

ASH 2009 Highlights for Patients with Myeloma

*Summaries of Multiple Myeloma Presentations
from the 51st Annual Meeting
of the American Society for Hematology (ASH)
held in New Orleans, Louisiana,
December 5–8, 2009*



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Introduction

The 51st Annual Society of Hematology (ASH) Annual Meeting was held December 5th through the 8th, 2009, in New Orleans, LA. On December 4, the International Myeloma Foundation (IMF) and the Postgraduate Institute for Medicine sponsored a symposium that provided participants with an overview of the most recent results from clinical trials along with expert commentary, analysis, interpretation of findings, and a discussion of how this might affect treatment of myeloma. Dr. Brian G.M. Durie introduced the presenters and topics at the symposium.

Multiple myeloma was the topic of many presentations at ASH, including the following:

- The PETHEMA/GEM clinical trial of bortezomib/melphalan/prednisone (VMP) vs. bortezomib/thalidomide/prednisone (VTP) followed by maintenance therapy with bortezomib/thalidomide (VT) vs. bortezomib/prednisone (VP) in elderly untreated patients, was presented by Maria-Victoria Mateos, Barcelona, Spain. This was one of the six talks selected for the plenary session by the ASH program committee as the most groundbreaking abstracts submitted to the meeting.
- At the ASH/ASCO Joint Symposium, Sundar Jagannath, St. Vincent's Comprehensive Cancer Center, New York, presented the final results of PX-171-003-A0, part 1 of an open-label, single-arm, phase II study of carfilzomib (CFZ) in patients with relapsed and refractory multiple myeloma. This joint symposium is a review of what the ASH meeting organizers feel represents some of the best science from the 2009 American Society of Clinical Oncology (ASCO) 2009 Annual Meeting, which was held in June.
- An education session was held on how to treat young patients, old patients, and patients with relapsed/refractory myeloma.
- A scientific session, "Scientific Linking of Unusual Manifestations of Myeloma," was held.
- At least 15 simultaneous oral sessions (about 6 presentations each) were held specifically on myeloma, with many other sessions presenting related information on

transplantation, venous thromboembolism (blood clots), stem cell collection, tumor cell biology, and other topics of interest.

- Three poster sessions featured hundreds of posters about myeloma and related topics, for example, new drugs in development.

This report summarizes information presented at the 2009 ASH Annual Meeting, organized by topics rather than by sessions, presenting an overview of information on new drugs in development, clinical trial results, treatment by patient characteristics such as eligibility for transplant or stage of disease, disease risk and stage, and a brief summary of some presentations that might be of interest to patients with myeloma and their families and caregivers.

New Drugs in Development

Relapsed Refractory Myeloma: The Role of New Drugs, was presented by A. Keith Stewart, MD, Mayo Clinic, Scottsdale, Arizona, who chaired the Multiple Myeloma Education Session. This topic was discussed in depth in a paper published in *Hematology* 2009, which is available through the American Society of *Hematology*. Dr. Stewart reviewed clinical trial results and the status of the newest therapies being developed. He pointed out that it is important to tailor treatment to individual patients at the time their disease relapses, taking into consideration the tempo of disease, previous side effects and responses, and how long the previous remission lasted. Practical issues should also be considered, and include access to drugs as determined by country or insurance, where patients live relative to where they receive treatment, and patient preference. Of the hundreds of drugs being tested in the laboratory and in animals (preclinical testing), only a few make it to clinical trials in patients, and are then licensed and available for use in treatment. Some drugs that have shown little or no activity as single agents in small trials might still be active when combined with other drugs. There may be subsets of myelomas that could respond to any given therapy. Advances in determining what genes in the myeloma are more or less active could provide information on the subtypes of myeloma that would respond to current therapies and those in development, as well as guide development of more specific therapies. Promising agents still in trials that Dr. Stewart

mentioned include bendamustine, pomalidomide, carfilzomib, perifosine, vorinostat, tanespimycin, and NPI-0052, all of which are discussed below.

Proteasome Inhibitors

Carfilzomib (PX-171)

Encouraging results for the second-generation proteasome inhibitor, carfilzomib, were reported in several talks and at least half a dozen posters. The final results of the phase 2 study in relapsed and refractory myeloma that were reported at the ASH/ASCO Joint Symposium by Dr. Jagannath are summarized below, followed by a list summarizing the results of other studies and trials of carfilzomib that were reported at ASH. It is anticipated that pivotal trials supporting a new drug application (NDA) for this promising agent will be completed by the end of 2010. A randomized international multicenter phase 3 study will begin enrollment of 700 patients in early 2010 to compare carfilzomib plus lenalidomide and low-dose dexamethasone (CRd) with lenalidomide plus low-dose dexamethasone (Rd).

Final Results of PX-171-003-A0, Part 1 of an Open-Label, Single-Arm, Phase II Study of Carfilzomib (CFZ) in Patients (pts) with Relapsed and Refractory Multiple Myeloma (MM) was presented by Sundar Jagannath, St. Vincent's Comprehensive Cancer Center, New York, NY. Dr. Jagannath reviewed carfilzomib and preclinical data showing that this proteasome inhibitor was active against bortezomib- (Velcade-) resistant solid tumor cells. In the first part of the PX-171-003-A0 trial in patients with relapsed, refractory myeloma who had received prior therapy including bortezomib and immunomodulatory drugs (IMiDs; thalidomide and/or lenalidomide), 26% of the 46 patients had a clinical benefit response (CBR), which included complete response (CR) plus partial response (PR) plus minimal response (MR). Dr. Jagannath concluded that single-agent carfilzomib is active in heavily treated patients including those with bortezomib-refractory myeloma. The A0 part 1 portion of this trial was expanded to PX-171-003-A1, a pivotal dose-escalation trial, increasing the dose of carfilzomib after the first cycle from 20 to 27 mg/m². This trial enrolled 269 patients as of October, 2009, and a safety review was available for 141 patients who received treatment for at least 6 months. Side effects have been minimal, with lower rates of serious side effects than were seen in the A0 portion of the trial. The rates of peripheral neuropathy (nerve damage) and acute kidney failure have also been low. Across all trials of carfilzomib to date, in which 357 patients have received the drug, the overall rate of serious neuropathy has been less than 2%. Dr. Jagannath concluded that carfilzomib

was well tolerated across all phase 2 trials. Carfilzomib will be tested in a phase 3, randomized, international trial in combination with lenalidomide later in 2010.

Some additional carfilzomib trials and conclusions (additional details are provided in the ASH 2009 Summary for Physicians):

- Updated Results of Bortezomib-Naïve Patients in PX-171-004, An Ongoing Open-Label, Phase II Study of Single-Agent Carfilzomib (CFZ) in Patients with Relapsed or Refractory Myeloma (MM), resented by Luhua Wang, MD Anderson Cancer Center, Houston, Texas (Abstract 302).. Phase 2 (004 trial) in 115 patients. Single agent carfilzomib shows significant activity in relapsed refractory myeloma. Side effects are generally mild and manageable. Trial is ongoing.
- PX-171-004, An Ongoing Open-Label, Phase II Study of Single-Agent Carfilzomib (CFZ) in Patients with Relapsed or Refractory Myeloma (MM); Updated Results From the Bortezomib-Treated Cohort, presented by David Siegel, Hackensack University Medical Center, Hackensack, New Jersey (Abstract 303). Phase 2 trial in 35 patients. Single-agent carfilzomib is tolerable, with durable response and disease control, lacks significant side effects, suggesting it is good for combination therapy.
- Phase Ib Multicenter Dose-Escalation Study of Carfilzomib Plus Lenalidomide and Low-Dose Dexamethasone (CRd) in Relapsed and Refractory Multiple Myeloma (MM), presented by Ruben Niesvizky, Weill Cornell Medical College, New York, New York. (Abstract 304). Phase Ib (006 trial) in 32 patients in combination with lenalidomide and dexamethasone. Combination is well tolerated in patients heavily pretreated with bortezomib and IMiDs. Maximum tolerated dose (MTD) was not reached, no dose limiting toxicities (DLTs, meaning side effects severe enough to require a dose reduction). Prolonged administration is possible for >16 months. More patients are being enrolled.
- Carfilzomib (CFZ), a Novel Proteasome Inhibitor for Relapsed or Refractory Multiple Myeloma, Is Associated with Minimal Peripheral Neuropathic Effects, presented by Ravi Vij, Washington University School of Medicine, St. Louis, Missouri (Abstract 430). Phase 2 trials (combined analysis of 003 and 004 trials) in 135 patients. No trend for worsening of neuropathy, 36% patients received more than 6 cycles of carfilzomib; peripheral neuropathy (PN) not a significant side effect of carfilzomib.

NPI-0052

Phase 1 Clinical Trial of the Novel-Structure Proteasome Inhibitor NPI-0052 in Patients with Relapsed and Relapsed/Refractory Multiple Myeloma (MM) (Abstract 431) was presented by Paul Richardson, Dana-Farber Cancer Institute, Boston, Massachusetts. NPI-0052 is a novel second-generation proteasome inhibitor that is not based on a protein structure and is different from bortezomib and carfilzomib. It exhibits fast, marked, prolonged inhibition of all activities of the proteasome, with side effects that are different than those reported for bortezomib. There are two formulations of NPI-0052, an old liquid formulation and a new lyophile formulation to which studies are being transitioned. NPI-0052-101 is a phase 1 study in patients with relapsed and relapsed/refractory myeloma for which no other approved treatment is available. To date 32 patients are enrolled. The study started at low doses of the liquid formulation and increased to higher doses of both the liquid and the lyophile formulation. NPI-0052 is well tolerated, with few serious side effects, mostly at highest dose, that are manageable with supportive measures. Fatigue, significant neuropathy, and decreased blood cell counts were not seen. Some side effects associated with the liquid formulation (the carrier, not the active drug) were not seen with the lyophile formulation. More trials are planned. Dr. Richardson thinks the future of NPI-0052 is in combination therapy.

Histone Deacetylase (HDAC) Inhibitors

Vorinostat (SAHA, suberoylanilide hydroxamic acid)

Combined Vorinostat, Lenalidomide and Dexamethasone Therapy in Patients with Relapsed or Refractory Multiple Myeloma: A Phase I Study (Abstract 305), was presented by David Siegel, Hackensack University Medical Center Hackensack, New Jersey. This study was based on the observation that in preclinical trials combining vorinostat with IMiDs increased their anti-myeloma activity. The primary objective was to determine MTD, which was not met. Secondary objectives included safety and response. Vorinostat was administered one week on, one week off in 28-day cycles, in combination with lenalidomide administered for 21 days of the cycle, and dexamethasone administered once a week. In 31 patients with heavily pretreated lenalidomide-refractory myeloma, there was one DLT of diarrhea at the highest dose in the dose-finding trial, and no further DLTs when more patients were treated; an expansion cohort was treated at a higher dose. Most patients in the expansion cohort experienced side effects, commonly

diarrhea and fatigue, and also decreased numbers of blood cells. Serious side effects included alterations in the electrical activity of the heart associated with vorinostat. There was possible activity in patients who had received prior lenalidomide. Because the MTD was not reached, enrollment in phase 2 will continue.

Vorinostat in Combination with Pegylated Liposomal Doxorubicin and Bortezomib for Patients with Relapsed/Refractory Multiple Myeloma: Results of a Phase I Study (Abstract 306) was presented by Peter M. Voorhees, Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina. Although single-agent vorinostat is tolerable, treatment resulted in no responses. There are good reasons to combine vorinostat with other agents, because in preclinical studies there was increased activity when vorinostat was combined with bortezomib and anthracyclines (drugs like doxorubicin). In this study, bortezomib was combined with standard pegylated, liposomal doxorubicin (PLD), a combination approved for patients with myeloma, plus increasing doses of vorinostat. There are not many patients currently enrolling at the highest dose levels. Side effects are common, and the doses may need to be adjusted for side effects affecting blood cells. Side effects include PN, hand-foot syndrome (a known side effect of PLD), an allergic-like reaction to PLD, and heart problems in two patients. The response rate for the small group (8 patients) in this trial was encouraging, but patients were chosen in such a way that they may have had less severe disease. Alternate dosing schedules for the next levels are being explored.

Vorinostat in combination with bortezomib in relapsed or refractory myeloma was also the subject of two posters, **Abstract 3886** by Sundar Jagannath, St. Vincent's Comprehensive Cancer Center, New York, and **Abstract 3890**, by David Siegel, Hackensack University Medical Center, Hackensack, New Jersey. In one study, MTD was not reached and doses were recommended for future study. The combination of oral vorinostat and bortezomib was described as showing promising activity with acceptable side effects. The second study, a phase 2b open-label trial (Vantage 095) is ongoing, and to date shows acceptable tolerability of the combination. Responses will be evaluated in 2010.

Panobinostat (LBH589)

Oral panobinostat (LBH589) has been tested in a phase 1b study in combination with bortezomib in relapsed myeloma (**Abstract 3852**, Jesús F. San-Miguel, Hospital Universitario de Salamanca, Salamanca, Spain). The study of increasing doses is ongoing, and the dosing schedule may need to be changed to allow better management of thrombocytopenia

(a decreased number of platelets, or "thrombocytes," the particles in the blood that allow it to clot).

Low-dose panobinostat has also been tested in a phase 1/2 dose-escalation study in combination with oral melphalan in relapsed/refractory myeloma (**Abstract 1855**, James Berenson, Oncotherapeutics, Los Angeles, California). The most common serious side effects were decreases in platelets and white blood cells that were reversible. Once the MTD has been determined and the dose and schedule optimized, an expanded phase 2 trial will be conducted.

Heat Shock Protein 90 (Hsp90) Disrupter

Heat shock protein 90 (Hsp90) protects cells against various stresses. Inhibiting Hsp90 may contribute to the destruction of some of the proteins that enhance the growth and survival of myeloma cells.

Tanespimycin (17-AAG)

Tanespimycin (17-AAG) disrupts heat shock protein 90 (Hsp90), and is being studied in several settings. Ashraf Z. Badros, University of Maryland Medical Center, Baltimore, Maryland, presented the poster, Tanespimycin + Bortezomib in Relapsed/Refractory Myeloma Patients: Results From the Time-2 Study (**Abstract 1871**). Paul G. Richardson, Dana-Farber Cancer Institute, Boston, Massachusetts, presented the poster Tanespimycin + Bortezomib Demonstrates Safety, Activity, and Effective Target Inhibition in Relapsed/Refractory Myeloma Patients: Updated Results of a Phase 1/2 Study (**Abstract 2890**). These studies reported similar findings, concluding that sufficient tolerability and activity were seen to support a phase 3 study of the combination of tanespimycin plus bortezomib. The studies in patients suggested that tanespimycin protects from bortezomib-mediated peripheral neuropathy (PN). An animal study, Tanespimycin Prevents Bortezomib Toxicity and Preserves Neuronal Morphology in Primary Rat Dorsal Root Ganglion Cultures (**Abstract 2847**) presented as a poster by Oliver P. Flint, Research and Development, Discovery Toxicology, Bristol-Myers Squibb, Princeton, New Jersey, showed that protection from bortezomib neuropathy by tanespimycin depended on the dose.

Monoclonal Antibodies (mAbs)

A monoclonal antibody is an immune protein that is clonal, that is, derived from one type of anti-body-producing immune cell, and has the ability to bind specifically to one target. As you know, the M-protein produced by myeloma cells is a type of monoclonal antibody. Therapeutic

monoclonal antibodies are produced to react to a particular protein, for example, one that is produced on the surface of myeloma cells but not on the surface of most normal cells. Elotuzumab, discussed below, was the most promising monoclonal antibody reported on at the meeting.

Elotuzumab (HuLuc63, anti-CS1 mAb)

Phase 1/2 Study of Elotuzumab in Combination with Lenalidomide and Low-Dose Dexamethasone in Relapsed or Refractory Multiple Myeloma: Interim Results (Abstract 432) was presented by Sagar Lonial, Winship Cancer Institute, Emory University, Atlanta, Georgia. Elotuzumab is a human monoclonal antibody (mAb) of the IgG1 type targeting CS1, a cell surface glycoprotein. CS1 is highly and uniformly expressed on myeloma cells, with restricted expression on natural killer (NK) cells, and little to no expression on other normal tissues. The anti-tumor activity of elotuzumab was enhanced by lenalidomide in a mouse model of myeloma. This report is an early look at results of a phase 1/2 clinical trial in 28 patients. Side effects were expected for lenalidomide plus dexamethasone, and there were some reactions as expected for monoclonal antibody therapy, including allergic shock and infusion reactions. The dose determined to be effective in animals is achievable in patients with biweekly dosing. The results look promising, and further studies are planned to determine the best dose, and whether after weekly dosing during initial treatment with the higher dose, treatment could subsequently be given every other week.

A poster, **Phase 1/2 Study of Elotuzumab in Combination with Bortezomib in Patients with Multiple Myeloma Following 1 to 3 Prior Therapies: Interim Results (Abstract 3876)** was presented by Andrzej Jakubowiak, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan. This was a dose-escalation study of elotuzumab plus standard bortezomib. The interim data from 26 patients showed manageable side effects, with two serious adverse events (SAEs, or serious side effects) in one patient but no DLTs, and MTD was not reached. Enrollment is ongoing.

Immunomodulatory Drugs (IMiDs)

Pomalidomide

A Phase 1/2 Multi-Center, Randomized, Open Label Dose Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of Pomalidomide Alone or in Combination with Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide and Bortezomib (Abstract 301)

was presented by Paul Richardson, Dana-Farber Cancer Institute, Boston, Massachusetts. Pomalidomide is a novel, third-generation IMiD, structurally similar to thalidomide and lenalidomide, showing increased activity in preclinical studies and different clinical efficacy and safety profiles. In this study, pomalidomide was administered alone and with low-dose dexamethasone in patients with relapsed/refractory myeloma and prior therapy with at least 2 cycles of lenalidomide and bortezomib. Phase 1 determined the MTD; phase 2 was a randomized study of pomalidomide with and without low-dose dexamethasone, with a white blood cell growth factor (G-CSF) administered after the first cycle. The most common side effect was decreased blood cell counts, including white blood cell counts; patients also experienced fatigue. Serious blood clots occurred in two patients and significant PN occurred in one patient. Nearly half of patients received dexamethasone, which improved the response in about half of the patients. Phase 2 is ongoing, with completion anticipated in the last quarter of 2010 for 200 patients, and will include an analysis of the altered expression of genes that may affect treatment and response.

Pomalidomide (CC4047) Plus Low-Dose Dexamethasone (Pom/dex) Is Active and Well Tolerated in Lenalidomide-Refractory Multiple Myeloma (MM) (Abstract 429) was presented by Martha Q. Lacy, Mayo Clinic, Rochester, Minnesota. Results for 60 patients on this trial have been presented. An additional 34 patients have been enrolled to further determine response rate and toxicity. More patients in this study had high-risk disease than in the general patient population. Patients received pomalidomide plus dexamethasone. The combination was generally well tolerated. The major side effects included decreased white blood cell counts and PN. Dr. Lacy concluded that pomalidomide plus dexamethasone had significant activity in heavily pre-treated myeloma refractory to lenalidomide with manageable toxicity. The overall response rate and duration of response appear similar to those obtained with novel therapy combinations, such as those containing thalidomide, lenalidomide, or bortezomib, but pomalidomide combinations need further investigation.

Other New Drugs

Perifosine, an oral drug that modulates signal transduction, is in a phase 1/2 trial in combination with bortezomib in patients with relapsed/refractory myeloma previously treated with bortezomib (**Abstract 1869**, Paul Richardson, Dana-Farber Cancer Institute, Boston, Massachusetts). The combination showed activity (ORR 41%), durable responses, a median OS of 25 months, and good tolerability. These results form the basis of a phase 3 trial that is expected to

begin soon comparing perifosine, bortezomib, and dexamethasone to bortezomib plus dexamethasone

There are other new drugs that are in early stages of development as single agents or in combination therapy. Several drugs are also being developed to target and kill myeloma cells specifically, leaving other cells untouched. These are based on combining a molecule such as a mAb or binding agent that attaches to a component on the surface of myeloma cells (but not other cells) with an agent capable of killing the myeloma cell.

Newly Diagnosed Myeloma

Transplant-Eligible Patients

Several important issues for transplant-eligible patients continue to be investigated, including whether there is a difference in early or delayed transplantation in the era of novel agents; if patients can be considered to be cured; what the best combination of drugs is; and how many drugs a combination should include.

How to Treat a Young Patient, focusing on the role, advantages, and disadvantages of some of the many proposed therapeutic approaches for the newly diagnosed, younger patient with myeloma (younger than age 65 to 70 years), was discussed by Jesús F. San Miguel, Hospital Clinico Universitario de Salamanca, Salamanca, Spain, at the Multiple Myeloma Education Session. Dr. San Miguel addressed this topic in depth in a paper published in *Hematology* 2009, which is available from ASH. This paper summarizes all relevant studies to date. Therefore, only the main points are summarized here. For a young patient with high-risk disease, novel drugs, especially bortezomib, seem to overcome the risk, but the number of patients studied is limited and follow-up is short. It is premature to base specific therapy on the chromosome pattern (cytogenetics) of a patient's myeloma. Large clinical trials need to enroll both standard-risk and high-risk patients and collect information. Experimental pilot studies are a potential option for those with high-risk cytogenetics, for example, targeted therapy for t(4;14), FGFR kinase inhibition, or combinations of therapies where each drug kills myeloma cells in a different way. Outside of clinical trials, one option is induction (initial therapy) with a novel agent (bortezomib, lenalidomide, or thalidomide) or a drug combination, followed by autologous stem cell transplant (ASCT; patients receive their own blood cells) with high-dose melphalan (MEL). Then, if the myeloma is in complete remission (CR), maintenance therapy with lenalidomide can be given, and if the disease is not in CR, consolidation with a novel agent combination

can be given. An alternative option is to postpone transplant and treat with novel combination therapy, although because there is always a significant increase in CR rate after ASCT, induction with novel therapies and ASCT are complementary. The efficacy of conditioning regimens, with MEL 200 as the standard, could be improved with the addition of busulfan or bortezomib.

Young patients at the beginning of therapy are more fit and may tolerate intensive treatment and SCT better. This is associated with a long survival period free of myeloma-related problems, and good quality of life (QoL). If disease relapses after MEL 200, it will still respond to novel agents but it isn't known what will happen after relapse following treatment with novel agents. Dr. San Miguel pointed out that early vs. delayed transplant is still being investigated, and the joint randomized IFM/DFCI clinical trial may provide an answer. Dr. San Miguel believes that allogeneic transplants for patients with myeloma (where patients receive cells from a donor, not their own cells) should be considered an investigational treatment and preferably be performed as part of a clinical trial. Although allogeneic transplants have the potential to cure myeloma, they are associated with high treatment-related death rate, and availability of suitable donor cells is limited. His group's policy is not to use allogeneic transplant for initial therapy, but to consider it at relapse for high-risk patients, including those with early relapses after ASCT, provided their myeloma is under control at the time of the allogeneic transplant. The role of maintenance in CR, duration of maintenance, and outcome after relapse need to be investigated further, as does which novel therapies can overcome which particular high-risk factors. Dr. San Miguel observed that progress in the last decade has only been possible because of the participation of patients and doctors in clinical trials. There are now a large number of drugs being developed, such as the HDAC inhibitors, that are looking for a place in treatment.

Updates in therapeutic approaches for transplantation-eligible patients was presented by Philippe Moreau, University Hospital Hôtel-Dieu, Nantes, France, as part of the IMF Symposium. He (and the audience) believes that ASCT remains the standard of care for eligible patients. The preferred induction regimen prior to ASCT is currently bortezomib plus dexamethasone, but a bortezomib plus dexamethasone plus an IMiD combination may soon replace it, because this combination triggers two different cell-killing pathways in malignant plasma cells. The audience agreed with Dr. Moreau that achievement of CR or very good partial response (VGPR) prior to ASCT should be the primary goal of induction therapy. Although a majority of the

audience believed that consolidation is needed after ASCT, Dr. Moreau pointed out that there are no reliable results showing the need for consolidation, which is the subject of investigation. There are results that show the importance of maintenance therapy, something much of the audience was aware of. The benefit of thalidomide maintenance has been shown; more information is needed to support the use of lenalidomide, and studies are ongoing to answer that question. A topic addressed in Dr. Moreau's presentation was one that was discussed in other presentations at this meeting, namely whether combination therapies incorporating novel agents without ASCT are superior to ASCT. Most of the audience thought novel combinations were not more effective than ASCT, and Dr. Moreau pointed out that there is no information. The joint IFM/DFCI 2009 clinical study in newly diagnosed patients who are SCT candidates will answer this question. Patients will be randomly assigned to one of two groups. One group will receive lenalidomide plus bortezomib plus dexamethasone (RVD) induction, stem cell (SC) mobilization and collection, MEL 200 and ASCT, then RVD consolidation, followed by lenalidomide maintenance therapy. The other group will receive RVD induction, SC mobilization and collection, then RVD consolidation, and lenalidomide maintenance therapy, with the option of SCT at relapse.

A discussion among the panelists raised several unresolved issues, including the necessity of conducting a phase 3 trial if early-phase trial results are striking, the effect on trial enrollment when drugs are available in some countries but not others, which combinations should be considered a standard of care for patients with standard-risk disease, the true efficacy and risks of the novel agents, particularly for long-term maintenance, and how best to manage newly diagnosed patients, for example, should all or most patients be enrolled into clinical trials or should patients have more choices? There appeared to be a consensus that VGPR and CR after ASCT resulted in similar survival curves, but partial response (PR) after ASCT warranted a second ASCT, and with no further improvement, more therapy. It was pointed out that the percentage of eligible patients who receive transplants varies by country, and the eligible age cutoff varies as well.

Timing of Transplant

Novel Agents for Initial Therapy of Multiple Myeloma: Comparable Results with Continued Initial Therapy and Delayed Transplantation at Relapse Versus Early Transplantation (Abstract 956) was presented by Shaji Kumar, Mayo Clinic, Rochester, Minnesota. This study looked back at results for approximately 290 transplant-eligible,

newly diagnosed patients treated with an IMiD at the Mayo Clinic from 2001 to 2008 to see if there was a difference in response or survival between those who received early vs. delayed SCT. There did not appear to be a difference in response rates, time to disease progression following SCT, or overall survival. Because the study looked back at information already collected, it was not possible to determine what influenced the decision to transplant early or late. Someone in the audience commented that patients whose disease was likely to have a better outcome could have been selected for later transplantation. There were no quality of life measurements (QoL), and no information on the time to next therapy. Dr. Kumar noted that a lot of patients received IMiD-based therapy until the time of relapse, and that it would be important to collect information about the decision-making process, specific therapy before and after SCT, and QoL in a new trial going forward.

Cure Rate with Total Therapy (TT)

Modeling for Cure with Total Therapy (TT) Trials for Newly Diagnosed Multiple Myeloma (MM): Let the Math Speak (Abstract 744) was presented by Bart Barlogie, University of Arkansas for Medical Sciences, Little Rock, Arkansas. Dr. Barlogie reviewed the results of the Total Therapy (TT) 1, 2, and 3 trials in the context of modeling for cure in these trials. The model takes into account event-free survival (EFS), including reversion to a state resembling MGUS (monoclonal gammopathy of undetermined significance) and duration of complete response, to predict cure fractions. The model takes survival curves (known as Kaplan-Meier plots) and looks for the presence of a plateau, that is, the time from treatment when the group of surviving patients who received a particular treatment continue to survive, with no or few additional deaths in the group. Relative survival ratios were calculated by comparing the actual survival of patients with expected survival of a comparable group of people in the general population. The amount of time it takes for the relative survival ratios to be equal are 17 years for TT1, 10 years for TT2, and 5 years for TT3. Dr. Barlogie concluded that, particularly with more recent treatment regimens, cure is a realistic goal of myeloma therapy. The high cure fraction value in TT3 (55%) for patients with low-risk myeloma is evidence that inclusion of both bortezomib and thalidomide increases efficacy of TT3. However, more effective therapy is still needed to improve outcomes for patients with high-risk disease, which still has a relatively low average survival. Dr. Barlogie suggested that improvements in looking at the genes expressed in myelomas might allow researchers to identify curable and currently incurable myeloma. Trials that will incorporate this type

of information include the joint Dana-Farber/IFM clinical trial and the Arkansas trials, TT4 for low-risk myeloma and TT5 for high-risk myeloma, where treatment assignment is based on gene expression information. Dr. Shaughnessy commented that genes over-expressed in patient tumors showing the cure fraction appear mostly on chromosome 5, which agrees with Dr. Avet-Loiseau's information that patients with increases in chromosome 5 have the best outcome. Notably, the glucocorticoid receptor (the molecule to which dexamethasone and prednisone can bind on the surface of myeloma cells) occurs on chromosome 5, which would explain the efficacy of dexamethasone therapy.

Three-Drug Combinations

A Phase II Trial Comparison of Once- Versus Twice-Weekly Bortezomib in CyBorD Chemotherapy for Newly Diagnosed Myeloma: Identical High Response Rates and Less Toxicity (Abstract 616) was presented by Craig B. Reeder, MD, Mayo Clinic, Scottsdale, Arizona. This was a phase 2 single-arm trial investigating the role of novel agents plus an alkylating agent that can cause damage to the DNA of myeloma cells. The three-drug combination CyBorD (cyclophosphamide, bortezomib, dexamethasone) was previously shown to be safe and well tolerated in patients with relapsed refractory myeloma. The goal of this study was a high-depth, fast response prior to SCT. Some results have been published showing rapid response and ability to collect stem cells. However, dose reductions were needed for all drugs due to side effects. A new group received a modified CyBorD regimen, with weekly bortezomib and cyclophosphamide, and reduced doses of dexamethasone after the first 4 weeks. This resulted in reduced side effects, although moderate PN was still a problem. The modified regimen resulted in less toxicity, so there were fewer dose reductions and higher overall doses could be given; it was more convenient, and it allowed for successful stem cell harvest. Dr. Reeder said that this regimen doesn't protect patients with high-risk myeloma from relapse, and that although the initial response was good for both regimens, high-risk patients need either a different conditioning regimen or maintenance therapy.

Velcade, Intravenous Cyclophosphamide and Dexamethasone (VCD) Induction for Previously Untreated Multiple Myeloma (German DSMM XIa Trial) (Abstract 131) was presented by Hermann Einsele, University of Würzburg, Würzburg, Germany. The aim of this study was to improve CR rates before and after transplant by using novel agents as part of the induction regimen on the assumption that improving CR + VGPR rates could result in further

improved long-term outcomes. There were 395 evaluable patients, and a quarter of them had serious side effects. Dr. Einsele concluded that 3 cycles of bortezomib, cyclophosphamide, dexamethasone (VCD) for induction therapy is among one of most active regimens, and overcomes traditionally poor-risk cytogenetics for response, although data are not yet available for progression-free survival or overall survival. This regimen has a good safety profile, with a treatment-related mortality of less than 1%. With an acceptable rate of mild to moderate polyneuropathy and low risk of blood clots, use of VCD is feasible in an outpatient setting. Final results will be available at the 2010 ASH Meeting. This study is forming the basis for a larger intergroup study. In response to a question, Dr. Einsele explained that in Germany patients are only eligible for high-dose therapy and ASCT up to age 60 years. For patients age 60 to 70 years there is a different high-dose melphalan 140 (instead of 200 mg of melphalan per square meter of body mass) SCT protocol, so it is difficult to compare across trials. One reason for using this intravenous treatment regimen was to ensure that newly diagnosed patients are seen weekly and receive treatment for infections and other supportive care if necessary.

Three- and Four-Drug Combinations

Novel Three- and Four-Drug Combinations of Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide, for Newly Diagnosed Multiple Myeloma: Encouraging Results From the Multi-Center, Randomized, Phase 2 EVOLUTION Study (Abstract 127) was presented by Shaji Kumar, Mayo Clinic, Rochester, Minnesota. Because three-drug combinations of bortezomib with dexamethasone, cyclophosphamide, or lenalidomide have shown significant activity in untreated myeloma, this study looked at all 4 drug classes together. The results of the phase 1 portion have already been presented elsewhere. The safety and efficacy of the phase 2 portion, which was intended to increase the complete response rate and determine the best phase 3 trial design, were reported at this meeting. Four treatment arms were compared: VDCR (bortezomib, dexamethasone, cyclophosphamide, lenalidomide); VDR (bortezomib, dexamethasone, lenalidomide); VDC (bortezomib, dexamethasone, cyclophosphamide); and VDC modified to include an extra dose of cyclophosphamide on day 15 because the response seen with VDC seemed lower than expected from published results. The best response rates are similar in the VDCR and VDR arms. About a third of patients in each arm have had stem cells harvested, with 2 or 3 failures to collect in the VDCR and VDR arms. This did not occur in the VDC arms. Nearly all of the 138 patients have had had at least one side effect, with

more serious reduced white blood cell counts in patients receiving cyclophosphamide. During the discussion, Dr. Kumar pointed out that more follow-up was needed to determine if the 4-drug combination would result in longer progression-free survival, and if it was better to use bortezomib plus an IMiD together or sequentially. He said that if the use of the 4 drugs resulted in a deep response and changed the natural history of the disease to get to the lowest minimum residual disease, then it might be possible to use all 4 drugs again later at relapse.

Bortezomib, Melphalan, Prednisone and Thalidomide (VMPT) Followed by Maintenance with Bortezomib and Thalidomide for Initial Treatment of Elderly Multiple Myeloma Patients (Abstract 128) was presented by Antonio Palumbo, University of Turin, Turin, Italy. The aim of this study was to compare the best experimental treatment to the standard of care for the newly diagnosed, elderly myeloma patient population. In Dr. Palumbo's opinion, the best 4-drug combination is VMPT (bortezomib, melphalan, prednisone, thalidomide), and the standard of care is the 3-drug combination VMP (bortezomib, melphalan, prednisone) for this population. VMPT was followed by VT maintenance. Bortezomib was initially given twice weekly, then reduced to once weekly, which reduced the rate and severity of PN. Responses, time to next therapy, and progression-free survival were significantly longer for patients receiving VMPT vs. VMP, but there were no differences in overall survival. Serious side effects were as expected, and increased by the inclusion of thalidomide. Dr. Palumbo concluded that VT maintenance improves progression-free survival, and longer follow-up is needed to assess overall survival.

Thalidomide / Dexamethasone (TD) Vs. Bortezomib (Velcade) /Thalidomide / Dexamethasone (VTD) Vs. VBMCP/VBAD/Velcade® as Induction Regimens Prior to Autologous Stem Cell Transplantation (ASCT) in Multiple Myeloma (MM): Results of a Phase III PETH-EMA/GEM Trial (Abstract 130) was presented by Laura Rosiñol, Barcelona, Spain. There were 306 patients in this study randomized to one of 3 arms: VBMCP/VBAD, TD, or VTD. Patients receiving VTD had the highest response rates. Patients with higher-risk disease based on cytogenetics had better responses to bortezomib-containing regimens. Side effects were similar, but TD was associated with a higher rate of blood clots, and VTD was associated with a higher rate of PN. The CR rates increased after ASCT. Patients receiving TD had significantly shorter times to progression and progression-free survival. There is no difference among treatments for overall survival at the current time.

Bortezomib in Combination with Pegylated Liposomal Doxorubicin and Thalidomide (VDT), An Effective Steroid-Independent Regimen for Previously Untreated Multiple Myeloma Patients: Final Result of a Phase II Study (Abstract 618) was presented by Taimur Sher, Roswell Park Cancer Center, Buffalo, New York. In this study in 40 patients, the steroid-free regimen of bortezomib (every other week schedule) plus PLD plus thalidomide resulted in good response rates and time to progression. There were significant side effects, including hand-foot syndrome, infections, neuropathy, and some blood clots. Dr. Sher concluded that this regimen would be an acceptable alternative for patients who can't tolerate steroids.

Transplant-Ineligible Patients

Dr. Maria-Victoria Mateos's presentation during the Plenary Session was introduced by Dr. Donna Weber, MD Anderson Cancer Center, Houston, Texas, who reviewed randomized trials in elderly patients who are not transplant candidates. Dr. Weber noted that there are more questions than answers as the number of possible combinations of novel and conventional chemotherapy agents increases. Although there have been improvements in response rates and progression-free survival, these don't necessarily translate into improved overall survival. Questions remain about the role of consolidation therapy for elderly patients who may go on to SCT. The study presented by Dr. Mateos is the first time a combination including a novel agent has been used as the comparator arm for another novel agent-containing regimen. A review of trials of maintenance therapy after ASCT has shown various results from negative effects to no effect to improved results. Novel agents for induction therapy in cytogenetic high-risk myeloma, for example, the inclusion of bortezomib in TT2, may lead to improved survival, but the use of novel agents such as lenalidomide in maintenance therapy needs further study.

Plenary Session

A Prospective, Multicenter, Randomized, Trial of Bortezomib/Melphalan/Prednisone (VMP) Versus Bortezomib/Thalidomide/Prednisone (VTP) as Induction Therapy Followed by Maintenance Treatment with Bortezomib/Thalidomide (VT) Versus Bortezomib/Prednisone (VP) in Elderly Untreated Patients with Multiple Myeloma Older Than 65 Years (Abstract 3) was presented by Maria-Victoria Mateos, University of Salamanca, Salamanca, Spain, during the Plenary Session. This study randomly assigned 260 patients to VMP vs. VTP as induction therapy followed by maintenance with VT vs. VP for up to three years. Therefore, there are 4 treatment groups, VMP

followed by VT, VMP followed by VP, VTP followed by VT, and VTP followed by VP. Study goals included determining the best agents to add to bortezomib therapy, decreasing side effects by reducing doses of bortezomib, and adding maintenance therapy to maintain efficacy. There was no difference in the overall response rate for VMP vs. VTP. The side effects were generally higher in the VMP group, but serious side effects, including PN, and discontinuations were higher in the VTP group. The rate of confirmed complete response increased after maintenance therapy. There is no difference in progression-free survival with VMP vs. VTP. Dr. Mateos concluded that alkylating agents (in this case, melphalan) should remain important drugs for the treatment of elderly untreated patients. The weekly schedule of bortezomib significantly reduced PN. Maintenance therapy increased the CR rate with low side effects. VT maintenance showed superior time to events, but lenalidomide should be explored as maintenance therapy. Currently, the combination of VMP followed by VT is significantly superior to VTP followed by VP in this patient population. Notably, high-risk cytogenetics are overcome by either regimen.

How to Treat an Elderly Patient: Combination Therapy or Sequencing was presented by Antonio Palumbo, MD, University of Torino, Torino, Italy, as part of the Multiple Myeloma Education Session. This topic is presented in depth in a paper, co-authored by Dr. Palumbo and Francesca Gay, published in *Hematology* 2009, which is available through ASH. This paper reviews diagnosis and treatment of myeloma in general, and historically for elderly patients, summarizes current treatment options, including the efficacy of regimens used for front-line treatment of this patient population, the role of maintenance therapy, and management of AEs. Dr. Palumbo believes that MPT should be considered a major standard of care in elderly patients. Both thalidomide and lenalidomide treatment should include a drug to prevent blood clots, and previous clots, infection, lack of mobility, conventional chemotherapy, or doxorubicin add to the risk of clots. The best agent to prevent deep vein thrombosis (DVT), a type of life-threatening blood clot, remains a question; however, low molecular weight heparin (LMWH), which has been tested against aspirin and warfarin, may be best for patients at highest risk for clots, and aspirin, which can protect the heart, may be best for standard-risk patients. VMP is also a current standard of care, with PN as a major side effect. Reduction of bortezomib from twice weekly to once weekly may reduce both the risk of neuropathy and the discontinuation rate. MPR also has the potential to become a standard of care. Dr. Palumbo currently suggests MPT (if reduced blood cell counts are a concern) or MPR (if neuropathy is a concern) for older patients

at standard risk and VMP (if clots and/or kidney failure are concerns) for high-risk younger patients.

Future options include moving to combination therapy with 4 drugs, e.g., VMPT, to increase response, and adding maintenance, e.g., with bortezomib, thalidomide, or lenalidomide plus low-dose dexamethasone, to improve the duration of remission. Alternative options include using single agents in a sequential “friendly” approach, with 1 or 2 drugs up front, and a different drug at relapse. Dr. Palumbo recommends adjusting therapy to the patient, with full-dose therapy for those age 65 to 75 years if they have normal heart, lung, liver, and kidney function. If they are younger than age 65 years they can probably tolerate full-dose therapy even if some organ functions are abnormal. Reduced-dose chemotherapy is recommended for those with normal organ function if they are older than age 75 years. Melphalan especially requires adjustment for patient age and side effects affecting blood cell counts, but so do lenalidomide, thalidomide, and bortezomib. As an example, bortezomib may be reduced from twice to once a week to reduce nerve damage.

Practical recommendations for myeloma patients ineligible for transplantation was presented by Mario Boccardo, University of Torino, Torino, Italy, as part of the IMF Symposium. He reviewed published results of phase 3 trials in the non-transplant eligible, newly diagnosed population. Results show equivalence of TD and MP, superiority of MPT and MPV over MP. Trials of MRP vs. MP and VMPT vs. VMP presented at this ASH meeting are described elsewhere in this summary. Cyclophosphamide plus TD, and lenalidomide plus reduced-dose dexamethasone are also being tested. Dr. Boccardo discussed the increasing incidence of frail patients in the population of age 75 to 101 years at diagnosis, which he believes is the result of an increase in the older population rather than an increase in the incidence of myeloma. This frail population is at risk of early discontinuation from treatment as a result of toxicity, so regimens must be modified by dose reductions. Dr. Boccardo presented a scheme for dose reductions for patients over age 75 years that could be further modified if necessary for frail elderly patients to keep them on therapy longer. It was pointed out that although in some settings, thalidomide maintenance after SCT is well established, it is not used in France. Dr. Orlowski observed that it is difficult to compare the non-transplant population in the US to that in Europe because the US population is older and therefore probably has a higher rate of other diseases in addition to myeloma.

Phase 3b UPFRONT Study: Interim Results From a Community Practice-Based Prospective Randomized Trial Evaluating Three Bortezomib-Based Regimens in Elderly, Newly Diagnosed Multiple Myeloma Patients (Abstract 129) was presented by Ruben Niesvizky, Cornell/New York Presbyterian Hospital, New York. This study is ongoing and still recruiting patients. In this open-label, community-based trial, patients were randomly assigned to one of three bortezomib-based regimens: VTD (bortezomib, thalidomide, dexamethasone), VD (bortezomib, dexamethasone), or VMP (bortezomib, melphalan, prednisone), followed by maintenance with bortezomib. Patients receiving VTD also were given either aspirin, full-dose warfarin, or LMWH to prevent clots unless there was a reason not to. Patients also received treatment to prevent shingles (herpes zoster). Results for patients who had received 4 cycles were presented. The highest rate of PN occurred in patients receiving VTD, while side effects affecting blood counts were highest in the VMP arm. There were more deaths and pneumonia in patients receiving VD. In general side effects were similar, and responses were good, but more follow-up is needed. In a QoL assessment, improvement was seen for all treatments, but patients receiving VTD reported worse physical and role functions, that is, more interference with activities, including their usual daily activities. The Independent Data Monitoring Committee concluded that the study should continue with enrollment for all three treatments.

A Phase III Study to Determine the Efficacy and Safety of Lenalidomide in Combination with Melphalan and Prednisone (MPR) in Elderly Patients with Newly Diagnosed Multiple Myeloma (Abstract 613) was presented by Antonio Palumbo, University of Torino, Torino, Italy. In this study, patients age 65 to 75 years were randomly assigned to one of 3 treatment arms: MPR-R (melphalan, prednisone, lenalidomide followed by continuous lenalidomide maintenance), MPR, or MP. All patients could receive lenalidomide plus or minus dexamethasone if their disease progressed. The patient population had a higher than usual percentage of patients with more advanced myeloma. At a short follow-up time, the data monitoring committee recommended revealing which patients received which therapy because there was a significant difference between the MPR and MP groups. MPR combinations had a better overall response rate and shorter time to response than MP alone. Side effects were as expected, and nearly half of patients receiving MPR-R needed a blood cell growth factor. Dr. Palumbo concluded that continuous lenalidomide (MPR-R) was superior to treatments of more limited duration because it led to higher and more rapid responses and a 50% reduced risk of progression. In response to a question, he said that there

are no survival data to determine whether bortezomib plus MP (MPV) or MPR or MPT would be the better combination in this patient population. He thought an IMiD plus MP might be more suitable for frail patients or those at standard risk, whereas the bortezomib MP combination could be recommended for more fit patients or those with aggressive disease.

Melphalan and Prednisone (MP) Versus Melphalan, Prednisone and Thalidomide (MPT) as Initial Therapy for Previously Untreated Elderly and/or Transplant-Ineligible Patients with Multiple Myeloma: A Meta-Analysis of Randomized Controlled Trials (Abstract 615) was presented by Prashant Kapoor, Mayo Clinic, Rochester, Minnesota. This study was a review of previously published results. The authors did not have access to original patient information, but are now reviewing that information. They found that the addition of thalidomide to MP improved response rates and progression-free survival, and also increased side effects, but did not support the use of MPT over MP for improved overall survival. However, Dr. Kapoor thinks that once their analysis is updated with results from the HOVON study, it will show significant increased overall survival for MPT vs. MP, but at the cost of additional side effects. He pointed out that other effective regimens in elderly patients include MPR and VMP, which need to be analyzed in comparison with MP, and concluded that MPT can be considered an appropriate front-line regimen in newly diagnosed, transplant-ineligible elderly patients. The role of maintenance therapy has not been analyzed.

Relapsed/Refractory Myeloma

New approaches for patients with relapsed or refractory disease was presented by Robert Z. Orlowski, MD Anderson Cancer Center, Houston, Texas, as part of the IMF Symposium. He observed that despite therapeutic improvements for both transplant-eligible and non-eligible patients, most patients will eventually have relapsed disease. He reviewed the 2009 National Comprehensive Cancer Network (NCCN) guidelines by the quality of evidence for available treatments, as well as what is currently known about active combinations and single agents, and mentioned many of the studies of new agents being reported at this ASH meeting. He pointed out that although monoclonal antibodies (mAbs) have made a big difference in the treatment of lymphomas and leukemias, they have not played a major role in the treatment of myeloma. He speculated that CNTO 328, an anti-interleukin-6 (IL-6) mAb, particularly in combination with bortezomib, may prove useful in the treatment of myeloma, but the results of a current randomized study will

not be available until later in 2010. He presented the case of a patient whose disease relapsed repeatedly. He pointed out that if a therapy worked once, it could be repeated or “tweaked” and could continue to provide benefit as long as the patient had the relapse while off that therapy, had at least a year of benefit, and tolerated the therapy. Otherwise, a regimen containing a class of agent the patient had not previously received would be a better choice. Dr. Orlowski stated that in the relapsed/refractory setting, lenalidomide plus dexamethasone or bortezomib plus PLD are standards of care. Carfilzomib and pomalidomide as single agents and new combinations are showing promise, including combinations of bortezomib with HDAC inhibitors and other new classes of agents. He concluded that patients with relapsed/refractory myeloma are now doing better than at any other time in the past.

Diagnosis, Risk Stratification, and Staging

The evolving role of diagnostic testing and response criteria was presented by Dr. S. Vincent Rajkumar, MD, Mayo Clinic, Rochester, MN, as part of the IMF Symposium. He presented a case study of a man diagnosed with MGUS as a result of routine blood tests. Two years later, this patient developed lytic bone lesions and was then diagnosed with advanced stage multiple myeloma. Dr. Rajkumar reviewed diagnostic tests, including serum protein electrophoresis (SPEP), which can show the presence of an M-spike in the immunoglobulin (Ig) region; immunofixation electrophoresis (IFE), which is used to identify the type of antibody forming the M-spike; and the free light chain (FLC) assay, which can detect unbound Ig light chains. IFE is the test of choice to detect residual monoclonal Ig. He recommended SPEP and a 24-hour urine PEP (UPEP) for screening along with serum IFE and FLC. He prefers using both the Durie-Salmon and ISS staging systems because the Durie-Salmon system measures disease burden. Once a patient is diagnosed, the ISS can be used. Criteria in the mSMART (Mayo Clinic) classification of high- vs. standard-risk active myeloma need to be re-examined in the age of the novel and even newer therapies. Both PET (positron emission tomography) and MRI (magnetic resonance imaging) are useful for imaging. Reading the discussion of imaging in the International Myeloma Working Group (IMWG) paper in *Leukemia* (which is available through the IMF at http://myeloma.org/pdfs/IMWG_consensus_imaging.pdf) was recommended.

Dr. Rajkumar reviewed the definitions of MGUS, SMM (smoldering MM or asymptomatic MM—AMM), and MM. In both MGUS and SMM there is neither anemia nor bone lesions,

and calcium and kidney function are normal. MGUS and SMM are distinguished by the amount of M-protein and percentage of plasma cells (PC), and should not be treated. MM is distinguished by the presence of anemia (low red blood cell counts or reduced hemoglobin, the oxygen-carrying protein in the blood), bone lesions, high calcium, and/or abnormal kidney function related to the PC and M-spike. The diagnosis of MM should be based on clinical factors (signs and symptoms), not just laboratory test results. The risk of MGUS progressing to MM over time is related to M-spike size and type and FLC. SMM is more likely to progress to MM than MGUS over time. Progression of MGUS to MM may require the presence of two cancer-inducing events (“hits”), similar to what has been seen for the development of other types of cancers. The first hit resulting in the development of MGUS is associated with primary cytogenetic abnormalities such as IgH translocation (exchange of pieces between two different chromosomes involving an immunoglobulin or antibody region) and hyperdiploidy (too many copies of chromosomes) The second hit resulting in progression of MGUS to multiple myeloma includes mutations (genetic changes) in cancer genes (the oncogenes ras and myc), secondary translocations, increased formation of blood vessels (angiogenesis), and other abnormalities. Currently there is no way to prevent this progression.

MGUS and SMM

High-Risk SMM

Open-Label, Phase III Trial of Lenalidomide-Dexamethasone (Len/dex) Vs Therapeutic Abstention in Smoldering Multiple Myeloma at High Risk of Progression to Symptomatic MM: Results of the First Interim Analysis (Abstract 614), was presented by Maria-Victoria Mateos, University of Salamanca, Salamanca, Spain. This was an interim analysis of a PETHEMA/GEM trial. SMM is defined as M-protein at least 30 g/L and/or bone marrow clonal plasma cells (PCs) at least 10%, but no end organ damage. Several factors predict the risk of progression over time, e.g., the type and amount of M-protein and the percentage of abnormal plasma cells in the bone marrow. The standard of care for managing SMM is close follow-up and no active therapy. There have been attempts to treat SMM, including a comparison of MP to no treatment. Thalidomide has been shown to cause toxicity, and in one trial, led to responses but a shorter time to myeloma therapy. This PETHEMA trial included patients at high risk for progression. The treatment was lenalidomide plus dexamethasone, then lenalidomide maintenance at a lower dose compared to no therapy. Dr. Mateos concluded that the preliminary results are promising and the side effects are acceptable. Dr. Dimopolous

observed that to change treatment practice, a survival advantage has to be demonstrated. Dr. Mateos responded that it was notable that most of the patients with progressive disease in the no treatment arm had bone lesions, which are irreversible in myeloma, although only a few patients had bone surveys other than the basic skeletal survey at the time of entry into the study unless they had symptoms. They have not observed cytogenetic differences between the two treatment groups. Longer follow-up is needed, and it is possible that the interim analysis may indicate whether patients with high-risk SMM should be treated. Dr. Durie commented that these were interesting results, but that it was not yet time to change treatment recommendations from observation to active treatment for patients with SMM.

Myeloma Biology

Natural History of Multiple Myeloma Relapsing After Therapy with IMiDs and Bortezomib: A Multicenter International Myeloma Working Group Study (2878), was presented by Shaji Kumar, on behalf of the IMWG. This was a retrospective case study of 270 patients to determine the overall survival of patients with myeloma that was refractory to bortezomib and at least one of the IMiDs. Median time from diagnosis to development of refractory disease was 32 months. Median overall survival from development of myeloma refractory to the novel agents is 8 months for all patients in the cohort, and 7 months for those without a first SCT. In an analysis taking multiple factors into account, at the time of development of refractory disease, being less than 60 years old and having had at least one SCT predicted at least a partial response, and normal creatinine and albumin (suggesting normal kidney function) best predicted better overall survival. A beta-2-M of less than 3.5 mg/dL at diagnosis, a measure of disease severity, was associated with better event-free survival at the time of development of refractory disease. Therefore, the factors that have usually been used to predict outcome are still important for survival outcome for patients with myeloma resistant to novel agents.

Ad Hoc Scientific Committee on Plasma Cell Biology: Scientific Linking of Unusual Manifestations of Myeloma

Chair Raymond Powles, Parkside Oncology Clinic, Wimbledon, United Kingdom, said that although this scientific committee is still ad hoc, they were hoping to get full status as a scientific committee by 2010. This session was an attempt to find commonality among the topics of plasma cell leukemia, extramedullary myeloma, and bone-spared myeloma to further the understanding of myeloma in general.

Plasma Cell Leukemia (PCL) was discussed by Rafael Fonseca, Mayo Clinic, Scottsdale, Arizona. Plasma cell leukemia (PCL) represents an aggressive variant of multiple myeloma characterized by the presence of a large number of circulating PC in the peripheral blood. It is arbitrarily defined as more than 20% of leukocytes being PC in the peripheral blood or more than 2×10^9 cells/L. PCL may be the primary indication of a PC tumor, which often responds to treatment, occasionally with a durable response and overall survival of nearly a year. It can also occur as a secondary leukemic transformation of myeloma, with a very poor prognosis and overall survival of 1.3 to 7 months. The rarity of PCL has limited the ability to study its genetic features. Dr. Fonseca focused his discussion on genetic alterations that he believes drive the ability of PC to escape from the bone marrow and contribute to disease by multiplying out of control. IgH translocations, hypodiploidy (missing chromosomes), del 17p13 at the TP53 locus, mutations in the cancer gene *myc*, and del 13 are common. Deletions of p53 are not common, but are an important prognostic factor, because overall survival is greatly reduced for patients with loss of p53 compared with those in whom it is present. Deletions of p53 are rare in MGUS and SMM, and are seen in increasing frequency over the spectrum from newly diagnosed myeloma to first relapse to second relapse to PCL to myeloma cells becoming capable of growing in culture outside the body. Therefore, Dr. Fonseca suggests that long-term maintenance therapy should address pathways affected by p53 deletion, and p53 status could be included in a molecular staging scheme that might in the future replace clinical staging (such as ISS). PCL is so rare that randomized trials are not possible, and there is no defined standard of care. Therefore, treatment of PCL should resemble that of high-risk myeloma, and should include combinations of IMiDs, bortezomib, doxorubicin, and SCT. Dr. Fonseca predicts that with increasing survival of patients with myeloma, secondary PCL will become an increasingly common and difficult problem to manage.

Extramedullary Myeloma was discussed by Joan Bladé, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. There are several patterns in the development of extramedullary (outside the bone marrow) myeloma, including local soft-tissue growth from adjacent bone lesions; hematogenous spread (from the blood) resulting in single or multiple large subcutaneous plasmacytomas (plasma cell tumors); spreading of nodules to the skin, liver, kidney, breast, lymph nodes, brain, or other organs or tissues; or local spread occurring after surgery, resulting in plasmacytomas at the sites of surgical procedures or wounds, and in the case of bone surgery, leading to invasion of muscles. Soft-tissue

extramedullary plasmacytomas (EMPs) may be present at diagnosis or develop during the course of the disease, and occur in up to one third of patients with myeloma. Factors associated with the development of EMPs appear to include aggressive myeloma, relapsed disease, and independence of myeloma cells from the bone marrow microenvironment. Possible mechanisms of spread include decreased amounts of proteins that cause cells to adhere to their environment, decreased amounts of receptors for chemicals that control the behavior of cells, decreased oxygen, and decreased adhesion of PCs to bone marrow stromal cells, leading to escape of the myeloma cells from the bone marrow. Another possible mechanism is decreased amounts of tetraspanins, which are expressed on the cell surface and are involved in cellular adhesion, movement, activation, and spread, and interaction with molecules involved in signaling and immune function. EMP is associated with shorter survival. EMPs may respond to high-dose therapy, alkylating agents, and/or radiation therapy, and may be more likely to occur after reduced intensity conditioning allogeneic SCT than after ASCT. EMP does not respond to thalidomide but does respond to bortezomib. There are no formal studies of sensitivity to lenalidomide, but case reports suggest the possible efficacy of lenalidomide plus dexamethasone. Dr. Bladé also referred to an entity known as macrofocal extramedullary myeloma, which occurs in young patients (<40 years old) and is associated with multiple skeletal lesions, $\leq 10\%$ bone marrow plasma cells, and a favorable outcome. Dr. Bladé suggested that the focus of future research should include investigations of how myeloma cells move out of the bone marrow and around the body, adhere to other cells and structures, and survive; myeloma stem cell characteristics; molecular genetics; and drug sensitivity and resistance. There are appropriate animal models of EMP that can be used for preclinical drug testing. During the question session, Dr. Bladé noted that there are 2 types of EMPs: 1) those that spread directly from bone and have a better outcome; and 2) those that spread to organs such as the liver and have a worse outcome. Dr. Bladé suggested the use of VTD or VRD for young patients with EMD.

Bone-Spared Myeloma was discussed by Gregory R. Mundy, Vanderbilt University, Nashville, Tennessee, who pointed out that the signs, symptoms, and biology of myeloma related to bone are still not well understood. Dr. Mundy reviewed what is known about osteoblast (bone-forming) and osteoclast (bone-destroying or remodeling) pathways and function in myeloma, including various signaling and molecular pathways, and the roles of molecules that are known to alter development of osteoblasts and regulation of other molecules required for proper bone development

and function, some of which are produced by myeloma cells. He speculated that osteoporosis (thinning of bones) could be considered a cancer-related process because bone formation is impaired in this condition. As patients live longer, the probability of experiencing cancer-related bone disease increases for patients with breast and prostate cancer as well as for those with myeloma. Experiments in animal models should be useful for determining if myeloma can be separated from bone disease, and if that would alter its natural history, including response to therapy. In response to the other presentations in the session, Dr. Mundy noted that the staging of myelomas in remission and at relapse is important. Research needs to focus on detecting disease present outside the bone marrow in the absence of symptoms. He speculated that treatment, with bortezomib in particular, might be turning myeloma cells into cells more capable of spreading.

Of Particular Interest to Patients

Alpha Lipoic Acid and Bortezomib

Alpha Lipoic Acid (ALA) Inhibits the Anti-Myeloma Effects of Bortezomib (Abstract 3832) was presented by Eric Sanchez, Institute for Myeloma and Bone Cancer Research, West Hollywood, California. Alpha lipoic acid (ALA), an anti-oxidant supplement that is used in the management of peripheral neuropathy (PN) in myeloma, has been shown to inhibit the anti-myeloma effects of bortezomib in myeloma cell lines (cells capable of growing in the laboratory outside the body). This is being investigated further in myeloma cells taken from patients and in an animal model. In addition, possible ways to overcome the inhibitory effects of alpha lipoic acid on bortezomib while preserving the beneficial effects of the supplement in PN are being looked at.

Obesity and Melphalan

Effect of Obesity and Renal Insufficiency On Toxicity of High-Dose Melphalan for Multiple Myeloma (Abstract 1177) was presented by Dan T. Vogl, Myeloma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania. This study in 39 patients receiving high-dose melphalan (MEL) followed by ASCT investigated the role that obesity and kidney damage play in the side effects associated with melphalan. The authors concluded that more obese patients, as measured by percent body fat, have more severe lesions in the mouth (oral mucositis) after high-dose melphalan, independent of melphalan dose, body weight, and kidney function. Dr. Vogl's group is in the process of looking at how melphalan acts in obese patients.

Further study is needed to determine if changing the dose of melphalan in obese patients is necessary.

Conclusions

The trend of increased survival for patients with myeloma that began in the era of novel agents (bortezomib, lenalidomide, and thalidomide) is continuing. The novel agents are no longer so novel, as they are now part of new standards of care. Even newer agents are being developed with promising results. Many of these may work best in combination therapies, and because many have unique ways of acting and different types of side effects, combination therapy attacking myeloma cells in several ways should lead to continued improvement in patient survival and quality of life.

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