Dexamethasone and Lenalidomide (Revlimid) Effects in Multiple Myeloma

**Presenter:** S. Vincent Rajkumar, MD, Professor of Medicine, Mayo Graduate School of Medicine, Rochester, Minnesota

In patients with newly diagnosed multiple myeloma (MM) who received combination induction therapy with lenalidomide (Revlimid, Celgene) and dexamethasone, a lower dose of dexamethasone was found to reduce the risk of adverse drug events (ADEs).

Dr. Rajkumar and colleagues recently reported a 91% overall response rate in a small clinical evaluation of lenalidomide and dexamethasone. However, grade 3 or greater (grade 3+) toxicity occurred in almost 50% of the patients.

In an effort to assess the effects on toxicity of a lower dexamethasone dose, the investigators randomly assigned 445 patients with newly diagnosed MM to receive one of these two regimens:

- **oral lenalidomide 25 mg/day plus either high-dose dexamethasone (40 mg on days one to four, nine to 12, and 17 to 20)**
- **low-dose dexamethasone (40 mg on days one, eight, 15, and 22).**

Serious hematological ADEs of grade 3+ were uncommon during the first four months of treatment. These ADEs occurred in a similar proportion of patients in both treatment groups. However, serious non-hematological ADEs occurred much more often with high-dose dexamethasone, including infection and pneumonia (in 16.1% of patients vs. 9%; *P* = 0.031) and fatigue (in 11.7% of patients vs. 4.1%; *P* = 0.004).

After the investigators noted a high rate of early venous thromboembolism (VTE), the protocol was amended to manage aspirin, and they also strongly recommended the prophylactic use of warfarin (Coumadin, Bristol-Myers Squibb) or low-molecular-weight heparin.

VTE occurred early (at four months or less) in 18.4% of patients receiving high-dose dexamethasone, in contrast to 6.3% of patients receiving the low dose (*P* < 0.001). The overall incidence of VTE was 22.4% with high-dose steroids and 6.8% with low-dose steroids.

Grade 4+ VTE occurred in 8% of patients in the high-dose dexamethasone group and in 3.2% of those in the low-dose group. Grade 3+ atrial fibrillation with flutter occurred significantly more often (*P* = 0.015) with the high dose.

Overall, early serious ADEs affected 54.3% of patients who received high-dose dexamethasone versus 39.6% of patients receiving the low dose (*P* = 0.002). Early mortality was almost 10 times greater with high-dose dexamethasone (in 4.9%), compared with the low-dose formulation (in 0.5%) (*P* = 0.006).

In conclusion, lenalidomide plus high-dose dexamethasone was associated with greater toxicity, including an increased number of thrombotic events.

Imatinib (Gleevec) and Dasatinib (Sprycel) in Chronic Myeloid Leukemia

**Presenter:** Neil Shah, MD, PhD, University of California, San Francisco, Comprehensive Cancer Center, San Francisco, California

The prognosis is poor for patients with chronic myeloid leukemia (CML) who are receiving imatinib (Gleevec, STI-571, Novartis) when their disease progresses to accelerated-phase or blast-phase CML. In the START-R trial of CML, which compared imatinib doses, increased to 800 mg, against switching to dasatinib (Sprycel, Bristol-Myers Squibb), progression-free survival was greater for those receiving the newer drug, dasatinib.

Data from the International Randomized Study of Interferon versus STI-571 (IRIS) trial showed that about 31% of chronic-phase CML patients discontinued imatinib therapy
within 4.5 years. About 50% of patients with chronic-phase CML stopped responding to treatment, or they progressed to accelerated-phase or blast-phase CML after 42 months. In addition, 15% of these patients who did not achieve a major cytogenetic response after 12 months of imatinib therapy had a significantly increased risk of disease progression. Although escalating the imatinib dose to 800 mg can be effective in patients with progressive disease, intolerance to the product and only brief periods of response are common.

In Dr. Shah’s international, open-label, phase 2 trial, 150 chronic-phase CML patients with disease resistant to imatinib at doses of 400 to 600 mg were randomly assigned to receive, in a 2:1 fashion, dasatinib 70 mg twice daily or imatinib 800 mg. The median average daily doses were dasatinib 103 mg and imatinib 796 mg.

A higher percentage of dasatinib-treated patients achieved and maintained a major cytogenetic response, compared with the imatinib-treated patients. At three months, 36% of the dasatinib group had a major cytogenetic response, which increased to 53% at 15 months. With the high dose of imatinib, 29% of the patients had a major cytogenetic response at three months, compared with 33% at 15 months.

Major molecular remission was reported in 16% of the dasatinib patients, in contrast to 4% of the high-dose imatinib group. The median duration of response with dasatinib was 13.7 months; with imatinib, it was 3.1 months.

Complete cytogenetic responses (CCRs) with dasatinib occurred most often in patients who had previously experienced a CCR with imatinib therapy. Whereas CML in 10 of 49 patients progressed in the imatinib group, disease in six of 101 patients progressed in the dasatinib group ($P < 0.0001$).

Although non-hematological side effects were similar between the patient groups, grade 3 and 4 cytopenias were more common in the dasatinib group. Neutropenia was reported in 59% of patients receiving dasatinib and in 39% of patients receiving imatinib; thrombocytopenia was reported in 55% of patients receiving dasatinib and in 39% of the patients had a major cytogenetic response at three months, compared with 33% at 15 months.

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Although non-hematological side effects were similar between the patient groups, grade 3 and 4 cytopenias were more common in the dasatinib group. Neutropenia was reported in 59% of patients receiving dasatinib and in 39% receiving imatinib; thrombocytopenia was reported in 55% of the dasatinib patients and in 14% of the imatinib patients. Grade 3–4 plural effusion and pulmonary edema were observed only in the patients receiving imatinib; thrombocytopenia was reported in 55% of patients receiving dasatinib and in 39% of patients receiving imatinib; grade 3 and 4 cytopenias were more common in the dasatinib group.

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

**Presenter:** Peter Hillmen, MD, Consulting Hematologist, Leeds General Infirmary, Leeds, United Kingdom

“Eculizumab is the first treatment that targets intravascular hemolysis, the primary clinical manifestation of PNH (paroxysmal nocturnal hemolysis),” stated Dr. Hillmen.

Eculizumab (Soliris, Alexion) is a monoclonal antibody with activity against complement protein C5, a protein that blocks terminal complement activation on red blood cells in PNH. PNH results from an acquired genetic mutation in hematopoietic stem cells that allows terminal complement-mediated cell lysis. Thromboembolism, the most feared complication, accounts for about 45% of PNH deaths. Although a causal link between hemolysis and thrombosis has not been established, thrombosis is temporally associated with increasing hemolysis.

In clinical trial experience with eculizumab to date (including about 250 years of treatment among 195 patients), the agent has reduced intravascular hemolysis significantly and has improved PNH symptoms.

In Dr. Hillmen’s analysis of all the eculizumab trials, the pretreatment rate of major adverse vascular events (MAVEs) per 100 patient-years was 7.37 over a total of 1,683 patient-years. These trials included a pilot study plus an extension trial. TRIUMPH was a single, pivotal double-blind, randomized, multicenter, placebo-controlled phase 3 efficacy study. SHEPHERD was an open-label nonrandomized, non–placebo-controlled, multicenter safety study.

For eculizumab-treated patients (three events in 281.03 patient-years), the MAVE rate was 1.07 ($P < 0.001$), an 85% reduction in thrombosis. In a further sensitivity analysis, the MAVE rate in the 12 months prior to treatment was 17.21, compared with 1.07 for eculizumab treatment (a 94% reduction; $P = 0.0002$). The pretreatment MAVE rate for patients receiving antithrombotic therapy was 14.00; the rate for these patients with eculizumab treatment was 0.62 ($P < 0.001$), a 96% reduction in thrombosis.

Similarly, the MAVE rate with eculizumab for patients with prior thrombosis compared favorably with pretreatment rates at 2.27, versus the pretreatment MAVE rate of 21.42 ($P < 0.001$), an 89% reduction. Intravascular hemolysis was reduced by 86%, and clinical thrombosis by an extremely highly significant ($P < 0.000000001$) 85%.

Although only three thrombotic events occurred in eculizumab-treated patients, two of them occurred early at the sites of prior thromboses. The author suggested that these events might have been pre-existing.

Dr. Hillmen characterized the eculizumab effect as “robust” and noted that with treatment continuing for more than four years, patients have remained well and transfusion-independent. He concluded that long-term treatment with this agent should have a beneficial impact on survival in patients with PNH.

Eculizumab was approved by the FDA on March 19, 2007.

**Zoledronic Acid (Zometa) and Pamidronate (Aredia) in Multiple Myeloma**

**Presenter:** James R. Berenson, MD, Medical and Scientific Director of the Institute for Myeloma and Bone Cancer Research, Los Angeles, California

Preclinical data suggest that zoledronic acid (Zometa, Novartis), a calcium modifier, has an anti-myeloma effect, but clinical evidence has been largely anecdotal.

Dr. Berenson conducted a retrospective analysis of a large international clinical trial comparing the effects of pamidronate 90 mg (Aredia) and zoledronic acid 4 mg on bone complications. The purpose of this exploratory subset analysis, however, was to investigate whether zoledronic acid produced a survival benefit, compared with pamidronate, among patients with MM. Zoledronic acid is 100 to 1,000 times as potent as pamidronate.

The patients were stratified according to their bone-specific complications. The purpose of this exploratory subset analysis, however, was to investigate whether zoledronic acid produced a survival benefit, compared with pamidronate, among patients with MM. Zoledronic acid is 100 to 1,000 times as potent as pamidronate.

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alkaline phosphatase (bone ALP) levels at the baseline evaluation. Bone ALP is a marker of osteoblast-mediated bone formation, and elevated levels of this marker in patients with malignant bone disease from solid tumors or myeloma correlate significantly with the risk of skeleton-related events and shorter survival, Dr. Berenson said.

The trial included 353 patients with MM. The analysis included the trial’s 212 MM patients who were assessed for bone ALP. They were classified as having “high” levels (146 IU/liter or greater) or low levels (below 146 IU/liter) of baseline bone ALP. The 25-month survival levels were higher for all bone ALP–assessed patients receiving zoledronic acid (76% vs. 63%, or a 43% reduction; \( P = 0.026 \)), but were similar for 123 patients with low bone ALP levels (73% for zoledronic acid, 71% for pamidronate).

Among 89 patients with high bone ALP levels, the survival rates were 82% with zoledronic acid and 53% with pamidronate, or a 57% reduction (\( P = 0.041 \)). Overall survival was significantly longer in patients with high baseline bone ALP levels (\( P = 0.04 \)).

Dr. Berenson listed several mechanisms of zoledronic acid’s anti-myeloma effects:

- immunostimulation of the effects on gamma-delta T cells
- inhibition of angiogenesis
- promotion of tumor cell apoptosis
- reduction of cytokines (e.g., interleukin-6)

Among adverse events, he said that the main concerns with bisphosphonates in MM patients were osteonecrosis of the jaw and impaired renal function. These need to be monitored, he advised.

“Zoledronic acid significantly improved survival compared with pamidronate in the subset of patients with multiple myeloma and high baseline BALP,” the author concluded. The benefit needs to be corroborated in a prospective study, he added.

Alemtuzumab (Campath) or Standard Treatment with Chlorambucil (Leukeran) for B-Cell Chronic Lymphocytic Leukemia

**Presenter:** Peter Hillmen, MD, Consulting Hematologist, Leeds General Infirmary, Leeds, United Kingdom

In another trial reported by Dr. Hillmen, both response rates and overall survival rates were superior in patients with B-cell chronic lymphocytic leukemia (B-CLL) who received alemtuzumab (Campath, Berlex) instead of the standard treatment, chlorambucil (Leukeran, GlaxoSmithKline).

In the phase 3, randomized, open-label CAM307 trial, 297 patients (mean age, 59.5 years) with progressive B-CLL in Rai stages I to IV were assigned to receive first-line alemtuzumab (30 mg IV three times per week for 12 weeks) or oral chlorambucil (40 mg/m² one time for 28 days for 12 cycles or less). The primary endpoint was progression-free survival.

Alemutuzumab was significantly favored in terms of overall response rates—83% for patients receiving alemtuzumab and 55% for those receiving chlorambucil—and in complete response (CR) rates—24% for those receiving alemtuzumab and 2% for those receiving chlorambucil (\( P < 0.0001 \)).

After a median follow-up period of approximately 25 months, progression-free survival favored the alemtuzumab group (hazard ratio, 0.58; \( P = 0.0001 \), as did the time to an alternative treatment (23.3 months for alemtuzumab and 14.7 months for chlorambucil; \( P = 0.0001 \)). The treatment-free interval was more than double in the alemtuzumab group.

Compared with 0% of patients in the chlorambucil arm, 26% of those in the alemtuzumab arm with CRs achieved minimal residual disease.

Most non-hematological ADEs were infuson-related for alemtuzumab, consisting of fever, chills, nausea, and urticaria. Nausea and vomiting were the most common ADEs associated with chlorambucil.

Grade 3 and 4 hematological toxicities were similar between the groups for anemia and thrombocytopenia, but neutropenia was more common in the alemtuzumab arm (46%) than in the chlorambucil group (28%) (\( P = 0.0002 \)). Infections, however—not including cytomegalovirus (CMV) events—occurred at a similar rate: in 46% of patients receiving alemtuzumab and in 50% of those receiving chlorambucil.

CMV positivity with symptoms was reported in 23 alemtuzumab patients (16%). All of these patients recovered without sequelae; 22 had received antiviral agents.

Of the 21 patients who experienced interruptions from therapy with the study drug, 17 resumed treatment after resolution of the infection, and they achieved overall response and CR rates comparable to those of the rest of the population.

“Alemtuzumab therapy was manageable and predictable with no treatment-related deaths,” Dr. Hillmen said.

He emphasized that alemtuzumab is currently given via subcutaneous injections, which are much better tolerated than the intravenous infusions that were used in the CAM307 trial.

He added, “This allows us to consider this treatment as a front-line therapy in poor-risk CLL and in consolidation after chemotherapy where it may have its principal role.”

**REFERENCES**