

American Society of Hematology

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The 54th American Society of Hematology (ASH) Annual Meeting and Exposition hosted almost 21,000 attendees (including exhibitors) from 108 countries. This article focuses on aspects of multiple myeloma treatment, along with research summaries on therapies for myelodysplastic syndromes and mantle-cell lymphoma.

Pomalidomide/Low-Dose Dexamethasone In Relapsed or Refractory Multiple Myeloma: Phase 3

- Meletios Dimopoulos, MD, Alexandra Hospital–University of Athens School of Medicine, Athens, Greece

Outside of clinical trials, currently there are no treatment options for multiple myeloma (MM) that has become refractory to both lenalidomide (Revlimid, Celgene) and bortezomib (Velcade, Millennium). At an ASH press briefing, Dr. Dimopoulos said:

“Today we expect median survival of the average myeloma patient to exceed 7 years. However, as more and more patients survive for extended periods of time, they eventually become resistant to the most effective commercially available agents today, such as bortezomib and lenalidomide.”

There is a need, he added, for new treatment options for this population, given that the expected overall survival in these patients is 8 months.

Celgene’s pomalidomide, an investigational oral immunomodulatory agent, has potent direct anti-melanoma activity, working by inhibiting stromal cell support and through immune modulation. In studies prior to this first phase 3 randomized trial, pomalidomide plus low-dose dexamethasone demonstrated clinical efficacy in disease refractory to lenalidomide and bortezomib.

In the current multicenter, randomized, open-label study, presented in a late-breaking clinical trial session, the following two regimens were compared with each other:

- pomalidomide (n = 302): 28-day cycles of 4 mg/day on days 1–21 plus low-dose dexamethasone (40 mg for patients 75 years of age or younger on days 1, 8, 15, and 22; 20 mg for those 75 years of age and older on days 1, 8, 15, and 22) *and*
- high-dose dexamethasone alone (n = 153): 40 mg for patients 75 years of age and younger on days 1–4, 9–12, 17–29; 20 mg for those 75 years of age and older on days 1–4, 9–12, and 17–29

Treatment was continued until disease progression or unacceptable toxicity.

All patients had to have MM that was refractory to prior

therapy, had to have received at least two prior therapies (i.e., consecutive cycles of lenalidomide and bortezomib, alone or in combination) and had received adequate prior alkylator therapy (i.e., a stem-cell transplant or six or more cycles, or progressive disease after two or more cycles).

Progression-free survival for the high-dose dexamethasone treatment was 8 months compared with 15.7 months for the pomalidomide/low-dose dexamethasone combination. Median overall survival for the high-dose dexamethasone monotherapy arm was 34 weeks. Median overall survival for the pomalidomide combination has yet to be reached.

Overall response rates were 16.6% for pomalidomide/low-dose dexamethasone and 3.9% for high-dose dexamethasone alone. At a median follow-up of 18 weeks, progression-free survival was significantly longer with pomalidomide/low-dose dexamethasone than with high-dose dexamethasone ($P < 0.001$). The difference in overall survival was also statistically significant in favor of the novel drug combination ($P < 0.001$). Included in these results were data from 45 patients who crossed over to the pomalidomide/low-dose dexamethasone treatment arm after experiencing disease progression with high-dose dexamethasone alone.

Patients receiving pomalidomide had higher rates of adverse events, experiencing more grade 3 and 4 neutropenia (42% with pomalidomide vs. 15% with high-dose dexamethasone) and febrile neutropenia (7% vs. 0%, respectively). Otherwise, the treatment was well tolerated, Dr. Dimopoulos said.

“Most of these patients were clearly refractory to both lenalidomide and bortezomib,” commented Dr. Dimopoulos, “and we believe, given these results, this may become the new standard of care for these hard-to-treat patients.”

Second-Line Lenalidomide Following Initial Relapse of Multiple Myeloma: MM-015, Phase 3

- Meletios Dimopoulos, MD, Alexandra Hospital–University of Athens School of Medicine, Athens, Greece

Earlier studies of lenalidomide (Revlimid) plus dexamethasone established this combination as standard of care in the treatment of relapsed or refractory multiple myeloma (MM), Dr. Dimopoulos, said, with the greatest benefits observed when lenalidomide/dexamethasone was administered at the first relapse.¹ MM-015, a pivotal, double-blind, randomized, placebo-controlled phase 3 trial, was conducted to compare the efficacy and safety of melphalan (Alkeran, GlaxoSmithKline)/prednisone/lenalidomide, followed by lenalidomide maintenance (MPR-R) (n = 152) with fixed-cycle melphalan/prednisone (MP) (n = 154) and melphalan/prednisone/lenalidomide (MPR) (n = 153).

Participants were elderly patients with newly diagnosed MM who were ineligible for autologous stem-cell transplantation (ASCT). A final analysis demonstrated unprecedented improvements in progression-free survival for MPR-R, compared with

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MP (31 vs. 13 months; $P < 0.001$) with manageable toxicity.²

Dr. Dimopoulos' objectives, in this *post hoc* analysis, were to assess the impact of first-line therapy on second-line outcomes and to assess the impact of second-line therapy on second-line outcomes. In the second-line treatment extension, patients with progressive disease ($n = 325$) could enroll in the open-label extension study to receive either lenalidomide 25 mg, with or without high-dose dexamethasone, or therapy selected by the physician.

The analysis showed that first-line lenalidomide did not have a negative impact on second-line lenalidomide use. In a follow-up evaluation at 53 months, time to disease progression was statistically equivalent regardless of the second-line regimen. When the results were broken down by second-line treatment options, regardless of the first-line treatment, second-line lenalidomide provided superior progression-free survival times compared with other second-line agents (i.e., bortezomib [Velcade]) ($P < 0.5$ for all):

- 18 months for lenalidomide vs. 12 months for bortezomib in the MP treatment arm
- 23 months for lenalidomide vs. 16 months for bortezomib in the MPR cohort
- 18 months vs. 14 months in the MPR-R treatment group

Neutropenia, thrombocytopenia, and fatigue were the most commonly reported adverse events, but all of these were manageable.

"It was reassuring to see that the toxicity was as expected," Dr. Dimopoulos said.

"The main finding," he concluded, "was that median time to disease progression is the same regardless of the primary treatment, indicating that prior treatment with lenalidomide is not inducing resistance in this disease."

Lenalidomide in Mantle-Cell Lymphoma Refractory to Bortezomib: EMERGE, Phase 2

- Andrew Goy, MD, The John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, New Jersey
- Session moderator, Joshua Brody, MD, Stanford University, Stanford, California

Relapsed/refractory mantle-cell lymphoma (MCL) is characterized by frequent chemoresistance and limited treatment options. In two phase 2 studies among patients with relapsed/refractory aggressive non-Hodgkin's lymphoma (including MCL), however, single-agent lenalidomide (Revlimid) had previously demonstrated activity and tolerability.

EMERGE, a global, multicenter, single-arm, open-label study, examined overall response rates and duration of response in 134 MCL patients who were treated with a median daily lenalidomide dose of 23.5 mg (range, 5.3–25.0 mg). The median duration of treatment was 95 days (range, 1–1,002 days).

All of the enrolled patients (mean age, 63 years, 81% male) had failed to respond to an anthracycline or mitoxantrone (Novantrone, Serono/OSI), cyclophosphamide (e.g., Cytosan, Bristol-Myers Squibb), rituximab (Rituxan, Genentech), and

bortezomib (Velcade). These patients either relapsed or experienced disease progression for 12 months or less from the last dose of bortezomib following a prior complete response (CR) or a partial response (PR), or they had MCL that was refractory with less than a partial response after two or more cycles of bortezomib.

High tumor burdens (i.e., at least one lesion 5 cm or larger or three lesions 3 cm or larger) were reported in 58% of subjects. Bulky disease was reported in 33%, and high-dose or dose-intensive therapy was reported in 33%.

Dose interruptions occurred in 60% of patients, with a 7-day median time to resumption of therapy (range, 1–59 days). Thirty-eight percent of patients required dose reductions, and 19% discontinued therapy because of adverse events. The most common causes of dose reductions and interruptions were neutropenia (any grade or grade 3 or 4) in 49% and 43% of patients and thrombocytopenia in 36% and 27%.

Dr. Goy reported that adverse events were manageable and consistent with those in other lenalidomide studies of non-Hodgkin's lymphoma. Among non-hematological adverse events, fatigue (any grade or grade 3 or 4) was experienced by 45% and 7% of patients, diarrhea by 31% and 6%, dyspnea by 18% and 6%, and pneumonia by 14% and 8%.

By central review, the overall response rate (ORR) was 28%, with CRs and unconfirmed CRs in 8% of patients and PRs in 20%. Stable disease was reported in 29%. Median time to response was 2 months. Duration of response was 16.6 months (range, 7.7–26.7 months) for the overall population and 16.6 months, as well, for the CR and unconfirmed CR groups.

Median progression-free survival was 4.0 months (range, 3.6–5.6 months), and median overall survival was 19.0 months (12.5–23.9 months).

Secondary primary malignancies were reported in 5% of patients at a rate of 2.21 per 100 person-years. This rate was similar, Dr. Goy said, to the rate in the general population. Eighteen patients (13%) died within 30 days of their last dose, and 10% of patients had progressive disease.

"Patients in other studies of new agents in MCL have had two or three prior lines of treatment," Dr. Brody noted. "Patients in [this study] have had four, yet they have a good response rate, very long duration of response, and reasonable failure-free survival."

Oral Azacitidine for Lower-Risk Myelodysplastic Syndromes: Phase 1

- Guillermo Garcia-Manero, MD, University of Texas, MD Anderson Cancer Center, Houston, Texas

Azacitidine (Vidaza, CC-486, Pharmion) is an analogue of cytidine with antineoplastic activity. It is incorporated into DNA, where by reversibly inhibiting DNA methyltransferase, it blocks DNA methylation. Administered via injection, it is known to prolong overall survival in myelodysplastic patients.

The goal of Dr. Garcia-Manero's investigation of oral azacitidine was to assess strategies with respect to maximizing treatment convenience for both doctor and patient, eliminating the potential of injection-site reactions and prolonging the therapeutic window for azacitidine. The phase 1 multicenter study

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enrolled patients with lower-risk myelodysplastic syndromes into one of two treatment arms: azacitidine 300 mg/day for 14 days (n = 26) or azacitidine 300 mg/day for 21 days (n = 27). Both treatments were administered in 28-day cycles. Half of the patients (average age, 71 years) were transfusion-dependent.

The analysis showed an overall response rate (ORR) of 36.9% for the two schedules. The rate of transfusion independence for these patients was well sustained, Dr. Garcia-Manero said, but differed according to the dosing schedule. ORRs were 42.3% for the 14-day regimen and 37.0% for the 21-day regimen. For sustained transfusion independence, 14 days was superior at the 56-day mark (53.5% vs. 40% for the 21-day regimen) but inferior at the 84-day mark (20% vs. 33.3% for the 21 days).

Fifteen percent of each cohort discontinued treatment because of adverse events, with 27% and 19% of patients, respectively, withdrawing because of treatment failure. The most common adverse events observed for oral azacitidine (with either schedule) were diarrhea, nausea, and infection (pneumonia). The most common hematological toxicities were neutropenia (in 18.5% of patients for the 21-day regimen vs. 7.7% for the 14-day regimen) and thrombocytopenia (in 3.7% of patients for the 21-day regimen vs. 11.5% for the 14-day regimen).

Noting that only one patient died during therapy, Dr. Garcia-Manero said, "This is a very safe intervention."

He concluded, "Oral azacitidine 300 mg once daily, administered in 14-day or 21-day cycles of 28 days, was active and well-tolerated in low-risk myelodysplastic syndrome."

Carfilzomib/Thalidomide/Dexamethasone For Newly Diagnosed Multiple Myeloma In Transplant Candidates

• Pieter Sonneveld, MD, Erasmus Medical Center, Rotterdam, Netherlands

For induction therapy prior to high-dose treatment in transplant-eligible multiple myeloma (MM) patients, bortezomib (Velcade)-based regimens are the first choice. In addition, the combination of bortezomib, thalidomide (Thalomid, Celgene), and dexamethasone (VTD) has been shown to achieve a high complete response (CR) rate after induction and after high-dose melphalan (Alkeran)/autologous stem-cell transplantation (ASCT). VTD is also an effective consolidation therapy for further improving CRs and reducing minimal residual disease. Toxicities (e.g., polyneuropathy) and costs have hampered the use of these regimens, Dr. Sonneveld said.

Carfilzomib (Krypolis, Onyx), an epoxy-ketone class proteasome inhibitor with proven activity in relapsed and refractory MM, has elicited more sustained proteasome inhibition than bortezomib's reversible inhibition and has exhibited greater target specificity than bortezomib. These properties enable carfilzomib to overcome resistance to bortezomib both *in vitro* and *in vivo* in preclinical studies. Dr. Sonneveld's study aimed to establish the feasibility of a carfilzomib/thalidomide/dexamethasone (CTD) combination. It also aimed to determine the combination's maximum tolerated dose, overall response rates (ORRs), CRs, and very good partial responses (PRs) after induction, after high-dose melphalan/ASCT, and after consolidation.

Among 50 evaluable patients (median age, 58 years), all received four cycles of CTD, followed by stem-cell harvest and intensification with high-dose melphalan and then consolidation with four cycles of CTD. Stem-cell harvest was successful in all eligible patients.

Premature discontinuation rates in the induction phase were 8%, 16%, and 10%, respectively, for carfilzomib, thalidomide, and dexamethasone. In the consolidation phase, these rates were 10%, 26% and 26%, respectively.

Grade 3 toxicities included peripheral neuropathy (2%), azotemia (4%), gastrointestinal disorders (6%), skin problems (12%), and cardiac events (6%). Dr. Sonneveld noted that no severe sensory neuropathy or dose-limiting toxicities were observed.

CR rates were high, Dr. Sonneveld said, at 44% overall and at 55% in high-risk patients. The high-risk patients were defined as having specific chromosome abnormalities, including t(4;14) and/or 17p deletions, 1q and/or ISS3 deletions, or both.

Very good or better PRs were observed in 90% of high-risk patients and in 84% overall. Rates for PRs or better were 95% in high-risk patients and 94% overall. Induction-phase response rates increased throughout the high-dose melphalan/ASCT and consolidation phases. Peripheral neuropathy was reported only at grades 1 and 2 and was related to thalidomide.

Calling the CTD combination "feasible, tolerable and effective," Dr. Sonneveld commented: "There is a need for affordable first-line treatments."

REFERENCES

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