**Lenalidomide (Revlimid) for Multiple Myeloma**

**Presenter:** Donna Weber, MD, MD Anderson Cancer Center, Houston, Tex.

In a clinical trial of patients with multiple myeloma, combining lenalidomide (Revlimid, Celgene) with dexamethasone yielded better responses than using dexamethasone alone.

Dr. Weber evaluated the time to progression (TTP) and long-term overall survival rates from pooled phase 3 results in trials MM-009 and MM-010. Included were 704 patients (mean age, 63 years). Patients had been treated with three or fewer therapies and were not dexamethasone-resistant. They were randomly assigned to receive oral lenalidomide 25 mg/day on days 1 to 21 plus oral dexamethasone 40 mg/day (Len/Dex) on days 1 to 4, days 9 to 12, and days 17 to 20, or to the same dose of dexamethasone (Dex) plus placebo on days 1 to 21. After four courses of therapy, the Dex dose was reduced and was to be taken only on the first to fourth days. Therapy was continued until disease progression.

The primary outcome measure was time to disease progression (TTP). The response rate of the Len/Dex subjects was excellent, Dr. Weber said, at 61%; the rate of complete responses (CRs) was 15%, and the rate of CRs plus nearly complete responses (nCRs) was 24%, higher than that of Dex alone (23%). Thus, the rate of CRs was 2%, and the rate of CRs plus nCRs was 3.4% ($P < 0.001$). The median duration of response overall was 16 months.

The TTP was significantly longer for the Len/Dex patients (median, 11.2 months) than for the Dex patients (median, 4.7 months) ($P < 0.001$). Median overall survival was 29.6 months for Len/Dex and 20.5 months for Dex ($P < 0.001$).

Dr. Weber said that after the interim analysis, unblinding was recommended. At that time, the Dex patients were allowed to cross over to Len/Dex. After 47% of the patients switched to Len/Dex, overall survival times remained significantly longer with Len/Dex (at 35 months) than with Dex (31 months) ($P = 0.015$). At the time of the ASH meeting, Dr. Weber reported that 58% of patients in the Len/Dex group were still living.

Among hematological adverse events, grade 3–4 neutropenia was the most common event with Len/Dex (in 13%), and grade 1–4 neutropenia was the most common event with Dex (in 11%). Among nonhematological adverse events, fatigue was the most common event with both regimens (in 45%).

Dr. Weber summarized her findings:

“Len/Dex improved response and TTP, compared with Dex. Also, these improvements were sustained despite crossovers, regardless of age, prior therapies, prior autologous stem cell transplantation, prior thalidomide therapy, and renal function status.”

**Eculizumab (Soliris) for Paroxysmal Nocturnal Hemolysis**

**Presenter:** Monica Bessler, MD, PhD, Washington University, St. Louis, Mo.

**Comment:** Charles J. Parker, MD, University of Utah School of Medicine, Salt Lake City, Utah

In a clinical trial among 187 patients with paroxysmal nocturnal hemolysis (PNH), treatment with eculizumab (Soliris, Alexion), a terminal complement inhibitor, significantly reduced hemolysis and thrombosis and improved anemia and fatigue in several participating subgroups. Dr. Bessler noted that the disease burden had not previously been determined in these patients, who had lower lactate dehydrogenase (LDH) levels, higher hemoglobin values, and minimal transfusion support.

Patients who had been enrolled in eculizumab trials (phase 2 pilot, phase 3 TRIUMPH, and SHEPHERD studies) and who continued to receive eculizumab in a long-term extension trial for a median of 22 months’ duration were stratified as follows:

- **Baseline LDH**:
  - below 1,490 U/L (n = 21)
  - 1,491–2,165 U/L (n = 106)
  - 2,166–2,785 U/L (n = 54)
  - above 2,785 U/L (n = 36)

- **Baseline hemoglobin**:
  - below 10.5 g/dL (n = 133)
  - 10.5 g/dL or higher (n = 54)

- **Transfusions**:
  - no episodes or one episode in the previous year (n = 21)
  - more than one episode in the previous year (n = 166)

Dr. Bessler noted, “All patients have a significant amount of hemolysis, as shown by LDH—even patients with mild anemia.
or rather low transfusion requirements.”

Although normal LDH levels generally fall between 250 and 300 units/liter (U/L), PNH patients in all four strata in this study had mean baseline levels exceeding 1,000 U/L. In the most recent six months with eculizumab treatment, this level dropped to between 347 and 461 U/L.

In the same time period, the mean LDH level of 2,426 U/L at baseline in patients with mild anemia (below a hemoglobin count of 10.5 g/dL) was reduced to 384 U/L, and the mean LDH level of 2,258 U/L at baseline among patients with low transfusion requirements fell to 399 U/L.

In those six months of eculizumab treatment, none of the patients needed transfusions. Dr. Bessler said that improvements in the patients with milder disease suggest that it was the change in hemolysis that brought the benefit, not the milder anemia or the lower need for transfusions.

She concluded that patients with low baseline levels of hemolysis and anemia and with low transfusion requirements, who might be expected to have less severe disease, did in fact bear a substantial PNH burden. Eculizumab therapy did decrease hemolysis, and it improved anemia and fatigue in these groups and in patients with evidence of bone marrow insufficiency. Benefits were sustained during long-term follow-up.

Finally, eculizumab reduced the risk of thrombosis in all patients regardless of their level of baseline hemolysis or anemia severity.

Commenting on eculizumab’s high cost (almost $400,000 per year) in a subsequent interview, Dr. Parker said that the pricing of orphan drugs is intended to motivate research that otherwise would not be supported. In this case, he said: “You can see PNH patients who turn around from being totally debilitated, wheelchair-bound with no quality of life, who are put on the drug and become productive people living normal lives,” he said.

RAD001 (Everolimus) in Lymphoma

Presenter: Craig B. Reeder, MD, Mayo Clinic, Scottsdale, Ariz.

RAD001 (Novartis) had single-agent activity in patients with relapsed aggressive non-Hodgkin’s lymphoma (NHL) and was well tolerated for an extended treatment interval. Dr. Reeder presented clinical trial data supporting the concept that “targeting mTOR is clinically relevant in NHL.”

Mammalian target of rapamycin (mTOR) is an intracellular protein kinase that regulates cell proliferation though activating kinases, which in turn control protein synthesis. Dr. Reed and his colleagues hypothesized that everolimus, which targets mTOR, would block the signaling needed for cell cycle G1→S progression, thereby producing tumor responses in relapsed or refractory lymphoma.

A Mayo Clinic/Dana Farber Cancer Institute trial (MC048G) assessed tumor responses in patients with aggressive histological changes, including diffuse large B-cell lymphoma (DLBC), mantle-cell lymphoma (MCL), and grade 3 proliferative lymphomas. Thirty-seven enrolled patients (mean age, 72) had received a median of four prior therapies, with some patients undergoing as many as 15. They received oral RAD001 at 10 mg/day, with dose reductions or stoppages allowed because of cytopenias or other toxicities.

At the interim analysis in this heavily pretreated NHL population who had received a median of two cycles of RAD001 (from 1 to 16 or more), the overall response rate was 32% in 12 of the 37 patients. The investigators recorded one complete response and 11 partial responses. The response rates for DLBC and MCL were 35% and 29%, respectively.

The overall time to disease progression (TTP) was 3.1 months, and the median duration of response for the 12 responders was 5.5 months. Five patients have remained free of disease progression at six months or more, and three patients have maintained a response at a median of 10.5 months (2.09 to 15.6 months or more).

Incidence rates for grade 3 toxicity were 11% for anemia, 16% for neutropenia, 30% for thrombocytopenia, and 11% for hyperglycemia. Grade 4 hyperlipidemia was reported in one patient (2%).

Dr. Reeder stated: “Oral RAD001 has single agent activity in relapsed aggressive NHL and is well tolerated for long periods of time.”

Deferasirox (Exjade) in Chelation of Iron Overload

Presenter: Alan F. List, MD, Professor of Medicine and Oncology, H. Lee Moffitt Cancer Center, Tampa, Fla.

Iron accumulation secondary to chronic transfusion therapy is associated with significant morbidity and mortality. The hazard ratio for incremental decline in overall survival rates for patients with iron overload and low-risk myelodysplastic syndrome (MDS) has been reported to be 1.36 for every 500-mcg/L increase in serum ferritin above 1,000 mcg/L.1

The mainstay of therapy for these patients, Dr. List explained, is supportive care, including red blood cell (RBC) transfusions to manage symptomatic anemia. Labile plasma iron (LPI) is a reactive oxidative species considered to be the main cause of toxicity in iron overload, and keeping it within normal limits at all times is a goal of iron chelation therapy, he emphasized.

In his core phase 3 study, the iron chelator deferasirox (Exjade, Novartis) was given at a dose of 20 mg/kg per day over one year in patients with lower-risk MDS and who had received more than 20 units of transfused RBCs. The endpoints were changes in the levels of serum ferritin and plasma iron.

The mean number of lifetime transfusions before the study was 63; the mean transfusion rate during the study year was 4.1 RBC units per month. At one year, the mean serum ferritin decrease was 859 mcg/L. About 51% of patients had serum ferritin reductions of 500 mcg/L or greater, and approximately 13% showed reductions between 200 and 499 mcg/L. The rest of the patients (10%) showed no changes or had elevations in serum ferritin (26%) that ranged from 200 to more than 500 mcg/L. Fifty-three patients with a baseline labile plasma iron level of 0.5 mcg/L or higher improved quickly.

Dr. List said, “Importantly, we had sustained decreases of mean LPI and got everyone to within normal range within three months.”

Among 165 patients eligible for the safety evaluation, 6% discontinued deferasirox treatment because of suspected adverse events, and 4% discontinued therapy secondary to
serious adverse events. Dr. List commented that deferasirox was fairly well tolerated, most frequently causing gastrointestinal side effects, and that patients stopped therapy usually because of diarrhea or elevated serum creatinine levels. Serum creatinine increases were noted in 25% of 119 patients whose levels had been normal at baseline and in 33% of patients (n = 11) with abnormal levels at baseline.

Dr. List stated: “These data indicate that deferasirox effectively reduces serum ferritin and LPI levels in a population of patients with low- and intermediate-risk MDS, with no unexpected safety concerns.” He also speculated that deferasirox might even have a beneficial effect on organ complications through sustained suppression of the labile iron.

**Dasatinib (Sprycel) in Chronic Myelogenous Leukemia**

**Presenter:** Gautam Borthakur, MD, MD Anderson Cancer Center, Houston, Tex.

In a clinical trial, responses to dasatinib (Sprycel, Bristol-Myers Squibb) were superior to those of imatinib (Gleevec, Novartis) in patients with early chronic-phase Philadelphia-positive (Ph+) chronic myelogenous leukemia (CML). Although chronic-phase CML patients receiving the standard dose of imatinib (400 mg/day) have excellent molecular improvements, polymerase chain reaction (PCR) analysis indicates that most of them have residual disease.

Dr. Borthakur said that dasatinib’s more potent inhibition of tyrosine kinase (which is 300 times higher than that of imatinib) led investigators to hypothesize that “dasatinib could induce more complete and faster responses among newly diagnosed CML patients and could eventually translate to improved long-term outcomes.”

Dr. Borthakur and his team enrolled 40 patients (median age, 41 years) with Ph+ CML in the early chronic phase. Patients either had undergone no previous treatment, or they had been treated for less than a month. Fifty percent of the patients were randomly assigned to receive dasatinib 100 mg once daily, and the other 50% received 50 mg twice daily. The study’s primary endpoint was a major molecular response (MMR).

All patients had cytogenetic responses (CyRs): 87% achieved complete CyRs (CCyRs), 3% achieved partial CyRs, 3% achieved minor CyRs, and 7% achieved early complete CyRs. Within three months, 72% had achieved CCyRs. One patient who did not achieve a CCyR was taken off therapy at nine months. CCyRs were sustained in all patients with longer follow-up.

An evaluation of molecular response (MR) rates showed that **ber-aBL** transcripts declined rapidly over time, with a median reduction of 2-log after six months and a reduction of 3-log after 18 months. These rates increased steadily over time to 57% at 18 months, including complete molecular responses (CMRs) in 5% of patients. There was a trend toward better molecular responses (MRs) in the once-daily group (MMR + CMR = 40% vs. 27% for the twice-daily group).

Hematological adverse events were minimal; grade 3–4 thrombocytopenia was observed in 10% of patients, neutropenia affected 5%, and anemia occurred in 3%. Treatment was generally well tolerated, with no significant differences noted between twice-daily and once-daily schedules.

Most nonhematological adverse events were grade 1 or 2; musculoskeletal pain was highest, at 50%. Grade 3 events, including fatigue, headache, skin, and infection (with normal absolute neutrophil counts) were reported in 5% or fewer patients. Grade 2 pleural effusion was observed in 13% of patients, and dose interruptions were needed for three participants.

Dr. Borthakur pointed out that MMR rates were better than those reported historically with the standard imatinib dose. The MMR rates, however, were similar at 18 months: for imatinib 800 mg, the MMR rate was 52%, and for dasatinib, the MMR rate was 57%.

He summarized his findings as follows: “Dasatinib induced rapid CCyRs in most patients, and most patients were able to receive the target dose.”

**Nilotinib (Tasigna) in Chronic Myelogenous Leukemia**

**Presenter:** Philipp le Coutre, MD, Charite Campus Virchow Klinikum, Humboldt-Universität, Berlin, Germany

Nilotinib (Tasigna, Novartis), the most recently approved tyrosine kinase inhibitor (in October 2007), demonstrated rapid and significant responses among patients with accelerated-phase imatinib-resistant or imatinib-intolerant Philadelphia-positive chronic myelogenous leukemia (Ph+ CML) in an open-label pivotal phase 2 study. Noting nilotinib’s greater potency than imatinib (by 30-fold), Dr. le Coutre started patients with inadequate responses with nilotinib 400 mg twice daily. If there were no safety concerns, the dose was escalated to 600 mg twice daily.

The primary endpoint was hematological response (HR). The study included 136 patients with a median age of 58 years (55% were men) with a median CML duration of 71 months. Additional chromosomal abnormalities beyond Ph+ were detected in 31% of subjects. Eighty percent of patients were imatinib-resistant, and 20% were imatinib-intolerant.

The HR rate among patients completing at least one nilotinib cycle was 54% (53% for imatinib-resistant patients and 56% for imatinib-intolerant patients). The rate of complete HRs was 26%.

Major cytogenetic responses (mCyRs) were noted for 31% of patients (29% were imatinib-resistant, and 40% were imatinib-intolerant), and complete cytogenetic responses (CCyRs) were noted in 19%. At 12 months, HRs were sustained in 82% of patients, but responses were lost in 16. The overall survival rate at 12 months was 81% (27 patients died).

Dr. le Coutre commented that overall survival data for nilotinib were comparable to those seen years ago in the phase 2 trials of imatinib in CML patients who had not responded to interferon-alpha.

“The fact that the dose intensity is so close to the intended dose of [400 mg/day twice daily] indicates how well tolerated this compound is,” he said.

The median dose intensity was 781 mg/day, and the median duration of exposure was 210 days. For 49% of the patients, however, dose interruptions lasted a median of 22 days. The continued on page 117
authors attributed discontinuation of therapy to disease progression in 29%; to drug-related adverse events in 7%; and to death in 3%. Forty-two percent of the patients have continued treatment.

Most grade 3–4 myelosuppression occurred within the first cycle, with anemia reported in 25%, neutropenia in 39%, and thrombocytopenia in 41%. Nilotinib was generally well tolerated. Rash was the most common nonhematological adverse event, and the incidence of grade 3–4 myelosuppression was less than 1%.

Dr. le Coutre indicated that nilotinib was an effective therapeutic option in this advanced CML population. Major CyR rates have continued to increase with longer follow-up periods without changes in the safety profile, he added.

REFERENCE