correlated with improved long-term outcomes. Derived from the imatinib molecule, nilotinib inhibits most imatinib-resistant bcr-abl kinase domain mutants except dasatinib (T3151, Sprycel, Bristol-Myers Squibb). Forty percent of chronic-phase CML patients who do not respond to imatinib achieve CCyRs with nilotinib.

Dr. Cortes’ clinical trial included 53 patients (median age, 47 years); nine had previously received imatinib therapy. He noted that responses occurred early and improved over time.

Best responses included complete hematological responses (CHRs) among all 47 patients not having CHRs at the start of treatment, CCyRs in 45 of 46 patients (97%) and MMRs in 25 of 47 patients (53%). Ten patients (21%) achieved complete molecular responses (CMRs).

Although there were fewer molecular responses at three months (7%), by 12 months (the primary endpoint), 47% had achieved molecular responses, with CMRs achieved by 7%. Molecular responses increased over time. At 18 months, MMRs were reported in 65% of patients; among these, 30% experienced CMRs. At 12 months, the event-free survival rate was 89% and the overall survival rate was 100%.

Adverse events with nilotinib were generally lower than with other therapies, Dr. Cortes said. Elevated liver enzyme levels were transient, and grade 3 and 4 neutropenia (11%) and thrombocytopenia (9%) occurred in the first two to three months and were seldom seen thereafter. Median duration of dose interruptions was nine days among the 40% of patients requiring them. Six patients withdrew from treatment.

Compared with other experience in early chronic-phase CML, patients receiving nilotinib achieved MMRs sooner (Table 1).

Dr. Cortes concluded that nilotinib produced rapid CCyRs more quickly than imatinib did. Molecular responses at 12 months were similar to those for high-dose imatinib. A high percentage of patients achieved undetectable transcript levels, and the toxicity profile was favorable.

**Table 1 Percentage of Patients Achieving Major Molecular Responses with Imatinib And Nilotinib**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Imatinib 400 mg (%)</th>
<th>Imatinib 800 mg (%)</th>
<th>Nilotinib 800 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>0 (N = 50)</td>
<td>35 (N = 205)</td>
<td>40 (N = 53)</td>
</tr>
<tr>
<td>12 months</td>
<td>24 (N = 50)</td>
<td>47 (N = 205)</td>
<td>47 (N = 53)</td>
</tr>
<tr>
<td>18 months</td>
<td>42 (N = 50)</td>
<td>52 (N = 205)</td>
<td>65 (N = 53)</td>
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MEETING HIGHLIGHTS: American Society of Hematology

or, specifically, progression to the accelerated or blast phase.

“This really demonstrates that achieving a major molecular response is very solid evidence of achieving a safe haven for CML patients,” Dr. Hughes said. He concluded, “Both molecular and cytogenetic evaluations should be used to guide treatment decisions.”

**Prolonged Therapy with Lenalidomide (Revlimid) plus Dexamethasone Extends Survival in Refractory Multiple Myeloma**

• Jesus F. San Miguel, Professor of Medicine, University Hospital of Salamanca, Salamanca, Spain

Because extended treatment with lenalidomide (Revlimid, Celgene) and dexamethasone (Len/Dex) prolongs survival, every effort should be made to control adverse effects likely to cause withdrawal from treatment.

In an analysis of data from two clinical trials of multiple myeloma (MM), Len/Dex, when compared with Dex alone, had demonstrated significant improvements in response rates, median time to disease progression, and overall survival in patients with relapsed or refractory MM.

The objective of Dr. San Miguel’s clinical trial analysis was to determine whether maintaining treatment with Len/Dex after achieving best responses led to better overall survival and time to disease progression in MM patients compared with stopping treatment. The two trials (MM-009, MM-010) enrolled 353 patients treated with Len (25 mg/day on days 1 to 21 on an every-28-day cycle) and Dex (40 mg/day on days 1 to 4, 9 to 12, and 17 to 20, for four 28-day cycles and days 1 to 4 only from the fifth cycle onward).

Among 321 responding patients, 107 (33%) had stable disease and 214 (67%) had a partial response or better. A landmark analysis assessed outcomes in those 223 patients who, after achieving best response, continued treatment for 10 months or less versus 98 patients who continued treatment for more than 10 months. In the two groups, the actual median duration of treatment was 6.6 months and 17.6 months. A second analysis evaluated the impact of early discontinuation resulting from adverse events or withdrawn consent on overall survival and time to disease progression in patients who achieved stable disease or better.

In patients treated for more than 10 months, overall survival was significantly longer (more than 31.6 months) than in patients treated for 10 months or less (23.4 months, P < 0.0001). Furthermore, a significantly higher percentage of the patients treated for a longer time were alive at 24 months (93.8% vs. 48.4%; P < 0.0001).

For the 214 patients who achieved partial responses or better, the median overall survival was longer with extended treatment (more than 31.6 months) compared with 26.9 months for those treated for less than 10 months (P < 0.0001). Median overall survival was also longer for patients who con-
Eculizumab (Soliris) Reduces Pulmonary Hypertension in Paroxysmal Nocturnal Hemoglobinuria

Anita Hill, MD, Department of Hematology, Bradford Royal Infirmary, Bradford, U.K.

In patients with paroxysmal nocturnal hemoglobinuria (PNH), the complement inhibitor eculizumab (Soliris, Alexion) reduces pulmonary arterial hypertension (PAH), brain natriuretic peptide (BNP) levels, and PAH-related symptoms. PAH affects 30% of patients with sickle-cell disease, and it is an independent risk factor for death in these patients. It is also a complication of other hemolytic anemias (defined as having a dependent risk factor for death in these patients). It is also a complication of other hemolytic anemias (defined as having a dependent risk factor for death in these patients). It is also a complication of other hemolytic anemias (defined as having a dependent risk factor for death in these patients).

Symptoms of PNH include disabling fatigue, abdominal pain, shortness of breath, kidney dysfunction, thrombosis, and anemia; however, the most common clinical symptom, found in two-thirds of hemolytic PNH patients (defined as having a terminal prohormone BNP levels of 160 pg/ml or higher, as in thalassemia, stomatocytosis, and spherocytosis). Hemolysis (red blood cell destruction) releases free hemoglobin, which leads through two pathways to nitric oxide consumption and, ultimately, to platelet aggregation and the thromboses of PAH and other vascular disorders.

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Dr. Hill’s phase 3 randomized, placebo-controlled trial (TRIUMPH) assessed eculizumab’s impact on PAH in patients with PNH and evaluated levels of BNP. Elevated BNP indicates increased nitric oxide consumption far exceeds that noted in other hemolytic diseases. More than two-thirds of patients report shortness of breath, moderate-to-severe dyspnea, and dyspnea-related distress. Eculizumab blocks hemolysis in patients with PNH and reduces these symptoms.

Ofatumumab (HuMax-CD20) in Refractory Chronic Lymphocytic Leukemia: Interim Analysis of a Pivotal Trial

Anders Österborg, MD, Karolinska Hospital, Stockholm, Sweden

For patients with chronic lymphocytic leukemia (CLL) refractory to both fludarabine (Fludara, Berlex) and alemtuzumab (Campath, Berlex) or who have bulky lymph nodes, the prognosis is poor. In a pilot study of CLL, the human CD20 monoclonal antibody ofatumumab (HuMAX-CD20, Genmab) showed promising activity, with an overall response rate of 50% in 27 patients receiving high-dose therapy.

The study goal, Dr. Österborg said, was to assess efficacy and safety in a CLL population with double-refractory (DR) disease (refractory to fludarabine and alemtuzumab) or with bulky fludarabine-refractory (BFR) disease (refractory to fludarabine and, because of bulky nodes greater than 5 cm, inappropriate for alemtuzumab). The open-label, single-arm, multicenter study was conducted in Europe and the U.S.

The primary endpoint was objective response, according to 1996 National Cancer Institute–Working Group criteria. The median patient age was 63 years, with 73.5% male. These patients had received a median of 4.5 previous therapies. There was a high response rate for single-agent ofatumumab in this advanced-stage, CLL population with refractory disease.

The overall response rates were 58% in the DR group and 47% in the BFR group. Ofatumumab was effective independent of earlier treatment with rituximab (Rituxan, Genentech), age, Rai stage at entry, and number of previous regimens. Responses also correlated with significantly improved survival outcomes: median progression-free survival rates were 5.7 months in the DR group and 5.9 months in the BFR group, and median overall survival rates were 13.7 months in the DR group and 15.4 months in the BFR group. Although median overall survival has not been reached by responders in either group, the rate exceeds median overall survival among non-responders (DR, 9.8 months; P = 0.0424; BFR, 10.2 months; P = 0.0001).

Ofatumumab was well tolerated with no unexpected adverse events. The most common events in both groups were infections (affecting 25%) and neutropenia (affecting 10%). Nine patients died; six of the deaths occurred early and were not considered to be related to ofatumumab treatment.

“The most important finding of this trial,” Dr. Österborg said, “is that despite these patients being so heavily pretreated and having no evidence-based therapeutic possibilities left, we got new remissions in 50% to 60% of patients, and these were associated with prolonged survival.”

continued on page 100
Meeting Highlights: American Society of Hematology

Long-Term Oral Eltrombopag (Promacta) in Chronic Idiopathic Thrombocytopenic Purpura
• Gregory Cheng, MD, Chinese University of Hong Kong, Hong Kong, China

With standard intravenous (IV) treatment for idiopathic thrombocytopenic purpura (ITP) requiring two to five days of inpatient treatment, the convenience of oral eltrombopag (Promacta, GlaxoSmithKline) is likely to give this agent a clinical role, according to Dr. Cheng, lead investigator of RAISE (Randomized placebo-controlled ITP Study with Eltrombopag).

In chronic ITP, low blood platelet counts caused by increased platelet destruction or inadequate platelet production persist and can last indefinitely. Increased bleeding risk, along with excessive bruising, is a consequence. Serious hemorrhages, on rare occasions, are fatal. Eltrombopag is the first approved, oral small-molecule, nonpeptide thrombopoietin receptor agonist.

In preclinical research and clinical trials, eltrombopag stimulates the proliferation and differentiation of megakaryocytes, the bone marrow cells that give rise to blood platelets.

RAISE included 197 patients with platelet counts below 30,000 mcL. Patients received once-daily eltrombopag at 25 to 75 mg (initially at 50 mg, with dosing individualized based on response) or placebo for six months. About 50% of the enrolled patients had platelet counts below 15,000/mcL, and the other half had received at least three previous ITP medications.

Platelet counts of 50,000 to 400,000 mcL were achieved by 75% of patients receiving eltrombopag compared with 25% receiving placebo (P < 0.001). Eltrombopag also reduced the incidence and severity of bleeding. The odds of bleeding and significant bleeding were reduced by 76% with eltrombopag and by 65% with placebo. Baseline variables of prior splenectomy, platelet count, and ITP medications did not affect outcomes. The need for rescue or concomitant medications (predominantly corticosteroids) was reduced significantly, and health-related quality of life also improved (P < 0.05).

Eltrombopag was generally well tolerated. Adverse events leading to treatment withdrawal were experienced similarly between eltrombopag and placebo patients. Nausea and vomiting were more common with eltrombopag, as were liver-related adverse events (12% vs. 8% for placebo). Thromboembolic events were reported in 1.5% of patients receiving eltrombopag but in none of the placebo patients (0%).

Dr. Cheng concluded, “As compared with those receiving placebo, patients with chronic ITP were able to generate sustained platelet counts significantly more often with eltrombopag.”

In an interview, he added, “Eltrombopag will have a role among patients refractory to conventional ITP treatment and among elective surgery ITP patients.”

Deferasirox (Exjade) Reduces Cardiac Iron in Beta-Thalassemia Major: Cardiac Substudy of EPIC
• Dudley Pennell, MD, Royal Brompton Hospital, London, U.K.

EPIC, the first prospective, multicenter study of deferasirox (Exjade, Novartis) in beta-thalassemia patients with mild, moderate, and severe myocardial siderosis (iron overload), confirmed the chelation agent’s efficacy for removing cardiac iron. About 70% of patients with beta-thalassemia, which is endemic in the world’s malaria belt, die of heart failure related to iron overload. A beta-thalassemia patient receiving 2 to 3 units of blood monthly is taking on an iron load of 600 to 700 mg each month and needs daily chelation, Dr. Pennell said in an interview. He reported on the cardiac substudy of the EPIC trial.

In patients with beta-thalassemia, cardiac T2* magnetic resonance imaging (MRI) evaluates myocardial iron content and correlates with reduced left ventricular (LV) ejection fraction. Myocardial T2* values below 20 msec are indicative of iron overload. The cardiac substudy included patients who had MRI myocardial T2* between 5 and 20 msec, LV ejection fraction (LVEF) of 50% or above, serum ferritin above 2,500 ng/mL, increased MRI transverse relaxation rate (R2) liver iron concentration (above 10 mg of iron per gram, dry weight) and a lifetime minimum of 50 transfused blood units. Deferasirox was initiated at 30 mg/kg per day, and subsequent dose adjustments of 5 to 10 mg/kg per day were based on changes in serum ferritin, cardiac T2* at six months, and safety parameters.

The primary endpoint was the change in myocardial T2* from baseline to one year.

Among 114 patients, the mean baseline liver iron concentration was 28.2 ± 10.0 mg of iron per gram (dry weight). Median serum ferritin was 5,235 ng/mL, and the mean amount of transfused blood in the previous year was 185 mL/kg. Most patients (68.4%) had received chelation with injected deferoxamine (deferexamine, or DFO, Novartis) or combined DFO/deferoxprone (Ferriprox, Apo Pharma) (31.6%). The mean deferasirox dose over the one-year treatment period was 32.6 mg/kg per day.

At one year, myocardial T2* improved significantly from a baseline of 11.2 mg to 12.9 msec (P < 0.0001), representing an increase by a factor of 1.16 from baseline. Increases of more than 4% in T2* were seen in 69.5% of patients. There was no change in 14.3% of the patients, but worsening occurred in 16.2%. Increases in T2* were similar in subgroups with severe and mild-to-moderate iron overload. LVEF remained stable throughout the study.

At one year, mean liver iron levels were significantly reduced in the overall population (P < 0.0001) and in subgroups. Also, median serum ferritin decreased significantly from baseline (5,235 ng/mL) by ~1257 ng/mL and in the subgroups. Deferasirox was generally well tolerated, and most adverse events were mild to moderate.

“Showing that this oral iron chelator works is good news for patients,” Dr. Pennell said.