ASH 2010 SUMMARY OF MULTIPLE MYELOMA PRESENTATIONS

Introduction

The 52nd annual meeting of the American Society of Hematology (ASH) was held December 4–7, 2010, in Orlando, FL. Multiple myeloma was the topic of many presentations at ASH, including:

- Education sessions on advances in the basic science of plasma cell disorders and on supportive care in plasma cell dyscrasias.
- An education session on high-risk hematologic diseases, including ultra high-risk myeloma
- A scientific session on therapeutic targeting of the myeloma stem cell.
- Over a dozen simultaneous oral sessions (comprising about 6 presentations each) specifically on myeloma, with many other sessions on transplantation, venous thromboembolism, stem cell collection, tumor cell biology, and other topics of interest.
- Three poster sessions featured hundreds of posters about myeloma and related conditions.

On December 3, the IMF and the Postgraduate Institute for Medicine sponsored a symposium for physicians featuring the most recent data from clinical trials. This overview focuses primarily on new drugs in development. For more detailed information on other topics, please visit the IMF website at www.myeloma.org.

New Drugs in Development

Clinical trials are making a key contribution to progress in drug development and increased survival of patients with myeloma. Relapsed/refractory disease is the testing ground for all new drugs, as there is a clear need to have something for patients after they have exhausted their available therapeutic options.

Even patients who benefit from novel agents eventually develop relapsed/refractory disease. Existing agents that have been used previously can be used again effectively in different combinations. There is ample evidence for the efficacy of bortezomib, bortezomib plus pegylated liposomal doxorubicin (PLD), or lenalidomide plus dexamethasone; other possibilities include bendamustine, bortezomib plus dexamethasone, lenalidomide, high-dose cyclophosphamide alone or with VAD, thalidomide alone or with dexamethasone, dexamethasone alone, DCEP, or DT-PACE.

Several newer agents and therapies are being investigated for myeloma, and they are showing great promise. Carfilzomib, pomalidomide, and elotuzumab are just three of the newer agents farthest along the myeloma drug development pipeline. New combinations currently in trials that seem promising include bortezomib and lenalidomide in combination with histone deacetylase (HDAC) inhibitors, monoclonal antibodies, and proteasome inhibitors. Interesting HDAC inhibitors include panobinostat, vorinostat, and romidepsin. Interesting agents that target the PI3K/Akt pathway include perifosine and mTOR.

Carfilzomib: a proteasome inhibitor

Initial results of the phase I/II Multiple Myeloma Research Consortium (MMRC) study of carfilzomib, lenalidomide (Revlimid®), and dexamethasone (CRd) in newly diagnosed myeloma showed preclinical synergy and promising activity and tolerability in relapsed/refractory disease. This phase I study tested the hypothesis that CRd might be more effective and better tolerated in newly diagnosed patients, and determined the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) for a phase II trial. Newly diagnosed patients who were or were not transplant candidates were enrolled. Initial treatment was carfilzomib on days 1, 2, 8, 9, 15, and 16, dexamethasone on days 1, 8, 15, and 22, and lenalidomide continuously on days 1 to 21 of a 28- day cycle. CRd was given for 4 cycles. If response was at least partial response (PR), stem cells (SC) were collected, and autologous stem cell transplant (ASCT) was deferred while 4 more cycles of CRd were given. CRd was given every other week as maintenance, eliminating the doses on days 8 and 9. The phase I dose levels of carfilzomib were increased from 20 to 27 mg/m^2. Lenalidomide was 25 mg per day. A third dose level was added to increase carfilzomib to 38 mg/m^2. There were 31 patients in phase I. There was one case of DLT on level 2 and two DLT on level 3. The MTD was not reached. Toxicities were mostly mild. Grade 3 to 4 neutropenia was infrequent, with no fevers or decline in neutrophils with treatment. There was no emergence of clinically significant peripheral neuropathy (PN). In the 27 evaluable patients, the best responses were stringent complete response (sCR)/CR/near (n)CR in 55%, sCR in 22%, PR or better in 96%. After 4 cycles 59% of patients had at least VGPR, 100% had PR. After 8 cycles, responses increased to 83% at least very good (VG) PR and 67% CR/nCR. SC harvest was successful in 14 eligible patients of whom 1 continued to ASCT. At a median follow-up of 6 months, all patients are alive and there is no progressive disease (PD). Most patients are continuing maintenance with no dose reduction. The response rates (RR) seem to compare favorably with current best regimens. Phase I will be completed soon and the phase II portion will be initiated. A recently initiated phase III trial will assess CRd vs. Rd in relapsed myeloma.

Carfilzomib was well tolerated in the 257 evaluable pretreated patients enrolled in PX-171-003-A1 phase II study of relapsed and refractory myeloma. All study patients had PD after their last therapy with at least two prior lines of therapy, including bortezomib (100%) and thalidomide or lenalidomide (most patients). The registration cohort dose was 27 mg/m^2. The phase I dose was 20 mg/m^2. The median time from diagnosis was 5.4 years; 77% of patients had pre-existing PN; there was a median of 5 prior lines of therapy (range 1 to 20). Responses included an overall response rate (ORR) of 24%, at least VGPR 5.5% (0.4 % CR), PR 18.7%, and minimal response (MR) 10%. Responses were seen in higher risk subsets and not affected by prior lines of therapy, percent plasma cells in the bone marrow, or cytogenetics. Baseline PN didn't predict for response and didn't affect the ability to stay on therapy with carfilzomib. The number of prior

CONTINUES ON PAGE 8

ASH 2010 SUMMARY— continued from previous page

lines containing bortezomib did not affect response significantly. The median progression-free survival (PFS) was 3.7 months. The first monitoring of outcome occurred at 15 days and the second was before cycle 2, so if PD occurred at 15 days patients didn't get the next higher dose. Median overall survival (OS) was 15.5 months. This is a conservative analysis of OS. Patients could complete all 12 cycles and go on to the extension trial. Median OS was not reached in responders. Treatment emergent adverse events (AE) in the 266-patient safety population included few grade 3 to 4 hematologic toxicities. Neutropenia occurred in 10% of patients. Non-hematologic toxicities included 12% any grade PN and 0.8% grade 3 and 4 PN. Most discontinuations were due to PD and none to emerging PN. The 95 deaths on study were mostly due to PD; 16% of patients completed all 12 cycles. Duration of response (DOR) was 8.3 months and was identical in PR and MR populations with a median OS of 15.5 months. The clinical benefit (at least MR) was 34%. Carfilzomib was well tolerated in this heavily pretreated patient population.

Pomalidomide: an immunomodulatory drug (IMiD)

Pomalidomide, a newer IMiD, is structurally similar to thalidomide and lenalidomide but functionally different. Two sequential phase II trials looked at pomalidomide at 2 mg or 4 mg daily on days 1 to 28, plus dexamethasone 40 mg days 1, 8, 15, 22. Full-dose aspirin was suggested but physicians could use low-molecular-weight heparin (LMWH) or warfarin. If patients on the 2-mg dose of pomalidomide had PD, the dose could be escalated to 4 mg. Patients with relapsed myeloma resistant or refractory to both lenalidomide and bortezomib were enrolled, with 35 patients at each pomalidomide dose. Both groups had a median of 6 prior regimens. Median follow-up is 9.1 months for the 2-mg dose and 5.5 months for the 4-mg dose. Most patients experienced hematologic toxicity. There was a higher rate of neutropenia in the 4 mg group, but no dose response. Non-hematologic toxicities included fatigue and PN in most patients in this heavily pretreated population, which had 70% PN at study entry. Pomalidomide-related PN was 20% in the 2-mg group and 29% in the 4-mg group. In the 2-mg group there were 2 instances of deep vein thrombosis (DVT) and 1 myocardial infarction (MI); in the 4 mg group there were one DVT and one MI. PR or better occurred in 26% of each group and 49% vs. 40% had MR or better. Median time to response (TTR) was 1 vs. 1.7 months; DOR was 12 months for the 2-mg group and not reached for the 4-mg group. Survival at 6 months for 2 mg was 78%, and 69% for 4 mg. Median survival was not reached. Therefore, pomalidomide plus dexamethasone has significant activity in a heavily pretreated population that has lenalidomide- and bortezomib-refractory myeloma. Investigators conclude that this combination regimen has significant activity in patients with lenalidomide- and bortezomib-refractory myeloma, and are cautiously optimistic about its efficacy in heavily pretreated high-risk patients. There is an ongoing study testing the 4-mg dose for 21 days of treatment in a 28-day cycle for efficacy. However, there may be no reason to go over a dose of 2 mg.

A dose-escalation study of pomalidomide alone or in combination with low-dose dexamethasone in pretreated patients with relapsed/refractory myeloma reported results of phase I and preliminary results of phase II. The study was intended to determine the best dose of pomalidomide and if dexamethasone increased its activity. Patients had relapsed myeloma refractory to lenalidomide and bortezomib; many had also received pomalidomide. In phase I, the MTD of pomalidomide was determined to be when given 21 of 28 days with and without low-dose dexamethasone. For 38 patients participating in phase I, doses were 2 mg, 3 mg, 4 mg, 5 mg. If PD or no response occurred after 4 cycles, there was an option to add low-dose dexamethasone at 40 mg per week. Patients discontinued due to PD, with a low rate of discontinuation due to AE. Myelosuppression was the dominant AE, with low incidences of venous thromboembolism (VTE) and PN. MTD was 4 mg. There may be a dose-related response. PR or greater was 27% for the 4 mg dose. The phase I OS was a median 79.6 weeks, and responses seem clinically durable. Phase II Arm A is testing pomalidomide 4 mg plus low-dose dexamethasone vs. Arm B testing pomalidomide 4 mg alone. Enrollment of 221 patients was completed, and data analysis was done on the first 120 efficacy-evaluable patients enrolled. The best response of at least PR, combining both arms of the trials, by EBMT (European Group for Blood and Marrow Transplantation) criteria was 25% and 28% by IMWG (International Myeloma Working Group) criteria. Toxicities were manageable, with the most common AE being grade 3 to 4 myelosuppression. There were very low incidences of grade 3 to 4 PN and DVT. The final analysis of phase II, including gene expression profiling (GEP) and surrogates, is pending.

Relapsed/refractory disease is the testing ground for all new drugs, as there is a clear need to have something for patients after they have exhausted their available therapeutic options.

A randomized phase II study examined two modalities of pomalidomide plus low-dose dexamethasone in patients whose disease was refractory to at least 2 cycles of lenalidomide and bortezomib, and who had a creatinine clearance (CrCl) of 50 mL/min. All patients had myeloma that was refractory either while on therapy or within 60 days of therapy. Arm A received 4 mg pomalidomide and low-dose dexamethasone for 21 days of 28-day cycle; Arm B got 28 days of continuous 4 mg pomalidomide plus low-dose dexamethasone. After 6 patients per arm were assessed for tolerance, 17 patients per arm were enrolled. After the data-monitoring committee assessed efficacy, more patients were enrolled. All patients were assessed for response, safety, TTR, and DOR. Patients were treated until progression. Final enrollment was 43 patients on Arm A and 41 patients on Arm B. Median age was 53 to 54 years; most received aspirin, most of the rest received LMWH. ORR was 42% for Arm A vs. 39% for Arm B. TTR was 2 months vs. 1.7 months for Arms A and B respectively. Most responses were PR (33% vs. 34%); almost half of patients had stable disease (SD). The median follow-up time was 6.5 vs. 7 months. TTP was similar in both arms, with 88% vs. 85% of patients surviving at 6 months. TTP according to the presence of del 17p or t(4;14) were similar between arms. About a

ASH 2010 SUMMARY— continued from previous page

quarter of the AE were hematologic, with 66% vs. 77% grade 3 or more. The most common hematologic AE was neutropenia. Erythropoietin, growth factors, and transfusion were allowed. There was some PN, and no DVT. Dose reduction for pomalidomide was required for 49% vs. 41%. About half of patients required dexamethasone reduction. Pomalidomide at 4 mg per day was well tolerated. Because this is a phase II trial, the study arms cannot be compared.

Elotuzumab: a monoclonal antibody (mAb)

Elotuzumab (HuLuc63) is a humanized monoclonal antibody (mAb) targeting CS1, a cell surface glycoprotein expressed on myeloma cells, with restricted expressed on natural killer (NK) cells. It has shown activity in a mouse model, enhanced in combination with lenalidomide. Phase I results of 5, 10, and 20 mg/kg dosing were presented. Elotuzumab-related AEs were primarily infusion-related in 89% patients, mostly grade 1 to 2, with no DLT, and MTD was not reached. Median TTP was not reached at a median follow-up of 12.7 months. Elotuzumab saturated the CS1 binding sites in bone marrow myeloma cells at 10 mg/kg. The phase II study objectives were to evaluate the ORR of elotuzumab plus lenalidomide and dexamethasone in patients with relapsed/ refractory myeloma after 1 to 3 prior therapies, and to evaluate doses of 10 and 20 mg/kg. Dosing was weekly for the first 4 cycles, then every other week. Lenalidomide was given at 25 mg and low-dose dexamethasone was administered weekly. Patients also received Solu-Medrol (methylprednisolone) and other drugs to prevent infusion reactions. Patients had received no prior lenalidomide. The safety population of 63 patients received 10 mg/kg or 20 mg/kg doses. Most patients had had a prior transplant, and most had received prior thalidomide. ORR was 90% with the 10-mg/kg dose. The best confirmed response of at least PR occurred in 90% of patients on the 10-mg/kg dose and in 72% of patients on the 20-mg/kg dose. The study was not powered to determine the differences between doses; both doses had a sCR/CR rate of 5%. VGPR occurred in 37% of patients overall, and was 42% for the 10-mg/kg dose. Patients with higher beta-2-microglobulin (β2M) responded. Median time to best response was 2 months for both arms. Median follow-up was 4.9 months, and median PFS was not reached. The AE profile was mostly as expected with lenalidomide and dexamethasone. Higher grade hematologic AE were as expected and were manageable. Elotuzumab-related AE included fatigue and low-grade fever and were manageable. There was no treatment-related mortality. Infusion reactions occurred in 89% in the phase I portion of this trial, but with proper management were cut in half in phase II (typical of mAbs). The 10-mg/kg dose is recommended for the open-label phase III trial to start next year.

Other mAbs in development

DR (death receptor) anti-TRAILR (tumor necrosis factor-alpha-related apoptosis-inducing ligand receptor) mAbs kill myeloma cells. One study analyzed two mAbs: mapatumumab, which is anti-TRAIL-R1 (DR4), and lexatumumab, which is anti-TRAIL-R2 (DR5). Regulation of DR4 and DR5 are different. Mapatumumab kills p53 mutant cell lines. Death induced by mapatumumab depends only on the extrinsic pathway of apoptosis, involving caspase. In contrast, lexatumumab kills p53 wild-type myeloma cell lines, which express more DR5 than mutant lines. Melphalan increases DR5 in wild-type p53 lines. In p53-mutant lines melphalan does not increase DR5 or p53. Melphalan doesn't affect DR4 expression; it increases lexatumumab killing of wild-type p53 lines, and does not increase mapatumumab killing of either wild-type or mutant cell lines. p53 activation increases only DR5 expression and sensitivity. Mapatumumab could be of interest in combination with melphalan for patients with wild-type p53 and lexatumumab could be of interest for patients with p53 mutations. These agents are in clinical trials but no results are available at this time.

Other new targeted therapies in early development

mTOR (Mammalian Target of Rapamycin): Final results were presented from the phase I/II trial of weekly bortezomib in combination with temsirolimus (CCI-779) in relapsed or relapsed/refractory myeloma in patients refractory to bortezomib. The PI3K (phosphoinositol 3 kinase) pathway is important in enhancing cell survival by stimulating cell proliferation and inhibiting apoptosis. mTOR inhibitors may overcome resistance to bortezomib because they are synergistic with bortezomib *in vitro* and in co-culture. All of the 63 patients (20 in phase I and 43 in phase II) had at least one prior therapy and were heavily pretreated with dexamethasone; most had received thalidomide, bortezomib, and lenalidomide. There was a high percentage had ISS stage III disease. IV temsirolimus was given at 15 to 25 mg weekly on days 1, 8, 15, 22, and 29 on 35 day cycles. Bortezomib at 1.3 to 1.6 mg/m^2 was given weekly on days 1, 8, 15, and 22. Dexamethasone was not permitted. Phase I was a dose-escalation study; the most common toxicity was thrombocytopenia. In phase II, toxicities included thrombocytopenia and fatigue; there was no sensory neuropathy due to temsirolimus or weekly bortezomib. ORR in phase II was 40% excluding unevaluable patients. In patients with bortezomib-resistant disease the ORR was 20%; with bortezomib-sensitive disease the ORR was 53%. Median PFS for phase II was 5 months. Median TTP was 5.7 months. The combination is active and warrants further evaluation.

Several newer agents and therapies are being investigated for myeloma, and they are showing great promise.

Dual-targeting of –TORC1 and –TORC2: *In vivo* antitumor activity of TORC1 (which contains raptor) and TORC2 (which contains rictor) inhibition, including phosphorylated proteins in the activation pathway, was analyzed. TORC1 and TORC2 both are activated by growth factors, cytokines, and PI3K/Akt. TORC1, but not TORC2, is inhibited by rapamycin and its analogues. Deptor is an mTOR-interacting protein expressed by myeloma cell lines. Downstream targets of TORC1 include Erk, and of TORC2 include pAkt and Akt. TORC2 is activated in myeloma. INK128 is a novel, orally available small molecule that inhibits TORC1 and TORC2. INK128 inhibits the proliferation of myeloma cells and plasma cells but not normal lymphocytes or granulocytes. Inhibition of TORC1 and TORC2 induces apoptosis and overcomes the bone marrow microenvironment

CONTINUES ON PAGE 10