ASCO 2010 Highlights for Patients



ASCO 2010 Myeloma Highlights for Patients

Introduction

The 46th Annual Meeting of the American Society of Clinical Oncology (ASCO) was held from June 4 through June 8, 2010, in Chicago, Illinois. This year's education sessions on myeloma addressed older patients with lymphoma and myeloma and complications of myeloma and myeloma therapies. The clinical science symposium presented novel therapies for myeloma. The lymphoma and plasma cell disorders poster discussion concerned personalized therapy and new agents in myeloma, and included two main themes: 1) improving on the efficacy of lenalidomide (Revlimid[®]) with or without dexamethasone, especially for relapsed and/or refractory myeloma, and 2) 1q21 amplification as a poor-risk feature.

The most encouraging developments presented at this meeting include the following:

- Lenalidomide maintenance therapy
- Progress in the development of new antimyeloma agents
- The role of transplant in the era of novel agents
- Identification of risk factors
- Anti-myeloma effects of zoledronic acid (Zometa^{*})

Lenalidomide-Based Maintenance Therapy

CALGB 100104 A phase III randomized, double-blind study of maintenance therapy with lenalidomide (CC5013) or placebo following autologous stem cell transplantation for multiple myeloma.

Dr. Philip L. McCarthy, Roswell Park Cancer Center, Buffalo, New York, presented Abstract 8017 on behalf of CALGB, ECOG, and BMT CTN (Blood and Marrow Transplant Clinical Trials Network). The original title was Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous

stem cell transplant (ASCT) for multiple myeloma (MM).

There is a need for maintenance therapy because induction therapy followed by autologous stem cell transplant (ASCT) alone reduces the number of myeloma cells, but does not cure the disease for most patients with myeloma. The Cancer and Leukemia Group B (CALGB) 100104 clinical trial included patients younger than age 70 years who were treated with at least 2 months of induction (initial) therapy to which they had a response of at least stable disease (SD). Patients were also 1 year or less from the start of therapy, and had adequate numbers of stem cells (SC). Patients received one round of high-dose (HD) melphalan followed by autologous stem cell transplantation (MEL200 ASCT), then were restaged 90 to 100 days after recovery. Patients who had a response of SD or better were randomly assigned to receive placebo (inactive pill) or to lenalidomide at 10 mg per day, which could be increased to 15 mg/day or decreased to 5 mg/day as tolerated. The study also took into account the patients; beta 2 microglobulin (B2M) levels, which is a risk factor and whether patients had received lenalidomide as induction therapy. The objectives of the study were to determine if lenalidomide prolonged time to progression (TTP) following ASCT. The study was designed to detect an increase in TTP from 24 months to 33.6 months. Secondary objectives included the rate of complete remission (CR) post-ASCT, progression-free survival (PFS), overall survival (OS), and how practical it was to give lenalidomide for long-term maintenance.

In November, 2009, results were analyzed for 418 patients, half randomly assigned to either lenalidomide or placebo. Patients receiving lenalidomide for maintenance therapy generally had more serious side effects, the most significant of which were decreased white blood cell counts, and to a lesser extent, decreased numbers of red blood cells and platelets. Patients who received lenalidomide also had higher rates of infections.

The use of lenalidomide was associated with a longer TTP, and fewer deaths. The follow-up is

not long enough to determine a difference in OS. In December, 2009, the study was unblinded, that is, it was revealed which patients received lenalidomide vs. placebo. This allowed patients who received placebo to then receive lenalidomide. Those patients treated with lenalidomide maintenance therapy do better regardless of their B2M level or whether they had previously been treated with thalidomide or lenalidomide. For those who received prior thalidomide, the benefit of lenalidomide maintenance is not seen early on, but develops over time.

Dr. McCarthy concluded that maintenance with lenalidomide vs. placebo significantly prolongs TTP. There is no difference in OS at a median follow-up of 1 year post-ASCT. Lenalidomide prolonged TTP regardless of B2M level or prior thalidomide or lenalidomide induction therapy. The side effects associated with lenalidomide maintenance therapy were not severe.

Lenalidomide maintenance after transplantation for myeloma: first interim analysis of a prospective randomized study of the Intergroupe Francophone du Myélome (IFM 2005-02 trial)

Dr. Michel Attal, Hôpital Purpan, Toulouse, France, presented Abstract 8018 on behalf of the IFM.

Relapse of myeloma after single or double ASCT occurs because this treatment does not destroy all myeloma cells, leaving behind what is known as residual myeloma. The ideal maintenance treatment is not known. What is known is that maintenance with conventional chemotherapy, interferon, or corticosteroids is not effective. Thalidomide maintenance after ASCT increases the rates of CR, event-free survival (EFS) or progression-free survival (PFS), and OS. In a previous trial conducted by the Intergroupe Francophone du Myélome (IFM), the benefit of thalidomide was not seen if a part of chromosome 13 was missing [deletion 13 (del 13)] or if the response was a very good partial response (VGPR) or better after ASCT. This suggests that the major role for thalidomide was to reduce residual myeloma that was still present after ASCT rather than to prolong the duration of CR or VGPR. This result could be explained by the high rate of peripheral neuropathy (PN) that shortened the duration of thalidomide treatment.

Therefore, the IFM designed the trial reported on here, IFM 2005-02 phase III randomized trial, to determine if lenalidomide could be safe and effective when administered for a long time. Lenalidomide is an oral agent, so administration is convenient, and it is known to be active in myeloma when HD therapy had failed, and is less likely to be associated with PN than other drugs. The IFM 2005-02 trial included 614 patients younger than age 65 years with non-progressive disease within 6 months of ASCT as their first therapy. Patients received 2 months of treatment (consolidation) with 25 mg/day of lenalidomide, then were randomly assigned to maintenance therapy with either placebo or 10 to 15 mg/day lenalidomide. The primary endpoint was PFS; the secondary endpoints were CR rate, TTP, OS, and feasibility of long-term lenalidomide therapy. In December, 2009, the results were examined.

For with patients treated lenalidomide consolidation both CR and VGPR rates increased, although not significantly, and PFS doubled, which was significant. The benefit of lenalidomide maintenance was observed in all of patients regardless of the initial response, B2M levels, presence or absence of del 13, or type of induction therapy. Longer PFS was seen in patients who received lenalidomide maintenance or had a response of VGPR or better after ASCT or consolidation. Therefore, even with effective maintenance therapy, having a response of VGPR or better is still predictive of a better outcome.

Lenalidomide maintenance was well tolerated. Similar numbers of patients had side effects or discontinued from the study for each treatment group, although more patients treated with lenalidomide had decreased numbers of white blood cells. The OS for both groups was similar after 3 years from the beginning of the study, which was 4 years after diagnosis. Dr. Attal said that the survival rates 80% to 88% are higher than has been seen in all previous IFM trials.

Dr. Attal concluded that maintenance with lenalidomide was well tolerated, resulted in a low discontinuation rate due to severe side effects, and caused no increased risk of serious blood clots [deep vein thrombosis (DVT)] or PN. Longer follow-up is required to see the effect of lenalidomide on OS. The final analysis of this trial is expected in August, 2010.

Formal Discussion

After the presentations, Dr. Sergio Giralt, Memorial Sloan-Kettering Cancer Center, New York, New York, discussed these two studies (abstracts 8017 and 8018) in a presentation entitled: Post-transplant maintenance therapies. What do these studies mean for the practicing physician?

Dr. Giralt said that these are two of the most important presentations in myeloma in the last couple of years. The question is now what to do in the clinic based on the results presented at this meeting. The goals of treatment should be to provide patients with the longest life and best quality of life (QoL) with a minimum burden of therapy. Maintenance is important in myeloma therapy because induction therapy followed by ASCT alone will reduce the number of myeloma cells but will not cure most myeloma. He thinks maintenance therapy should be called "posttransplant continuous therapy." Post-transplant therapy is active treatment, as it implies further reduction of myeloma cells, may involve more effective drugs, and is not seen as long-term treatment. The maximum time this treatment can be given should be investigated. Post-transplant therapy generally shows a benefit for thalidomide in PFS and OS, although side effects are an issue. Thalidomide maintenance might need to be compared with lenalidomide maintenance, because, at least for areas of the world where cost is an issue, thalidomide is much cheaper.

Dr. Giralt noted the similarities of these two studies, which involved young patients receiving a single ASCT. In the IFM study, 10 to 15 mg/day lenalidomide is administered until relapse with dose modification for toxicity. He thought the best responses were somewhat disappointing, with CR of 25% in the lenalidomide arm, but 77% of patients had at least VGPR. What is most important is that the benefit of lenalidomide is seen regardless of the response to transplant. Lenalidomide maintenance cancels the bad effects of del 13. The response after consolidation is the most important factor for determining outcome. The most important side effect is decreased white blood cells counts, and it will be interesting to see why this was significantly lower than in the CALGB study and to see if they were monitoring more often or if it was due to the pre-ASCT induction regimen. The most important message is that as of today, there is no survival benefit for lenalidomide maintenance, and this needs further study.

The CALGB study also showed that the PFS was better with lenalidomide maintenance, with no benefit for OS. This trial also showed that the benefit of lenalidomide is seen regardless of whether thalidomide or lenalidomide were used for induction. Decreased white blood cells counts were significant side effect. Because there was a significant increase in fever associated with decreased white blood cells counts, this therapy should be monitored when it is used in the community to prevent severe side effects, such as severe, general infections.

If the goal of treatment is to delay progression of myeloma, patients should probably receive lenalidomide maintenance whether they are in CR after ASCT, or there is residual disease after ASCT. However, maintenance therapy may not prolong survival. Other important questions to answer include what is the role of consolidation post-transplant, how long should maintenance be given, and what is the role of transplantation in the era of novel therapies?

A trial is planned to answer the questions, "What is the best consolidation regimen for patients undergoing a single ASCT in the context of lenalidomide maintenance? Should patients receive a second ASCT, or nothing at all, or 4 cycles of lenalidomide plus Velcade (bortezomib) and dexamethasone (RVD)?" Lenalidomide maintenance is planned for 3 years, and it will be interesting to compare the results to 1 year of maintenance or maintenance until myeloma progression.

Dr. Giralt concluded that both studies show that lenalidomide prolongs TTP when compared with placebo, with no OS benefit, although follow-up is short. An OS benefit may not be seen because when the trials were unblinded, patients who had not received lenalidomide maintenance could receive it. There is a lenalidomide benefit regardless of B2M, abnormal chromosomes, type of induction therapy, or response to initial therapy. Neither study addresses issues of duration of therapy, if there is a benefit for patients in CR after ASCT, the effect of early vs. late treatment, or the effect of the depth of CR. It is also not possible to determine yet who would and who would not need maintenance.

Dr. Giralt also said that thalidomide maintenance should be considered. It is essential for the global community, because thalidomide is what will be available in the developing world. The best posttransplant therapy is an open question. There is also a need to figure out the best way to measure residual disease. Dr. Giralt said that if there is any sign of residual disease after ASCT, he lenalidomide recommends they go on maintenance. If the response was CR but patients have high-risk disease, he recommends they go on lenalidomide maintenance. For the few patients with low-risk disease who do not have a lot of myeloma cells, maintenance can be discussed with their healthcare provider. He wouldn't switch patients on thalidomide maintenance who tolerate it well to lenalidomide.

New Anti-Myeloma Agents

Progress is being made in the development of new therapies for myeloma. Some of these are second and third generations of already approved classes anti-myeloma agents, proteasome of e.g., inhibitors, e.g., bortezomib, and immunomodulatory agents (IMiDs), e.g., thalidomide and lenalidomide. Others represent classes that may have been approved for other cancers, e.g., histone deacetylase (HDAC) inhibitors, and mTOR (mammalian target of inhibitors. Yet rapamycin) others, e.g., monoclonal antibodies (mAbs) may be designed specifically to treat myeloma.

Pomalidomide

Dr. Martha Lacy, Mayo Clinic, Rochester, Minnesota, presented Abstract 8002: Activity of pomalidomide plus dexamethasone (Pom/dex) in dual lenalidomide/bortezomib-refractory multiple myeloma (MM).

Pomalidomide is a novel IMiD derived from thalidomide. Although similar to thalidomide and lenalidomide, pomalidomide has a different clinical efficacy and side effect profile. Pomalidomide plus dexamethasone has shown activity in patients with relapsed myeloma and myeloma that dose not respond to lenalidomide (lenalidomide-refractory disease).

This phase II trial of pomalidomide plus dexamethasone in relapsed myeloma refractory to both lenalidomide and bortezomib (defined as progression on or within 60 days of last therapy) measured response rates (RR) and side effects. Patients received 2 mg pomalidomide continuously every day and 40 mg dexamethasone once a week. Patients also received 325 mg aspirin daily to prevent blood clots, although investigators could administer full-dose anticoagulant if they thought it necessary. If there was no response or progressive disease after 2 cycles, the dose of pomalidomide could be increased to 4 mg.

Of the 35 patients enrolled, there were 15 patients with high-risk myeloma by mSMART (Mayo clinic) criteria. The median number of prior treatments was 6 regimens, and all patients had at least 3 prior regimens, including 100% prior lenalidomide and bortezomib (by definition), and most had received thalidomide and ASCT. Dose reductions were both per protocol and for side effects, primarily decreased white blood cell counts (neutropenia). The median follow-up was 5 months, at which time 66% of patients experienced no progression.

Neutropenia was the major serious side effect concerning the blood in 34% of patients; side effects not affecting the blood were not common, and included one event of blood clots. Mild to moderate neuropathy occurred in 5 patients. Four of the five patients had neuropathy at the time they entered this study that worsened with treatment.

The RR of confirmed PR or better was 26%, and of minimal response (MR) or better was 54%. There was no difference in best response for patients with high compared with standard risk factors (determined by mSMART). Of nine patients with stable disease(SD) who received an increased dose of pomalidomide, one had an increased response. The median time to response (TTR) was 1 month and duration of response (DOR) and OS have not yet been reached. PFS was 8.0 months.

Dr. Lacy concluded that the pomalidomide plus dexamethasone combination had significant activity in lenalidomide- and bortezomibrefractory myeloma. Responses were rapid. Side effects were manageable and were mostly decreased white blood cell counts. Further studies are ongoing to see if starting with a 4-mg dose of pomalidomide will result in higher response rates.

Discussion

Dr. Bart Barlogie, University of Arkansas for Medical Sciences, Little Rock, Arkansas, pointed out that the median time to response of 1 month

is very rapid, and he wondered if Dr. Lacy thought there are enough data to be certain. If the response is really so rapid, it would be the best treatment to be given up front. Dr. Lacy said she suspected it would be very effective up front. Dr. Barlogie then commented that when his group treats patients with everything available using TT3, the median time to CR is 6 to 8 months, and it's gradual, so what Dr. Lacy is seeing in this trial may be due to small numbers of patients. He wanted to warn about high- vs. low-risk and incidence of remission. He thinks the issue for patients with high-risk disease is not remission but rather durability of response. He doesn't think there are data showing that patients with high-risk disease do less well with initial response. Dr. Lacy agreed. DOR with high-risk disease is hugely important, but in their experience, once relapse occurs, it's hard to get the disease into remission. Dr. Lacy said that the median follow-up was not long enough to look at TTP in high- vs. standardrisk disease.

Carfilzomib

Dr. Ravi Vij, Washington University School of Medicine, St. Louis, Missouri, presented Abstract 8000: Results of an ongoing open-label phase II study of carfilzomib in patients with relapsed and/or refractory multiple myeloma.

Carfilzomib is a novel, selective proteasome inhibitor with highly selectable and irreversible proteasome binding and target inhibition and minimal off-target activity. It overcomes bortezomib resistance and has not been associated with nervous tissue damage or neutropenia in animal studies.

The PX-171-004 trial enrolled 155 patients with relapsed or refractory myeloma following 1 to 3 prior treatment regimens. Two groups of patients were enrolled. The first group consisted of 34 patients who had received bortezomib previously and 53 patients who had not. The second group included 53 patients who had not received bortezomib. These numbers refer to patients who could be evaluated at the end of the trial. The first group was treated with 20 mg/m²; the second group received a dose of 20 mg/m² in cycle 1 that was increased to 27 mg/m² in subsequent cycles.

ORR, clinical benefit response (CBR), defined as at least MR, and median TTP were highest for the second group of patients and lowest for the patients in the first group who had previously received bortezomib. Nearly half of the patients had mild to moderate neuropathy when they enrolled in the study, and occurred in 12% to 17% of patients during the study; a few patients developed more serious neuropathy. The highest rates of neuropathy occurred in bortezomibtreated patients. The most common side effects included manageable, mild to moderate fatigue, nausea, difficulty breathing, and decreased blood counts. There were 5 on-study deaths, 2 due to progressive disease, 2 due to study treatment, and 1 unrelated to treatment. At follow-up about 25% of patients remain on trial, about 25% have been treated with the full 12 cycles, and 9% (n=14) are on an extension protocol.

Dr. Vij concluded that single-agent carfilzomib shows significant activity in relapsed or refractory myeloma; although responses were seen in bortezomib-treated patients, responses were higher in patients who had not been treated with bortezomib, with durable responses in all treatment groups. Preliminary results suggest higher response rates with higher doses. Side effects were generally mild and clinically manageable. Severe PN was rare and does not limit therapy despite pre-existing symptoms. Carfilzomib was tolerated for at least 12 cycles. The lack of significant side effects suggests that carfilzomib could be used in combination with other anti-myeloma agents, and combinations are being tested. This trial is ongoing at a dose of 27 mg/m². In other trials in solid tumors, carfilzomib has been administered in doses up to 70 mg/m² using slower infusion rates.

A participant pointed out that in bortezomibresistant disease, the responses are lower but the TTP is equal to that in bortezomib-responsive disease, and asked why. Dr. Vij responded that he can't say why the response is lower, but the durability of response is encouraging even in this patient population. Someone asked why, given the mild side effect profile and the increasing responses observed with increasing doses, the dose was not increased beyond 27 mg/m². Dr. Vij said that in phase I trials, two different dosing regimens were tested. What was thought to have been side effects affecting the kidney could also have been the result of tumor lysis syndrome, a serious condition resulting from rapid destruction of cancer cells. It could also have been due to generalized infection, myeloma disease, or the drug, so the choice of dose was conservative. Now it is known that patients with solid tumors have received 70 mg/m² via a 30-minute infusion. Doses of 36 and 45 mg/m² are tolerable in myeloma patients. Perhaps higher doses with longer infusion times would result in a side effect profile that is no different from that seen with lower doses and might improve the response rate.

Vorinostat

Dr. Paul Richardson, Dana-Farber Cancer Institute, Boston, Massachusetts, presented the poster, Abstract 8031: Phase I study of combined vorinostat (V), lenalidomide (L), and dexamethasone (D) in patients (pts) with relapsed or refractory multiple myeloma (MM).

At this time, all data are preliminary, but they suggest vorinostat, a histone deacetylase (HDAC) inhibitor, combined with lenalidomide and dexamethasone may be a convenient, effective, and generally well-tolerated oral regimen for patients with relapsed or relapsed and refractory myeloma, including those who have received prior lenalidomide therapy. There were no treatmentrelated deaths and no maximum tolerated dose reported. A phase II study is planned.

Discussion

Dr. Robert Orlowski, University of Texas, MD Anderson Cancer Center, co-chair of the Lymphoma and Plasma Cell Disorders Poster Discussion, discussed this poster. He observed that this study enrolled patients with a median of 4 prior lines of therapy, so they were further along in the disease process than those in the study of combination panobinostat reported by Dr. Mateos, which is discussed below. Of the 31 patients, the majority had received prior thalidomide and/or lenalidomide, most had at least SD, that is, experienced a clinical benefit, and the response rate of at least PR in about half of the patients is encouraging. Responses in patients who had received lenalidomide and in patients whose disease was lenalidomide-refractory suggest that vorinostat may help overcome resistance.

Panobinostat

Dr. Kenneth Anderson, Dana-Farber Cancer Institute, Boston, Massachusetts, presented Abstract 8001 on behalf of Jesus San-Miguel and their colleagues: Phase Ib study of oral panobinostat (LBH589) plus intravenous bortezomib in patients (Pts) with relapsed (Rel) or Rel and refractory (Ref) multiple myeloma (MM).

Panobinostat, another histone deacetylase (HDAC) inhibitor, has limited activity as a single agent, so it is being tested in combination with other anti-myeloma drugs.

The LBH589B2207 study of increasing doses of panobinostat enrolled 47 patients with relapsed or relapsed and refractory myeloma. Panobinostat was given three times a week every week, bortezomib was given on the "classic" schedule for 2 weeks on and 1 week off, and dexamethasone was given on the day of and the day after bortezomib. The maximum tolerated dose was 20 mg panobinostat 3 times a week with 1.3 mg/m^2 bortezomib. Two groups that included a total of 17 patients were given this dose.

Side effects included a high rate of seriously reduced platelet counts, which was manageable with changing the dose and/or transfusions of platelets. Decreased numbers of white and red blood cells also occurred. Other side effects were primarily related to the digestive system as well as fatigue and weakness, and were mostly mild to moderate. The combination was associated with minimal serious PN, and there was no dose-related effects on the heart of the type that have been reported with other HDACs.

Responses were seen even at the lowest doses. About three-quarters of the patients receiving the highest dose had a clinical benefit response. ORR was 70% for all 47 patients, and was 60% for patients whose disease didn't respond to bortezomib. Panobinostat side effects limited the time many patients stayed on therapy.

Dr. Anderson concluded that oral panobinostat can be safely combined with bortezomib and dexamethasone, and that this is among the most active combinations in bortezomib-resistant myeloma. Future directions include a large, international, randomized phase III trial of bortezomib plus panobinostat vs. bortezomib (PANORAMA 1) in relapsed myeloma that is ongoing, and in the US a phase II trial of bortezomib plus panobinostat at the maximum tolerated dose (PANORAMA 2) in patients with relapsed and bortezomib-refractory myeloma.

Dr. María Victoria Mateos, Hospital Universitario de Salamanca, Salamanca, Spain presented poster Abstract 8030: Phase Ib study of oral panobinostat (LBH589) + lenalidomide (LEN) + dexamethasone (DEX) in patients (Pts) with relapsed (Rel) or Rel and refractory (Ref) multiple myeloma (MM).

Dr. Robert Orlowski, co-chair of the Lymphoma and Plasma Cell Disorders Poster Discussion, Personalized Therapy and New Agents in myeloma, discussed this poster.

High-dose dexamethasone plus lenalidomide and oral panobinostat was administered on an everyother-day schedule to the 46 patients enrolled. Patients with primary refractory myeloma (myeloma that didn't respond to the first treatment) were excluded. About half of the patients had myeloma that was refractory to last line of therapy; only 17% of them had prior lenalidomide. There was a 48% response of at least MR, but none of these were in patients in the lenalidomide-refractory group.

Hematologic side effects were commonly observed, with about half of patients having serious reductions in white blood cell or platelet counts. There were 7 deaths, three of which were suspected of being treatment-related; 10 patients discontinued due to side effects. Dr. Orlowski thinks this is a high rate of deaths, comparable to those seen in the study combining lenalidomide with high-dose dexamethasone. Future studies will use a lower dose of dexamethasone and less frequent administration of panobinostat.

Dr. Melissa Alsina, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, presented poster Abstract TPS308 (Trials In Progress Session), PANORAMA 2: A phase II study of panobinostat (LBH589) in combination with bortezomib (BTZ) and dexamethasone (DEX) in patients with relapsed and BTZrefractory multiple myeloma.

The design of this study was presented. It is enrolling approximately 47 patients in the US to determine, in part, if this combination can overcome bortezomib resistance in a population with an unmet medical need.

Elotuzumab

Dr. Sagar Lonial, Emory University School of Medicine, Atlanta, Georgia, presented Abstract 8020, Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma: a phase I/II study.

The presentation was an update of data presented at ASH, 2009. Elotuzumab is a monoclonal antibody (mAb) that has been designed to resemble a human antibody of the IgG1 type. It targets CS1, a modified protein that occurs in large amounts on the surface of myeloma cells. It occurs to a lesser extent on one type of immune cell, natural killer (NK) cells, and occurs to little or no extent on normal cells or tissues. Preclinical studies (studies in cells, tissues, or animals, which are done before drugs are tested in people) suggest that elotuzumab works by attaching to myeloma cells and helping natural killer (NK) cells to destroy the myeloma cells. As a single agent it has a safety profile that resembles that of other mAbs. Elotuzumab side effects are mostly infusionrelated reactions, and responses have been mostly SD. Combination studies in cells showed increased activity when elotuzumab is combined with lenalidomide.

The study objectives for the phase Ib portion of this trial were to determine the maximum tolerated dose of elotuzumab in combination with lenalidomide and low-dose dexamethasone. The phase II primary objective was to evaluate the safety and efficacy of two doses of elotuzumab, either 10 or 20 mg/kg, and to determine the best treatment to give prior to elotuzumab to prevent infusion-related reactions. In this phase, 60 additional patients with advanced disease were enrolled and those with prior lenalidomide treatment were excluded. In phase Ib, doses of elotuzumab were 5, 10, and 20 mg/kg in combination with 25 mg lenalidomide and lowdose dexamethasone. For the first 2 weeks, elotuzumab was given weekly; then it was given every other week until disease progression occurred. The phase I portion of the study was originally supposed to end after 6 months, but based on favorable responses, it was amended to continue to progressive disease (PD).

In the phase Ib portion, 28 patients were treated, and 12 are still on study. There were no doselimiting toxicities. The side effects were similar to those seen in lenalidomide trials except for infusion reactions thought to be related to elotuzumab, which occurred in 2 patients. The ORR was 82% for all 28 evaluable patients and 95% for the 21 patients who had not received lenalidomide; VGPR rates were 25% and 27%. Responses are improved over those reported at ASH, and are relatively independent of prior treatment with lenalidomide, thalidomide, or bortezomib. TTP was not reached at a follow-up of a median of 8 months. After initiation of new premedication treatments, there were no serious infusion reactions in the phase II expansion trial. Enrollment is continuing. Analysis of bone marrow-derived myeloma cells from patients in the phase II expansion group show that elotuzumab binds to all the CS1 present on the myeloma cells at both doses.

Dr. Lonial concluded that elotuzumab plus lenalidomide plus low-dose dexamethasone has a manageable safety profile in the phase Ib trial in 28 treated patients with a median of 2 prior therapies. There were no additional side effects over what is seen with lenalidomide and low-dose dexamethasone other than infusion reactions. The phase II expansion is ongoing to identify the best dose of elotuzumab in this combination.

Discussion

Dr. Todd Zimmerman, University of Chicago Medical Center, Chicago, Illinois, the session cochair, asked what drugs could be combined with elotuzumab. Dr. Lonial answered that the results with lenalidomide suggest immune-enhancing effects of IMiDs, so lenalidomide or maybe even pomalidomide might be interesting for combination therapy; Dr. Jakubowiak's results (presented below) suggest that the combination with bortezomib might be able to overcome bortezomib resistance. Dr. Lonial said what happens after CS1 is bound by the antibody needs to be understood, which could suggest whether alkylating agents, steroids, or other classes of drugs would be good in combinations.

Michael Bishop (NCI) asked Dr. why dexamethasone was included if steroids inhibit the immune response by reducing NK cells, if part of the way elotuzumab works is to enhance NK activity. Dr. Lonial replied that inclusion of dexamethasone was due to practical issues. There is concern about lenalidomide plus dexamethasone decreasing the number of NK cells. Dexamethasone was not used in the preclinical model. The effects on NK cells in the phase II expansion trial are being evaluated, but results are not available. Dr. Bishop observed that it is hard to argue with the results, and Dr. Lonial agreed he made a good point.

Dr. Andrzej J. Jakubowiak presented Abstract 8003: Elotuzumab in combination with bortezomib in patients with relapsed/refractory multiple myeloma: A phase I study.

The objectives of this study included establishing the maximum tolerated dose of elotuzumab in combination with bortezomib, determining safety and tolerability, and evaluating efficacy and immunogenicity (ability of elotuzumab to cause allergic reactions). Elotuzumab was given on days 1 and 11, bortezomib was given at the standard dose and regimen. Dose-limiting side effects were measured after cycle 1; the dose of elotuzumab only was increased for 3 more cycles. If PD occurred at cycles 2 or 3, dexamethasone could be added; if at cycle 4 there was no PD or toxicity, the patient could continue therapy. The study enrolled 28 patients with a median of 2 prior therapies; 25% had high-risk cytogenetics. Of these, 15 patients were treated in the phase of increasing dose, and there were no dose limiting toxicities in this phase; 13 patients were added at the expansion phase at a maximum tolerated dose of 20 mg/kg for elotuzumab.

The side effects were mostly mild, with the most common serious events being decreased numbers of lymphocytes (a type of white blood cell), fatigue, decreased numbers of platelets, abnormally high blood sugar, decreased numbers of white blood cells, pneumonia, and decreased numbers of red blood cells. The elotuzumabrelated side effects were mostly mild and were mostly infusion-related reactions. There were two elotuzumab-related serious side effects, chest pain and inflamed stomach and intestines. The best confirmed responses in 27 evaluable patients were PR or better of 48% and MR or better of 63%. There were responses in patients who had prior bortezomib or whose disease was refractory to bortezomib or their last therapy. Median TTP was 9.5 months for all patients (n=27) and for patients not previously treated with bortezomib (n=16).

Dr. Jakubowiak concluded that the combination was well tolerated. The maximum tolerated dose was not reached at doses up to the planned maximum dose of 20 mg/kg, and the key side effects attributable to elotuzumab were infusion reactions. The RR, including responses in bortezomib-refractory disease, and the median TTP of 9.5 months are encouraging. In this study, as well as the one reported by Dr. Lonial, elotuzumab binds to all the CS1 present on the myeloma cells at both doses. The possibility that elotuzumab and bortezomib have increased activity in combination will be investigated in further studies.

Discussion

A participant noted that given that bortezomib is at least additive to or increases activity with a mAb called anti-CD20 in lymphoma. Perhaps weekly bortezomib could be used with elotuzumab. Dr. Jakubowiak said that they are looking at the combination compared with bortezomib, and are considering different schedules for giving the drugs.

RAD001

Dr. Anuj K Mahindra, Massachusetts General Hospital, Boston, Massachusetts, presented Abstract 8032: Results of a phase I study of RAD001 in combination with lenalidomide in patients with relapsed or refractory multiple myeloma.

Lenalidomide was added to RAD001, an mTOR (mammalian target of rapamycin) inhibitor that does not have single-agent activity in myeloma, to create a non-steroid-containing regimen. The phase I trial was conducted to determine side effects and maximum tolerated dose as primary objectives, and to determine activity of the combination as a secondary objective. Doses of both drugs were increased and given for 21 days of a 28-day cycle until disease progression or doselimiting toxicity. Results are available for 26 patients who had a median of 4 prior lines therapy; 50% had prior lenalidomide; of those, 10 patients had a relapse and 3 had myeloma that was refractory. Dose-limiting toxicities included severely reduced white blood cell counts and platelet counts at doses of 20 mg lenalidomide and 5 mg RAD001, so 15 mg lenalidomide and 5 mg RAD001 for 21 days with a 7-day rest period was determined to be the maximum tolerated dose. Common mild to moderate side effects, which were manageable with supportive care, included nausea, fatigue, difficulty breathing, diarrhea, constipation, neuropathy, and muscle cramps. One patient discontinued due to RAD001-related non-infectious lung inflammation. A response of at least SD occurred in 68% of evaluable patients at a median follow-up of 8.7 months. PFS is 4.3 months. The authors concluded that the combination, which provides an oral, steroid-free regimen, warrants further evaluation in phase II studies.

General Discussion of Newer Agents

Dr. Sagar Lonial discussed abstracts 8002 and 8003, and called his presentation "The Death and Rebirth of Immunotherapy in Myeloma."

IMiD agents (thalidomide and especially lenalidomide) are effective as both single agents

and in combination in all phases of myeloma therapy; this activity is likely associated with improving immune function and allowing naturally-occurring anti-tumor activity to contribute to responses. The use of IMiDs and mAbs together may increase the response of myeloma by improving immune function, which has been seen in other types of cancer. Pomalidomide acts in myeloma in a way similar to lenalidomide and thalidomide; lenalidomide and pomalidomide might have more immuneenhancing activity, but this has not been shown formally. Thalidomide is useful as the first novel agent in myeloma; lenalidomide is able to overcome resistance thalidomide; to can pomalidomide overcome resistance to lenalidomide?

In asking how to make immunotherapy better, Dr. Lonial observed that it is an oncologic irony that myeloma is a disease that makes too much monoclonal antibody, yet there currently is no therapeutic antibody to treat myeloma. There are at least 10 potential mAb candidates in clinical development, some directed against proteins on the surface of myeloma cells, others against factors that increase the growth of myeloma cells, and still others aimed at the interaction of myeloma cells with their microenvironment within the bone marrow.

However, Dr. Lonial believes there is cause for celebration: refractory is the new relapsed; both elotuzumab studies presented at this meeting demonstrate significant efficacy in the context of refractory disease. Other trials show adding panobinostat to bortezomib overcomes bortezomib resistance; adding elotuzumab to bortezomib overcomes bortezomib resistance, and adding pomalidomide to bortezomib overcomes bortezomib resistance. In the last year, studies have shown that the new agents in development, vorinostat, romidepsin, and even perifosine, can overcome bortezomib resistance as well. So resistance and refractoriness may need to be modified, because refractory is not what it was 10 years ago, when all that was available were alkylating agents. The median PFS in the trials reported by Dr. Jakubowiak and Dr. Lacy is between 8 and 9 months despite patient populations with refractory myeloma, which is significantly longer than might be expected.

Questions remain, including how much is enough? What are the right doses and schedules? Is 5, 10, or 20 mg of elotuzumab the right dose? Dr. Lonial said that they hope to have an answer to that question based on the combination trial with lenalidomide he is updating at this meeting. If a dose of mAb binds to all of its targets on the myeloma cell, does giving a higher dose increase enhance the side effects or response? Pomalidomide responses have been seen with 1, 2, or 4 mg in different studies, so is there a relationship of the dose to the response? There may need to be a patient-specific dose or trialspecific approach, and the same may apply to mAbs. Dr. Lonial concluded that new agents are very exciting even if they are new versions of old drugs; particularly encouraging is activity in highrisk disease. Identifying how different drugs act together to create a better than expected response should be a high priority in order to define the best combination. It is critical to investigate this with bortezomib combinations because it may give insight into other effective combinations.

Dr. Paul Richardson discussed abstracts 8000 and 8001, Novel proteasome and HDAC inhibitors in myeloma: The emerging role of novel second generation proteasome inhibitors and HDAC inhibition in myeloma.

His key take-home points included the following:

- Proteasome inhibition has emerged as a highly active therapeutic approach for a range of cancers and in particular multiple myeloma.
- Bortezomib has efficacy as a single agent in myeloma and is approved for this indication.

- Second-generation proteasome inhibitors are showing promise, with carfilzomib and others in clinical development, demonstrating different tolerability profiles and potentially greater potency.
- Combination approaches with proteasome inhibitors, specifically bortezomib, and now carfilzomib, have shown remarkable activity in myeloma, especially when rationally combined with other targeted agents, such as IMiDs and HDAC inhibitors, and may help overcome resistance.

The first-generation novel agents are now used throughout the treatment course of myeloma, and improve the outcome of ASCT. Information from the International Myeloma Working Group (IMWG) suggest an average survival for patients with myeloma that is relapsed or refractory after treatment with these agents to be 6 to 9 months, which is dismal and an area of unmet need.

is the lead second-generation Carfilzomib proteasome inhibitor with a side effect profile that is different from that of bortezomib. The lack of severe side effects has allowed carfilzomib to be combined with other agents, including lenalidomide. It is controversial whether all proteasome inhibitors cause peripheral neuropathy (PN). There may be important differences between the drugs at different sites in nervous Other second-generation tissue. proteasome inhibitors include NPI-0052, a natural compound with a unique side effect profile that has been shown to be active against bortezomib-resistant cells. A phase I trial is ongoing and has shown particularly both tolerability, for a new formulation, and clinical activity. Several other second-generation compounds are in development, including a second-generation boronate proteasome inhibitor, CEP-18770, which is entering clinical trials; and MLN 9708, a high-potency and reversible compound with rapid on/rapid off properties that is orally bioavailable and in phase I trials.

Proteasome inhibition with first-generation bortezomib and second-generation proteasome inhibitors constitutes the backbone of myeloma therapy with novel, rational combinations, including HDAC inhibitors, to improve responses. This reflects the new treatment model of targeting both the tumor cell and its bone marrow microenvironment and other complex interactions that lead to resistance. Rational combinations may be able to target myeloma that occurs outside the bone marrow (extramedullary disease). Tailored approaches may provide new, more specific, and less toxic combinations therapies. Challenges include the best order in which to give drugs, drug resistance, and side effect management to have the best anti-myeloma effect and further improve patient outcome. Myeloma remains incurable and the need for new agents and continued studies is of highest importance.

The Role of Transplant in the Era of Novel Agents

Dr. Antonio P. Palumbo presented abstract 8015, A phase III trial of melphalan/prednisone/ lenalidomide (MPR) versus melphalan (200 mg/m²) and autologous transplantation (MEL200) in newly diagnosed myeloma patients.

This study challenges the use of ASCT for younger patients with the introduction of newer drugs. The aims of the study were safety and efficacy of lenalidomide plus low dose dexamethasone (Rd) induction for ASCT, and compared conventional chemotherapy incorporating a new drug vs. ASCT with a new drug as induction, and examined the role of lenalidomide maintenance after chemotherapy/ASCT. There are no results for maintenance therapy in this trial yet.

The study enrolled 402 patients younger than age 65 years. All patients received Rd for four 28-day cycles as induction; stem cells were collected; patients were randomly assigned to melphalan/prednisone/lenalidomide (MPR) for six 28-day cycles or to 2 courses of MEL200 ASCT. There was then a second random assignment to either no maintenance or maintenance with 10 mg per day of lenalidomide until disease progression.

In this trial, Rd had one of the best safely profiles for combinations containing novel agents. Within this study, a sub-study compared the use of lowmolecular-weight heparin (LMWH; enoxaparin 40 mg per day) vs. aspirin (100 mg per day) to prevent blood clots in patients who were taking MPR. The incidence of clots was slightly greater than 1% with LMWH; with aspirin, the combined risk was about 2.5%. Stem cell mobilization was adequate using chemotherapy (cyclophosphamide) plus a growth factor (G-CSF).

The response rates, PFS, and OS were similar for both treatments after a median follow-up of 14 months, but this is a short follow-up time. Combination therapy with new agents appears to reduce the difference between standard treatment and ASCT. Patients with International Staging System (ISS) stage 1 myeloma (least severe disease) appear to do somewhat better regardless of treatment. Patients with high-risk disease, defined as having del 17 or t(4;14) or t(14;16), appear to respond less well to either treatment than patients with standard-risk disease. The major advantage for MPR over ASCT is in side effects, with much fewer effects on the blood, and fewer infections effects. The and digestive tract side discontinuation rate is similar between therapies, and there were no early deaths. Dr. Palumbo concluded that Rd induction is effective with an excellent safety profile. Longer follow-up is needed to assess PFS and OS, and to evaluate the effect of maintenance on patients receiving conventional therapy vs. ASCT.

Paul Richardson presented abstract 8016 on behalf of Kenneth C. Anderson and colleagues, entitled Lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma (MM): final results of a multicenter phase I/II study.

Results presented here are an update with a longer follow-up, a median of over 27 months, of a trial (lenalidomide, of RVD bortezomib, and dexamethasone). Important features of the study design include giving of bortezomib twice weekly, giving dexamethasone on the day of bortezomib administration and the day after, and giving lenalidomide daily for 14 days followed by 7 days off. If the response was PR or better after 4 cycles, patients could receive an ASCT. After 8 cycles patients could have maintenance, with the frequency of bortezomib reduced to weekly, lenalidomide continued, and dose reduction or elimination of dexamethasone. The study required tests of bone marrow and the use of X-rays to determine the response.

Side effects were related to the use of high-dose (HD) dexamethasone, which has been seen in the ECOG trial. In the phase II portion of this trial the doses were: 1.3 mg/m² of bortezomib, 25 mg of lenalidomide, and 20 mg of dexamethasone for cycles 1 to 4, reduced to 10 mg for cycles 5 to 8 and 66 patients were treated. At a follow-up of almost 4 years, 15% patients remain on treatment, 47% went on to ASCT, and 59% received 8 or more cycles of all three drugs together. The most common side effects were PN in most patients, which was primarily mild to moderate, reversible in most, and manageable. Side effects affecting blood cells were manageable. The rate of clots was 6%. Only 1 patient died, unrelated to drug treatment.

All 66 patients in the study and all 35 patients in the phase II portion had at least PR as their best response. Response improved with continued therapy in 75% of patients from cycle 4 to 8, and in 53% of patients beyond cycle 8, with a median time to best overall response of 2.1 months. Of the 47% patients that went on to ASCT, stem cell harvesting and engraftment were successful. Updated outcomes at a median follow-up of 27.3 months show that 44 patients were alive without PD. Median DOR, median PFS, and OS were not reached. An analysis of PFS at one year by whether patients received ASCT or not showed no difference between those who received ASCT and those who did not. This is encouraging, but it is early, with a short follow-up. Although the patient numbers are small, there seem to be no differences in quality of response or in PFS according to genetic abnormalities. Patients with ISS stage 1 disease do very well, those with stage 2 and 3 disease do not do as well, which is significant and similar to results reported by Dr. Palumbo.

Dr. Richardson concluded that RVD is highly effective in previously untreated myeloma, and is the first combination to give results of a 100% response rate of at least PR, with high rates of CR/nCR and VGPR, and promising estimated PFS and OS with or without ASCT. There are ongoing trials to investigate the addition of other agents, e.g., alkylating agents or anthracyclines. Large phase III trials are ongoing to compare lenalidomide dexamethasone plus with bortezomib plus dexamethasone, and RVD after ASCT with other treatments; a study assessing RVD followed by continuous lenalidomide with or without ASCT will be conducted by the partnership of the IFM and the Dana-Farber Cancer Institute. Other studies that are ongoing or planned of novel combinations to reduce side effects and enhance efficacy will look at HDAC inhibitors such as vorinostat, and "RVD light," with a weekly schedule of bortezomib in elderly patients.

Dr. Zimmerman noted that there are different schedules used for dexamethasone dosing. Dr. Richardson said that in the study he reported, the reason for giving dexamethasone on the day of and day after bortezomib was based on their experience in relapsed and refractory myeloma. In the EVOLUTION trial they used a different schedule, administering weekly dexamethasone. Dexamethasone presents challenges, and it may affect the side effects of bortezomib. PN may involve inflammation that dexamethasone may modify, so the lower doses of dexamethasone are important, not just for side effects in general, but for preventing nerve damage. HD dexamethasone is a problem.

Dr. Richardson was asked about the best lenalidomide dosing schedule, and said that they know from phase I and II trials of lenalidomide development that giving lenalidomide every other day may have fewer side effects but is not as effective. In this study, the lenalidomide dosing of 3 weeks on and 1 week off was developed in phase I trials. The 2 weeks on and 1 week off for the RVD combination was designed to avoid overlapping side effects and to allow for a period of rest. So he thinks lenalidomide dosing is highly flexible, but daily dosing for a period of time is important, and he doesn't want healthcare providers to think they can give lenalidomide however they want. It can clearly be used for a 2 weeks on 1 week off schedule in combination effectively, and can be used for 3 weeks on and 1 week off in combination with low-dose dexamethasone, and continuously for maintenance therapy.

Dr. Jean-Luc Harousseau discussed abstracts 8015 and 8016, concerning the role of transplant for myeloma in the era of novel agents.

Until now ASCT has been shown to be superior to conventional chemotherapy in at least 7 randomized trials, with 6 trials showing an increased response rate, 5 trials showing an increased PFS, and only 3 trials showing an increased OS because of shorter survival after relapse (some patients received ASCT after relapse from conventional chemotherapy). Novel agents used as frontline therapy in the last few years have completely changed the outcome for elderly patients. The use of novel agents, even in elderly patients, can achieve results comparable or even better than those achieved with ASCT. In studies of novel agents used prior to ASCT in 2- and 3drug combinations, the 3-drug combinations are better, and both 2- and 3-drug combinations are better than standard therapy if the combinations include at least one novel agent. When thalidomide was used as maintenance therapy after ASCT, it improved the greater-than-VGPR response rate and extended the PFS in 4 trials, and increased the OS in 3 of the 4 trials. With Total Therapy (TT), addition of novel agents improves event-free survival (EFS) and OS.

These results lead to asking if, in the era of novel agents, HD MEL plus ASCT (HDM) should be used. Dr. Harousseau thinks this question should be answered in the context of clinical trials to avoid selection bias in the choice of therapy by physicians and patients. The study presented by Dr. Palumbo is the first randomized trial to address this important question. The updated results presented at this meeting indicate there is no difference in response rates, PFS, or OS. The follow-up is short, so it may not yet be time to abandon upfront ASCT. Questions raised by this presentation include the statistical hypothesis and design. The study may not be designed to detect a difference between MPR and HDM due to improved PFS in both arms. Two questions were addressed: 1) MPR vs. HDM, and 2) maintenance vs. no maintenance, which results in 4 arms if the effect of lenalidomide is not the same after MPR and HDM. With only 402 patients it might be difficult to show a benefit of HDM, and it will be impossible to compare MPR with HDM in some subgroups of disease risk. The follow-up is short at a median of 14 months, which is too early for OS (and because effective treatments exist in the case of relapse), and it is also too early to determine PFS because lenalidomide maintenance prolongs PFS after either ASCT or non-intense therapy. So currently for MPR vs. HDM the most important information is the response rate, which has only been evaluated in 239 patients of the 402 who were randomly assigned, and for which no difference by treatment is seen. The results of the final analysis are needed.

Is lenalidomide plus dexamethasone the best induction treatment prior to ASCT? In the ECOG study, after 4 cycles, lenalidomide plus dexamethasone was low-dose inferior to lenalidomide plus high-dose dexamethasone, which was not true in the study presented by Dr. Palumbo at this meeting. However, in other studies, treatment with vTD (reduced-dose bortezomib plus thalidomide and dexamethasone presented by Dr. Moreau at this meeting) or VTD (presented by Dr. Cavo at last year's ASH meeting) resulted in higher response rates before and after ASCT. For the non-intensive arm RVD might be a better treatment to use for comparison because of the response rates and PFS reported here by Dr. Richardson. So is RVD the best nonintensive frontline treatment? This question can't be answered without a randomized trial to compare non-intensive upfront treatments. The high response rates with RVD reported at this meeting have not been seen before with other combinations, treatment was generally well tolerated except for PN, and the results look better than those seen with lenalidomide plus low-dose dexamethasone (in the ECOG trial) or induction with lenalidomide plus low-dose dexamethasone followed by MPR/HDM (in the trial presented by Dr. Palumbo). However, in the RVD trial, 47% of patients went on to ASCT, whereas no patients did in the MPR/HDM trial, and only 20% of patients in the ECOG trial did. Dr. Harousseau concluded that the results of MPR vs. HDM do not show differences in RR, PFS, or OS, and that a longer follow-up is needed before drawing a definite conclusion. Upfront ASCT might be useful only in certain patients, and a large number of patients is needed to determine differences across subgroups with different risk factors. The IFM/DFCI trial to start in July will study VRD stem cell collection, induction, random assignment to VRD, lenalidomide maintenance, and HDM at relapse vs. MEL200 ASCT, VRD, then lenalidomide maintenance, and is planned to enroll 1000 patients, which will allow the investigators to look at subgroups with different risk factors. Dr. Harousseau thinks this trial is

using the best induction and non-intensive treatments.

Initial Therapy Prior to Transplant

Dr. Philippe Moreau, University Hospital, Nantes, France, presented abstract 8014 on behalf of the IFM: Comparison of reduced-dose bortezomib plus thalidomide and dexamethasone (vTD) to bortezomib plus dexamethasone (VD) as induction treatment prior to ASCT in de novo multiple myeloma (MM): results of IFM2007-02 study.

This study was designed to compare the two best treatments identified in the IFM 2005-01 and GIMEMA 26866138-MMY-3006 trials, VD and VTD. In this trial, the dose of bortezomib was reduced to 1 mg/m² and the dose of thalidomide was reduced from 200 to 100 mg/day in an attempt to reduce the PN rate. IFM2007-02 enrolled newly diagnosed patients up to age 65 years who were randomly assigned to VD for four 21-day cycles, or to reduced-dose bortezomib (v)TD. ASCT MEL200 followed 4 cycles of induction.

After 2 cycles, vTD resulted in a significantly higher PR than VD. After 4 cycles the CR rate was similar between arms, and the response of at least VGPR was significantly higher for vTD. After ASCT, the rate of at least VGPR was significantly higher with vTD than with VD. Again, there was no difference in the CR rate between arms. In previous studies rate of at least VGPR both after induction and after ASCT was an important goal because it was related to better outcome. In other VTD studies, the rate of at least VGPR is comparable, especially after ASCT, and is superior to VD. Stem cell (CD34 positive cells) collection was lower with vTD. Collection was not possible in 21% patients with the growth factor G-CSF alone as planned (vs. 6% with VD). Therefore the chemotherapy agent cyclophosphamide was used, so that in the end there was a similar low failure rate (2% vs. 1%

with VD). There was no difference in the recovery of cells and there were no toxic deaths in either arm. Side effects during induction were similar for the two treatment arm except for PN leading to discontinuations, which occurred only with VD. There were low rates of other serious side effects. One study goal was to reduce the PN rate, and they did see significantly lower rates of at PN that was moderate to serious in patients treated with vTD arm (28%) vs. VD (34%).

Dr. Moreau concluded that vTD was more effective than VD after induction and after ASCT, with a similar CR rate and a better CR+VGPR rate. Decreasing the doses of bortezomib and thalidomide does not decrease the efficacy of the combination. Cyclophosphamide is needed to collect stem cells with vTD. The incidence of serious side effects is low and the rate of moderate to serious PN is dramatically reduced. This new triple combination of vTD is superior to VD with good efficacy and low toxicity.

In discussing the IFM study, Dr. Michael Wang, MD Anderson Cancer Center, Houston, Texas, asked if there is already a 90% response after 2 cycles, wouldn't the 2 additional cycles not reduce the myeloma but increase PN? If so, then why not have induction with 2 to 3 cycles using a higher dose of bortezomib with faster response and lower total dose delivered? Dr. Moreau answered that the PR rate is 90% after 2 cycles, but their goal is not to achieve PR but to achieve VGPR or better, which is associated with a better outcome. Therefore, 2 additional cycles of induction (4 total cycles) are needed prior to ASCT, especially with low toxicity.

Dr. Joseph Mikhael, Mayo Clinic, Scottsdale, Arizona, said that this study is important in moving ahead to understanding the correct dose of these agents, including bortezomib. One option is to reduce the dose of bortezomib with twiceweekly administration of 1.0 mg/m², which gives a total dose of 4 mg/m² (vs. 5.3 mg/m² with twiceweekly doses of 1.3 mg/m²), or once-weekly bortezomib, as in the Italian study (with a total dose of about 4.5 mg/m²). In the long run, will the objective be once-weekly dosing with time between doses to reduce PN, or is it really a dose reduction? What was the total dose delivered compared with the planned dose? Dr. Moreau said that the answer is different in two different situations: one is in elderly patients where the goal is to keep patients on treatment for a long time with reduced side effects, so weekly bortezomib is favored. For patients going to ASCT, the goal is to lower the amount of myeloma cells as fast as possible with induction therapy, so twice-weekly bortezomib is preferable. Nearly all patients in this study received the planned dose of bortezomib from both treatments, except for the four patients who discontinued in the VD arm.

Dr. Ruben Niesvizky, New York Presbyterian Hospital-Cornell Campus, discussed sorting through the options for initial therapy of myeloma in light of abstract 8014 (as well as abstract 8013 in the section on non-transplanteligible patients).

Achieving a meaningful sustained response of at least VGPR has been shown to contribute to longterm survival in various phase II and III trials, and in the last several years 40% CR and over 70% VGPR have been achieved and will be the rates for comparing future studies. The Arkansas group has shown that in addition to high response rates, having a duration of response of at least 2 years also contributes to survival. Goals in myeloma therapy should be to achieve a response of at least VGPR, define maintenance regimens, and to understand how to combine proteasome inhibitors, IMiDs, steroids, and alkylating agents.

In the IFM2007-02 study, the effect of vTD is less than desirable before ASCT. There is a need to address the effect of IMiDs on stem cell harvest; Dr. Niesvizky suggested an alternative method of mobilizing and collecting stem cells, e.g., using Mozobil (plerixafor). The effect of reducing the dose of bortezomib is less PN, but the question remains whether the response rate can be improved for the 10% of patients who experience less than PR before ASCT. Dr. Niesvizky concluded that induction therapy must be improved to offer a VGPR or better of 70%. It not clear if the best approach is combination therapy or sequential therapy (one agent at a time). He cautioned about the benefit of weekly bortezomib; it is always used in combination with other anti-myeloma drugs, and the results may not apply to all settings. If a patient has high-risk disease, he hopes healthcare providers would use higher doses in a more intense fashion, that is, twice weekly.

Therapy for Non-Transplant Eligible Patients

Antonio Palumbo presented Abstract 8013 on behalf of Mario Boccadoro and the Italian Multiple Myeloma Network, GIMEMA: Bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) for initial treatment of elderly multiple myeloma patients.

This large randomized trial compared two approaches for treatment of patients who were older than age 65 years and not transplant eligible. The treatments included the four-drug approach of bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by bortezomib and thalidomide (VT) maintenance compared with what has been considered the best standard of care for elderly patients, the three-drug combination, bortezomib, melphalan, and prednisone (VMP) with no maintenance. The study also investigated the safety and efficacy of weekly bortezomib. The study included 511 patients with a median age of 71 years. The study began with twice-weekly bortezomib, but because the first 139 patients experienced neuropathy (PN) as a side effect, the schedule was modified to weekly bortezomib for patients receiving either treatment, and the dose of thalidomide was reduced to 50 mg per day for with patients treated VMPT. For VΤ maintenance, bortezomib was administered every other week.

Patients treated with VMPT followed by VT had a significantly longer time to next treatment and a significantly longer progression-free survival (PFS) after about two years of follow-up. The improvement in response was mostly in the CR rate, which contributes to increased survival. Most PR are seen by the first 5 to 6 months of treatment, but the majority of CR requires longer treatment, up to almost 1 year. Dr. Palumbo noted that PFS is usually around 2 years with the best current treatment, and the four-drug combination is increasing the probability of remission duration by a year. There was no difference in OS due to the short follow-up time. He stressed the concept that the issue is not a difference in survival but that probably the median OS will approach 6 years; for elderly patients this is a major improvement over the previous median survival of 3 years.

Serious side effects including reduced white and red blood cell counts and platelet counts were higher for the four drug combination of VMPT and were expected for a combination containing an alkylating agent and novel agents. Other side effects included PN, infections, and a higher risk of complications affecting the heart and more blood clots for patients receiving VMPT. Fewer patients discontinued the study than has been reported in the past for patients in this age group. The reduction from twice-weekly to once-weekly bortezomib did not decrease the CR rate or PFS compared with other studies. The risk of PN decreased from 14% to 2%, and the discontinuation rate decreased from 16% to 4%, which was attributed to the reduction in PN. The efficacy of the treatment was maintained because although patients received less bortezomib each week, they were able to stay on the study longer and therefore received more of the planned dose of the drug overall.

Dr. Palumbo concluded that today the best available treatment option for elderly patients is VMPT followed by VT maintenance. This combination significantly improves PFS in comparison with VMP. VMPT improves the response rate and PFS and increases the CR rate, with 90% of the improvement in CR rate occurring during the induction phase, and only 10% of the improvement in CR rate occurring during the maintenance phase. VT maintenance improves PFS (although the study didn't randomize for maintenance) and prolongs remission duration. Once-weekly bortezomib reduces PN with no change in efficacy, which is a major improvement in the safety profile of the VMPT combination.

Discussion

Dr. Jakubowiak and Dr. Harousseau both asked about how to separate the effects of induction from the effects of maintenance therapy. Dr. Palumbo replied that there is a question about how long to treat to increase the response rate. Maintenance does look important to increase the duration of response. There is a time period within which CR rate can be maximized. In this study, 9 cycles of therapy seems to be the right length because most of the CR rate occurred by 9 cycles.

Dr. Anderson commented that at ASH he showed that lenalidomide plus melphalan plus prednisone (MPR) followed by lenalidomide maintenance also gave good results, and wondered how to compare his study with VMPT followed by VT maintenance. He asked if it was possible to replace thalidomide here with lenalidomide. Dr. Palumbo responded that the major contribution of lenalidomide in the study of MPR followed by lenalidomide maintenance is as maintenance therapy, not induction therapy. If lenalidomide were substituted for thalidomide, he would be afraid that the side effect of decreased white blood cell counts would lower the efficacy of the fourdrug combination, which he also saw with MPR. This might explain the results in the EVOLUTION study in which the four-drug combination of bortezomib plus cyclophosphamide plus lenalidomide plus dexamethasone (VCRD) was not as good as the three-drug combination.

Dr. Barlogie asked a follow-up to Dr. Anderson's question. He wanted to know if maintenance could be replaced with bortezomib plus lenalidomide (VR), which should be feasible. Dr. Palumbo thought that VMP followed by lenalidomide maintenance could possibly be best. Dr. Barlogie wanted to challenge Dr. Palumbo's conclusions about the number of cycles needed to reach CR when it is defined in terms of M-protein levels. When response is measured by magnetic resonance imaging (MRI) to look for areas of remaining myeloma tumors in the bone, these tumors, known as focal lesions, may take 3 or 4 years to disappear. He believes that the proper techniques, e.g., particularly MRI or positron emission tomography (PET) scanning, should be used to measure CR over time. He proposed that a new yardstick, MRI-defined CR, should be developed. This lags 8 to 12 months behind immunofixation-negative CR (the point at which M-protein can no longer be detected in the blood). Dr. Palumbo agreed that CR in this study is defined by M-protein and plasma cell infiltration of the bone marrow, so more sophisticated ways to measure response could change the conclusion about the time to reach best response.

Dr. Ruben Niesvizky discussed abstract 8013.

In the older population the approach of induction followed by maintenance therapy using combination treatments has been effective. In the GIMEMA study, the VMP arm had no maintenance. Although the experimental arm meets the landmarks with CR of 38% and ORR of 89%, the design is biased because maintenance therapy is used in only one arm. The safety profile is good.

Dr. Noopur S. Raje, Massachusetts General Hospital, Boston, Massachusetts, presented 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 at the ASCO/ASH Joint Session, which was selected as an abstract of clinical relevance to clinical oncologists that had been presented at ASH 2009 (originally by Dr. Palumbo).

Dr. Raje, who was not involved in this trial, felt she gave an unbiased view about where MPR-R (lenalidomide added to melphalan plus prednisone followed by lenalidomide maintenance) fits in the treatment of patients with myeloma who are not transplant candidates. The primary comparison was MPR-R vs. melphalan plus prednisone (MP). A secondary comparison done at the request of the European Union regulatory agency, EMEA, of MPR-R vs. MPR for a stipulated 9 cycles, was to determine if lenalidomide maintenance would really make a difference in the treatment of patients at least age 65 years with newly diagnosed myeloma who were not eligible for a transplant. At the interim analysis, presented at ASH, there was a statistically significant difference between MPR-R vs. MP. The authors concluded that continuous lenalidomide is superior to regimens of shorter duration. They further concluded that MPR-R is superior to MP with higher and more rapid responses, a 50% reduced risk of progression, and a favorable safety profile; MPR-R should therefore be considered a new standard treatment option for elderly patients.

Dr. Raje discussed the strengths and limitations of this study. The strengths included that the regimen is given by mouth (orally) and fairly well tolerated, which is important for older patients, and other patients who are not eligible for transplant because they have other medical problems in addition to their myeloma disease. MPR-R offers a significant PFS advantage over MP, suggesting that lenalidomide maintenance may be a new standard. Limitations of the study include a short follow-up time, and the lack of difference seen among all three arms at 9.4 months for PFS. There is no difference in PFS between MP vs. MPR, and no difference in OS to date. Possible treatment for patients with myeloma who are not eligible for transplant currently includes combinations of thalidomide (T), bortezomib (B), and lenalidomide (R), as MPT, MPV, MPV-VT, Rd (lenalidomide with low dose dexamethasone), and MPR-R. MPT has been tested in the largest number of trials: responses in most studies are close to 60%, OS is 45 to 50 months, and the advantage of MPT vs. MP has been confirmed in an analysis combining several studies. Dr. Raje's overall conclusions are that MPR-R is certainly one additional possibility for the treatment of newly diagnosed patients with myeloma who are not eligible for transplant. The choice of therapy should be based on patient profile and therapyrelated side effects such as neuropathy, risk of clots, and kidney problems. The use of maintenance therapies in addition to antimyeloma therapy is showing some promise.

Discussion

Dr. Douglas Blayney, University of Michigan, Ann Arbor, Michigan, and ASCO president, observed that at this meeting lenalidomide maintenance does seem to be an emerging theme, but it is a toxic therapy, and it's interesting that there is no OS benefit. Dr. Raje responded that the follow-up of 9.4 months is short, and that those patients who did not receive lenalidomide at first did receive some of these new drugs later in the study. For patients with myeloma it's become incredibly difficult to see a survival benefit [when comparing newer treatment s] because of all of the treatment options available. In response to a follow-up question asking Dr. Raje what she recommended, she said she would take the patient profile into consideration. For an elderly patient who prefers an oral regimen, MPR is reasonable. For someone with severe kidney failure who needs rapid myeloma control, bortezomib makes sense. For maintenance therapy, results support using maintenance therapy even though there is no OS advantage. What will need to be done in the future is to divide patients into subgroups based

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on various risk factors and see if there is a subset of patients that benefits from therapy.

Bisphosphonates and Bone Disease

Gareth Morgan, Institute of Cancer Research, Royal Marsden NHS Foundation Trust, London, United Kingdom, presented Abstract 8021 -Evaluating the effects of zoledronic acid on overall survival in patients with multiple myeloma: results of the Medical Research Council (MRC) Myeloma IX Study.

This study is a randomized comparison of zoledronic acid (Zometa) vs. clodronate (Clasteon, which is not available in the US, but is available in Canada and in the UK where this study was done). An important observation is that myeloma cells are in close contact with stromal cells in the bone marrow. Interactions between osteoclasts, cells that break down bone, and osteoblasts, cells that form bone, contribute to the survival of myeloma cells. Treatment that affects these interactions may be beneficial. The objective of this trial was to ask the question, "Can bonetargeted therapy improve survival in patients with multiple myeloma?" Studies in myeloma cells and in mouse models of myeloma suggest that bisphosphonates, the class of drug that includes zoledronic acid and clodronate, may have antimyeloma effects.

The MRC Myeloma IX trial design enrolled 1960 patients receiving either intensive (transplant) or non-intensive therapy. Within each therapy group patients were randomly assigned to either zoledronic acid or clodronate until disease progression. The basic conclusion is that zoledronic acid improved OS by about 5.5 months, which is both clinically and statistically significant. Zoledronic acid significantly reduced the relative risk of death vs. clodronate, and significantly reduced skeletal related events (SRE), such as broken bones. The survival benefit was not due to prevention of SREs, but is an anti-myeloma effect. In analyzing side effects over both intensive and non-intensive therapies, there were no differences between the two bisphosphonates for acute kidney failure, blood clots, or infections. However, zoledronic acid was associated with an increased incidence of osteonecrosis of the jaw (ONJ), but it was at the rate of 3.6% vs. 0.3% rate of ONJ with clodronate. ONJ associated with zoledronic acid tended to heal on its own without surgery. After a median follow-up of 3.7 years, zoledronic acid significantly prolonged OS and PFS and significantly reduced the proportion of patients with SRE compared with clodronate. Both bisphosphonates were generally well tolerated with expected side effects. Zoledronic acid might work by directly causing myeloma cells to die, adding on to the effects of chemotherapy, and breaking the loop between osteoblasts and stromal cells. This is not isolated to myeloma, because there is evidence in other cancer types that zoledronic acid prolongs survival.

Dr. Morgan concluded that zoledronic acid is superior to clodronate for the prevention of SRE in patients with newly diagnosed myeloma. Adding zoledronic acid to standard anti-myeloma therapy is generally well tolerated and prolongs OS vs. clodronate, and the survival benefit is independent of SRE reduction. These results further support the anti-cancer activity of zoledronic acid and provide evidence that it should be considered for early addition to treatments for patients with newly diagnosed myeloma.

Discussion

In response to questions, Dr. Morgan said that 70% of patients had bone disease at the time they entered the study, and the benefit of zoledronic acid on SRE and OS was seen in patients with or without bone disease. They expect by next ASH to have results comparing older and younger patients and patients in CR vs. those not in CR. There seems to be an increased VGPR rate in the elderly patients, suggesting an anti-myeloma effect. Dr. Morgan said in his opinion he thought it would be best to continue zoledronic acid beyond disease progression, but they didn't collect those results. The doses of zoledronic acid and clodronate used in this study have an anti-myeloma effect and are safe, but giving them more frequently, e.g., every 2 weeks, might not be justifiable because of side effects. Dr. Morgan said he thinks zoledronic acid is the new standard of care for patients with myeloma.

During a discussion of the Education Session on Complications of Myeloma and Myeloma Therapies, session chair Dr. Todd Zimmerman asked Dr. David Roodman, University of Pennsylvania, Pittsburgh, Pittsburgh, who reviewed myeloma bone disease, about the MRC IX trial that included patients with non-lytic bone disease, that is, patients whose bones don't show the thinned areas on X-ray typical of myeloma bone destruction. Treatment of patients with nonlytic bone disease is not a typical practice according to ASCO guidelines, so he wanted to know what the approach would be for patients with osteopenia (general reduction of bone density) but not overt lytic bone disease. Dr. Roodman replied that previously the ASCO guidelines clear were on not giving bisphosphonates unless the patient had diffuse osteopenia or documented bone disease. In the MRC trial, 20% or 25% of those patients had no bone disease. Dr. Morgan reported that those patients had prolonged OS, like those patients who did have bone disease. This is an exciting result, similar to the situation in patients with breast cancer where bisphosphonates, particularly zoledronic acid, are considered as adjuvant therapy in patients on aromatase (hormone) therapy. Dr. Roodman said he thinks there is a need to see the published results and see what the comments by the reviewers are before everyone is treated with bisphosphonates, because they do have side effects, although small. No one knows how long to treat with bisphosphonates.

Dr. Richardson added that in patients with smoldering myeloma (SMM), there have been randomized trials looking at bisphosphonates, and a fact that is not well appreciated is that there is a significant reduction of time to first SRE. In their group, for patients with SMM and osteopenia, they are comfortable using periodic infusions of bisphosphonates. Dr. Roodman replied that patients with MGUS have an increased fracture risk, but they have osteoporosis (significantly decreased overall bone density) not myeloma bone disease, so they should be treated like patients with osteoporosis, e.g., with oral bisphosphonates. He also pointed out that patients should have their vitamin D levels checked because studies have shown that up to 60% to 70% of patients with myeloma at diagnosis are vitamin D-deficient, so replenishing vitamin D is important when treating myeloma bone disease. The question is how much vitamin D to give? The NIH is expected to provide new recommendations on supplementation. Now there are no good recommendations. The zoledronic acid prescribing information says to give patients calcium and vitamin D unless their calcium levels are abnormally high. Dr. Roodman pointed out that the current ASCO guidelines suggest to treat for two years, re-evaluate the patient, and consider stopping zoledronic acid if the myeloma is in CR or plateau, and to continue treatment if there is active disease. Other guidelines exist. Information from other cancers suggests that if treatment with zoledronic acid continues beyond two years, patients will continue to benefit. The question is how long to continue, and there is a question about whether measuring bone resorption markers is useful. In a review of all trials of zoledronic acid, the response isn't maximized, because the bone can take up large, possibly unlimited, quantities of bisphosphonates. There is now a concern about unusual fractures associated with bisphosphonates, the cause of which is not clear. Dr. Richardson commented that patients in the MRC trial were taking bisphosphonates for more than four or five years.

Dr. Roodman said that the incidence of ONJ has increased over the last five years in step with the increased use of zoledronic acid over pamidronate,

another bisphosphonate. Patients who receive pamidronate plus zoledronic acid are more likely to get ONJ than those who receive pamidronate alone. Novartis makes both drugs and the company reports that after reviewing 3 million patients, the incidence of ONJ is no higher with zoledronic acid than with pamidronate, but Dr. Roodman said to remember the source is the company producing both drugs. He thinks that the more active the bisphosphonate, the higher the risk of ONJ. However, the incidence has fallen dramatically with current recommendations for preventive dental care, dental hygiene, and followup at least in patients with breast cancer, and possibly with myeloma. He used to see ONJ once a month in his clinic, but hasn't seen any in the last two years with rigorous monitoring. Dr. Richardson agreed that there has been a dramatic reduction in ONJ in his practice. The dental expert he collaborates with believes the reduction could be due to the more widespread use of bortezomib, which activates osteoblasts. This needs to be proven, but it is interesting. Dr. Roodman replied that the change in incidence of ONJ in patients with breast cancer, who don't receive bortezomib, is the same, and probably the result of better dental hygiene.

A participant pointed out that results suggest that pamidronate and zoledronic acid are equally effective, so he wondered why zoledronic acid is being discussed rather than pamidronate, which is available at lower cost. Dr. Roodman replied that it was a valid question because pamidronate is now generic. Zoledronic acid is given in a 15-minute infusion. Pamidronate requires two hours to administer, not including the time patients need to add to get to the clinic, check in, start the I.V., etc., increasing the total time to 6 hours, so the choice is mostly patient convenience. However, now there is evidence from both the MRC trial and in breast cancer that zoledronic acid has the potential for anti-tumor activity, which has never been reported for pamidronate, although he would like to review the results to confirm this. That suggests an additional reason to give zoledronic

acid over pamidronate. Dr. Richardson mentioned the IFM study giving pamidronate with thalidomide as maintenance therapy. This large randomized trial showed no evidence of survival benefit, which provides additional support for zoledronic acid over pamidronate.

Risk Factors

Dr. Orlowski discussed 1q21 amplification as a poor-risk feature as presented in posters, Abstracts 8027 and 8028.

Abstract 8027, first author Dr. John Shaughnessy, University of Arkansas Medical Center, Little Rock, Arkansas, was titled Outcome with Total Therapy 3 (TT3) compared to Total Therapy 2 (TT2): role of gene expression profiling (GEP) 70gene array-defined high-risk disease with trisomy of 1q21 and activation of the proteasome gene PSMD4. Amplification of 1q21 has already been shown to be a poor prognostic factor. A lower copy number of 1q21 is associated with a better outcome (EFS and OS). Bortezomib neutralizes the effects of 3 copies but not 4 copies. This study looked at what genes in the 1q21 region might be conferring the high-risk feature and there are some interesting genes with respect to myeloma in the region, including PSMD4. PSMD4 expression is sensitive to 1q21 copy number, and may be a marker for the proteasome inhibitor bortezomib in myeloma. PSMD4 (S5a) may be involved in proteasome function. This needs further study, along with the roles of the other genes in the region.

Abstract 8028, first author Dr. David Joshua, Royal Prince Alfred Hospital, Sydney, Australia, was titled Response of newly diagnosed myeloma with 1q21 amplification to bortezomib-based PAD induction therapy. To overcome 1q21 amplification as a poor-risk feature, PAD (bortezomib plus doxorubicin plus dexamethasone) was tested in a phase II study in newly diagnosed patients who were eligible for stem cell transplants. There was a good response rate independent of 1q21 amplification despite the subgroup with 1q21 amplification containing more patients with higher ISS stage disease, so bortezomib may be preferred as an induction regimen. Follow-up is needed to see if this translates into a PFS and survival benefit.

Dr. Bart Barlogie presented Abstract 8019, Defining the prognostic variables in gene expression profiling (GEP)-defined high-risk multiple myeloma (MM): distinguishing early failures (EF) from sustained control (SC).

Dr. Shaughnessy's GEP 70-gene risk model reidentified and repeatedly validated that the 85% of patients with low-risk disease had a superior EFS and OS with TT2, whereas the 15% of patients with high risk had a median survival of only 2 years. For TT3, at 6 years 90% of patients are alive and event free, but the high-risk population shows a median survival of only 2.5 years, with a subsequent plateau emerging. His impression is that as new agents have progressively been introduced along with new concepts of consolidation and maintenance therapy, the major beneficiary has been the low-risk population, not the high-risk population.

The curves of OS and EFS (Kaplan-Meier curves) show a breakpoint for patients with high-risk disease at 3 years. The curve is steeper before the breakpoint, which Dr. Barlogie calls "early failures" (EF), and declines after that point less steeply to a plateau-like phase that he calls "sustained control" (SC). This presentation looked at what distinguishes EF from SC for patients with high-risk disease. The objectives are now to determine, among the 15% patients with high-risk disease enrolled in TT2 and TT3 who had gene array data (most of the patients in TT3), if EF and SC subsets can be distinguished at entry into the study by either standard risk factors or GEP of plasma cells. Biopsy samples are also available to look at the bone marrow. The ultimate goal is to define genes for EF and SC and find new targets of therapy.

EF and SC subgroups of 123 patients with highrisk disease in TT2 and TT3 were identified and GEP and standard tests were performed. There were no differences between the two groups in standards tests such as B2M, albumin, lactate dehydrogenase (LDH), and cytogenetic (chromosome) abnormalities. However, there were differences between EF and SC subgroups in the GEP median score. There are 14 genes that distinguish the EF and SC subgroups. The expression of 6 are increased and 8 are decreased. Among the genes with decreased expression are one involved in bone disease, one that controls cell division, and one involved in B-cell development. Among the genes with increased expression is one involved cell death. The Arkansas group has performed GEP analysis at study entry, and after single-agent therapy, e.g. before and after thalidomide-dexamethasone in TT2, and 48 hours after single-agent bortezomib in TT3, and they are now also doing GEP after high dose melphalan (MEL) in TT4 and TT5. One of the interesting genes involved in cell death, when low before treatment, was increased after bortezomib, VTD-PACE, or MEL.

In conclusion, Dr. Barlogie said that compared with SC, EF is characterized by higher GEP70 risk scores ("super risk") among other abnormalities. Among 14 EF- vs. SC-discriminating genes, one is of particular interest, because over-expression in SC is linked to cell death and better clinical outcome. This gene is rapidly increased by melphalan and bortezomib in patients with low levels of expression. Therefore, it is not only a marker, but a therapeutic target. Issues under study include the development of a "super highrisk" model; examination of the potential for super high risk among patients who seem to have lowrisk myeloma but who do poorly, and the role of the model in predicting survival after relapse. They are also planning to examine the super highrisk-associated genes in the setting of molecular subgroups; and to determine the features of EF vs. SC that are unique to the bone marrow environment. In addition, they want to examine how anti-myeloma agents like MEL and bortezomib affect super high-risk genes to restore myeloma cell sensitivity these agents.

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