Oblimersen Sodium in Acute Myeloid Leukemia

Speaker: Guido Marcucci, MD, Assistant Professor of Medicine, Department of Medicine and Comprehensive Cancer Center, Ohio State University School of Medicine, Columbus, Ohio

A highly sensitive and specific assay is now available for measuring plasma and intracellular levels of oblimersen sodium (Genasense®, Genta) and target down-regulation of Bcl-2 messenger RNA (mRNA) expression in older patients with acute myeloid leukemia (AML). Investigators found that this new antisense agent, directed against Bcl-2 protein, produced robust intracellular levels of drug in target tissue in vivo, which resulted in clinically relevant target down-regulation and correlated with disease response.

Twenty-nine patients older than 60 years of age who had not undergone earlier chemotherapy for AML received intravenous (IV) induction therapy with oblimersen, cytarabine (ara-C, DepoCyt®, Chiron/SkyePharma), and daunorubicin (e.g., Cerubidine®, Ben Venue). Upon achieving complete remission, the patients underwent two cycles of consolidation therapy of IV cytarabine (on days four to eight) and oblimersen (on days one to eight).

The enzyme-linked immunosorbent assay (ELISA)-based test, developed at the university’s cancer center, was used to measure plasma and intracellular levels of oblimersen. Bcl-2 mRNA and protein levels were quantified with real-time polymerase chain reaction (RT–PCR) testing and ELISA, respectively.

The first evidence that measurable in vivo uptake of antisense occurred in bone marrow cells in AML patients was obtained following 72 hours of oblimersen infusion. Intracellular levels of oblimersen appeared higher in the patients who achieved CRs (5.62 pmol/mg protein) than in the nonresponders (1.84 pmol/mg protein).

In 22 patients who were evaluable for both clinical response and Bcl-2 levels, the intracellular Bcl-2 protein content at the baseline assessment was significantly higher in the patients with CRs than in the nine nonresponders. After 72 hours of oblimersen IV infusions, the evaluable CR patients showed a marked reduction of Bcl-2 content, compared with a statistically significant increase in Bcl-2 content in the nonresponders.

A trend toward higher intracellular oblimersen concentrations was also observed in the evaluable CR patients compared with the nonresponders.

Meeting Highlights

46th Annual Meeting of the American Society of Hematology

Lawrence M. Prescott, PhD

More than 20,000 physicians, research scientists, radiologists, nurses, and other health care professionals attended the 46th annual meeting of the American Society of Hematology (ASH) in San Diego, California, from December 4 to 7, 2004, to hear the latest developments on malignant and nonmalignant hematological diseases.

Some unique approaches included a new antisense agent/chemotherapy combination for elderly patients with acute myeloid leukemia; a novel arsenic compound for adults or children with acute promyelocytic leukemia; a protein-tyrosine kinase inhibitor for newly diagnosed chronic myeloid leukemia; a monoclonal antibody and chemotherapeutic agent combination for relapsed chronic lymphocytic leukemia; two immunotherapeutic approaches for both previously untreated patients with non-Hodgkin’s lymphoma and patients with relapsed or refractory disease; a proteasome inhibitor for first-line multiple myeloma therapy; an immunomodulatory agent for maintenance therapy in myeloma; an investigational iron chelation agent for beta-thalassemia and transfusion-related iron overload; and a low-molecular-weight heparin as a bridging anticoagulant for patients with a mechanical prosthetic heart valve who need to discontinue warfarin therapy temporarily.

Oblimersen Sodium in Acute Myeloid Leukemia

Dr. Prescott is a medical, health, and science writer based in San Diego, California, and a former medical microbiologist and clinical pathologist for the World Health Organization.
**Arsenic Trioxide for Patients with Acute Promyelocytic Leukemia**

**Speaker:** Biju George, MD, Hematologist/Oncologist, Hematology Department, Christian Medical College, Vellore, Tamilnadu, India

An open-label study resulted in long-term hematological and molecular remission in more than 75% of adults and children with newly diagnosed acute promyelocytic leukemia (APML) who were treated with arsenic trioxide (Trisenox®, citi) alone.

Between 1997 and 2004, 58 patients who were unable to receive all-trans retinoic acid (ATRA)-based therapy were given arsenic trioxide. In an effort to induce remission, the investigators administered arsenic trioxide 10 mg/day to the adults and 0.15 mg/kg per day to the children until complete hematological remission was achieved for a maximum of 60 days. This was followed by a single course of consolidation therapy lasting 28 days, one month after the remission was achieved. Maintenance therapy was administered for 10 days every month for six months. Hydroxyurea was used to stabilize white blood cell counts.

The response to arsenic trioxide was evaluable in 49 patients. Nine patients died less than two weeks after treatment began. Forty-seven patients (95%) in the evaluable group achieved hematological remission. The two patients who did not achieve remission died during the third week of therapy, one from intracranial bleeding and the other from bacterial sepsis. One patient who did achieve hematological remission died of fungal pneumonia on day 60. Forty-six patients received subsequent courses of arsenic trioxide.

At a median follow-up of 23 months, four patients experienced a relapse; of these, three patients achieved a second remission with arsenic trioxide and ATRA. At the time of this writing, 45 patients (77.5%) were alive and in molecular remission, with a leukemia-free survival rate of 93.3%.

**Imatinib Mesylate in Newly Diagnosed Chronic Myeloid Leukemia**

**Speaker:** Francois Guilhot, MD, Professor and Head, Oncology, Hematology, and Cell Therapy Department, Centre Hospitalier Universitaire, La Miletrie, Poitiers, France

Patients with newly diagnosed chronic myeloid leukemia (CML) who were treated early with imatinib mesylate (Gleevec®, Novartis) were more likely to achieve complete cytogenetic responses (CCRs), resulting in the elimination of leukemic cells and in an improvement of long-term, progression-free survival.

Long-term data were assessed from the International Randomized Interferon vs. STI 571 study (IRIS), the largest clinical trial of CML ever conducted. The study enrolled 1,106 patients from 117 centers in 16 countries from June 2000 to January 2001. The patients were randomly selected to receive imatinib or interferon plus cytosine arabinoside (ara-C) (Depo-Cyt®, Chiron/SkyePharma). Initial findings demonstrated that imatinib was significantly superior to interferon plus ara-C in these patients.

In a long-term, 42-month follow-up, 98% of these patients receiving imatinib achieved complete hematological responses (CHR), 91% had major cytogenetic responses (MCR), and 84% achieved CCRs. For the patients achieving CCRs and a thousand-fold or greater reduction in Bcr/Ab1 transcript levels (a molecular response, at 12 months), the progression-free survival rate at 42 months was 98%. For the patients who did not achieve CCRs, the survival rate was 74%.

At the 42-month follow-up, the responses to imatinib were durable. Approximately 91% of the patients continued to achieve CHR, 91% maintained MCRs, and 87% of patients had CCRs. The overall survival rate, based on the number of CML-related deaths, was 97% for the patients treated with imatinib.

Patients taking imatinib as first-line therapy who achieved CCRs within 12 months of treatment had a progression-free survival rate of 93% at 42 months. Patients who did not achieve CCRs had a progression-free survival rate of 74%.

**Fludarabine Phosphate/Alemtuzumab Combination for Relapsed or Refractory Chronic Lymphocytic Leukemia**

**Speaker:** Andreas Engert, MD, Professor/Senior Consultant, First Department of Internal Medicine, University of Cologne, Cologne, Germany

Combination therapy with the chemotherapeutic agent fludarabine phosphate (Fludara®, Berlex) and the monoclonal antibody alemtuzumab (Campath®, Berlex) (FluCam) was safe and effective in eradicating both detectable minimal residual disease and in improving overall survival in heavily pretreated patients with relapsed or refractory chronic lymphocytic leukemia (CLL).

Because monoclonal antibodies such as alemtuzumab act synergistically with fludarabine both in vitro and in vivo, a phase 2 study was performed to evaluate a new FluCam combination regimen in 37 patients with relapsed or refractory disease.

Patients received FluCam after a short period of an alemtuzumab dose escalation. The doses were increased from 3 to 10 to 30 mg during the first 14 days. The FluCam regimen consisted of IV fludarabine 30 mg/m² for 15 to 30 minutes on days one to three; IV alemtuzumab 30 mg over four hours on day one; and IV alemtuzumab for two hours on days two and three. The FluCam regimen was repeated every 28 days for a maximum of six cycles.

Four-color flow cytometry was used to measure minimal residual disease. Staging of patients was performed at entry, at day 0 (zero) of the third and fifth cycles (if given), and at one month after the end of treatment. Follow-up staging was undertaken every 12 months until disease progression occurred.

The overall response rate was 83%, with 11 complete responses (CRs) (30.5%), 19 partial responses (PRs) (52.8%), one patient with stable disease, and five patients with progressive disease (13.9%). Disease resolved in all sites, particularly in the blood, bone marrow, and spleen.

The lymphocytosis that had been present at the baseline examination resolved rapidly during the first two treatment cycles. By the third month of follow-up, 16 of 34 patients for whom data were available (44%) had achieved immuno-continued on page 110
of age or younger (586 patients); group 2, ages 60 to 70 years or younger (250 patients); and group 3, older than 70 years of age (159 patients).

Substantial overall response rates were observed in each patient group: 66% in group 1, 50% in group 2, and 53% in group 3. Approximately 50% of these responses were complete responses (CRs); 37% for the group 1 patients, 23% for the group 2 patients, and 23% for patients in group 3.

The median duration for patients achieving CRs in all three age groups was 32.3 months; the median duration for those older than 70 years of age was 36.4 months. Generally, patients younger than 60 years of age had somewhat more favorable responses, but patients older than age 60 had poorer prognostic factors on presentation, with high International Prognostic Index scores and transformed histological features.

In all age groups, the clinical outcome following the combination treatment was superior to that reported after previous therapy.

Bortezomib in Multiple Myeloma
Speaker: Sundar Jagannath, MD, Chief, Bone Marrow and Blood Stem Cell Transplantation, St. Vincent's Comprehensive Cancer Center, New York, New York

Bortezomib (Velcade®, Millennium), a first-in-class proteasome inhibitor, appears to be a promising therapeutic modality for the first-line treatment of previously untreated patients with multiple myeloma.

A total of 42 treatment-naive patients were enrolled in a phase 2 trial. They received bortezomib 1.3 mg/m² twice weekly for the first two weeks of a three-week cycle, for a maximum of six cycles. Patients achieving less than a partial response (PR) after two cycles or less than a complete response (CR) after four cycles were given oral dexamethasone 40 mg on the day of and on the day after each bortezomib dose. The primary endpoint was the response rate.

Neurological assessments, including nerve conduction tests, were performed, and stem cells for transplantation-eligible candidates were harvested at the discretion of the physician.

At the time of this writing, 32 patients were evaluable for response. The overall response rates were 88% for patients achieving CRs and 25% for those achieving near-CRs. Six of eight patients (75%) achieved CRs or near-CRs with bortezomib therapy alone.

Stem-cell harvesting and engraftment were successful in 100% of patients (in eight of eight), and all transplant patients made complete hematological recoveries.

Adverse drug events were similar to those previously observed with bortezomib in other clinical trials. Toxicities (i.e., peripheral neuropathy, gastrointestinal events, fatigue, and hematological effects such as neutropenia) were manageable and reversible.

Thalidomide for Myeloma
Speaker: Michel Attal, MD, Hematologist/Oncologist, Hematology Service, Purpan Hospital, Toulouse, France

Thalidomide (Thalomid®, Celgene) appears to be a new and effective maintenance treatment after high-dose therapy with...
autologous stem cell transplantation (ASCT) in patients with myeloma. For patients with aggressive myeloma, high-dose therapy with ASCT is generally used, but because most of these patients still experience relapse, new strategies are being tested to manage residual disease.

The Intergroupe Francophone du Myeloma (IFM) instituted a trial to evaluate the impact of maintenance therapy with thalidomide on the duration of response after high-dose therapy. From April 2000 to October 2003, 1,004 myeloma patients younger than 65 years of age at the time of diagnosis were enrolled in the IFM99 study protocol. Of these, 780 patients, without any or with only one adverse prognostic factor, received three or four cycles of standard chemotherapy and two autologous transplants. The first cycle consisted of melphalan (Alkeran®, GlaxoSmithKline) 200 mg/m², and the second consisted of melphalan 400 mg/m².

A total of 580 patients (79%) were without progressive disease after two months and were randomly assigned to receive (1) no maintenance treatment, (2) maintenance treatment with pamidronate disodium for injection (Aredia®, Novartis), (3) a standard therapy used to treat bone diseases, or (4) maintenance treatment with thalidomide plus pamidronate.

At 40 months after their diagnosis, thalidomide improved progression-free survival and event-free survival rates. The probability of progression-free survival was 70% in the thalidomide patients, 53% in the pamidronate-alone patients, and 52% in the patients receiving no maintenance treatment. Approximately 60% of patients in the latter two study groups were given thalidomide at the time of relapse, so overall survival was similar in all three treatment groups.

**Deferasirox for Beta-­Thalassemia and Transfusion-­Related Iron Overload**

**Speaker:** Maria Cappellini, MD, Professor of Internal Medicine, Centro Anemia Congenite, Institute of Internal Medicine and Pathophysiologic Medicine, University of Milan, Milan, Italy

Deferasirox (ICL 670) (Exjade®, Novartis), an investigational once-daily oral iron chelator, induced a long-term, sustained, clinically relevant reduction in liver iron concentration in heavily transfused patients with beta-thalassemia and iron overload. The non-inferiority of the agent, at doses of 20 and 30 mg/kg per day, was demonstrated in a comparison with deferoxamine (Desferal®, Novartis), the current standard iron chelation therapy. This latter approach typically requires a slow infusion by pump over eight to 12 hours for at least five days a week.

A total of 586 patients with beta-thalassemia and transfusion-related iron overload were enrolled into an international, open-label, randomized phase 3 clinical trial. The patients were assigned, in a 1:1 ratio, to receive oral deferasirox once daily in doses of 5, 10, 20, or 30 mg/kg, respectively, or subcutaneous deferoxamine in doses of 20 to 60 mg/kg daily for five days a week.

Treatment initially was given for one year, to be followed by an extension phase, during which patients who had been randomly selected to receive deferoxamine could switch to deferasirox. The primary endpoint was achievement of a specified reduction in liver iron concentration after one year. Patients with lower initial liver iron levels at the baseline evaluation in the deferoxamine group were allowed to continue their pre-study doses. They were compared with patients receiving the lower doses of deferasirox 5 or 10 mg/kg per day. Many of these individuals, therefore, received significantly higher doses of deferoxamine relative to deferasirox.

Because of the disproportionately low dosing with deferasirox 5 and 10 mg/kg per day, compared with deferoxamine, non-inferiority was not shown in the overall patient population; however, it was demonstrated in patients receiving deferasirox 20 and 30 mg/kg per day.

At the one-year follow-up, there was a statistically significant absolute reduction of liver iron concentration in the overall patient population. The mean overall change from the baseline was −5.3 ± 8.0 mg of iron per gram dry weight for patients taking deferasirox 20 and 30 mg/kg per day. Patients taking comparable doses of deferoxamine achieved a reduction in liver iron levels of −4.3 ± 5.8 mg of iron per gram dry weight.

**Enoxaparin as a Bridging Anticoagulation Agent in Mechanical Prosthetic Heart Valve Patients**

**Speaker:** Alexander G. Turpie, MD, Professor, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Enoxaparin (Lovenox®, Sanofi-Aventis), a well-known low-molecular-weight heparin (LMWH), appears to be effective and safe as a bridging anticoagulation therapeutic agent; however, there has been concern about its use in patients with mechanical prosthetic heart valves because of reports of fatal thromboemboli in pregnant women with mechanical heart valves.

A prospective cohort study was conducted to assess the efficacy and safety of enoxaparin for bridging anticoagulation in 174 consecutive patients with a mechanical prosthetic heart valve who required temporary interruption of warfarin therapy because of elective surgery or other invasive procedures. Warfarin therapy was discontinued, and bridging anticoagulation therapy was given according to a standardized perioperative protocol. The patients underwent a clinical follow-up for three months after surgery.

Study outcomes included (1) the incidence and an associated 95% confidence interval during follow-up for major bleeding; (2) arterial thromboembolism, including stroke, transient ischemia attack (TIA), systemic embolism, or valve thrombosis; and (3) all-cause mortality.

No patients were lost to follow-up. After three months’ follow-up, only four patients experienced nonfatal bleeding, one patient had a nonfatal stroke, and four patients died as a result of non–drug-related serious adverse events. There were no episodes of valve thrombosis or systemic embolism. The results suggested that patients needing anticoagulation bridging therapy will now have a safe option.