

ASCO 2010 Highlights for Physicians



Compiled by Lynne Lederman, PhD

This publication is sponsored by unrestricted educational grants from Celgene Corporation and Onyx Pharmaceuticals.

ASCO 2010: Myeloma Highlights for Physicians

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 management of older patients with lymphoma and myeloma and complications of myeloma and myeloma therapies. The clinical science symposium addressed novel therapies for myeloma. The lymphoma and plasma cell disorders poster discussion addressed personalized therapy and new agents in myeloma, and included two main themes: 1) improving on the efficacy of lenalidomide with or without dexamethasone, especially in the relapsed/refractory setting, 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 anti-myeloma agents
- The role of transplant in the era of novel agents
- Identification of risk factors
- Anti-myeloma effects of zoledronic acid
- Identification of erythropoietin receptors on myeloma cells

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 ASCT alone results in cytoreduction, but not cure, for most patients with myeloma. CALGB 100104 included patients younger than age 70 years who were treated with at least 2 months of induction therapy to which they had a response of at least stable disease (SD), were 1 year or less from the start of therapy, and who 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. Those who had a response of SD or better were randomly assigned to placebo or to lenalidomide at 10 mg per day, which could be increased to 15 mg/day or decreased to 5 mg/day as tolerated. Patients were stratified by beta 2 microglobulin (B2M) and use of lenalidomide in induction therapy. The objectives were to determine if lenalidomide prolonged time to progression (TTP) following ASCT. The study was powered to detect prolongation of TTP from 24 months to 33.6 months. Secondary objectives included the complete remission (CR) rate post-ASCT, progression-free survival (PFS), overall survival (OS), and the feasibility of long-term administration of lenalidomide.

The accrual target was to register 538 patients with a goal of randomly assigning 462 patients based on an estimated 10% dropout rate; however, the actual dropout rate before randomization was 15%. Enrollment was slow until after the BMT CTN 0102 cooperative group study closed, after which time accrual was more rapid. This demonstrates that having two cooperative group studies open at the same time competing for patients is not ideal. Results were analyzed in November of 2009 for 201 patients randomly assigned to lenalidomide and 208 randomly assigned to placebo (n=418).

An analysis of adverse events (AE) for 368 of 418 randomized patients during the maintenance phase receiving lenalidomide (n=194) vs. placebo (n=174) show significantly

more grade 3 and 4 hematologic toxicities with lenalidomide, and more grade 3 non-hematologic toxicities, but no difference in grade 4 and 5 non-hematologic AE. (Note that the abstract showed AE from ASCT, and transplant overwhelmed the AE and the difference between the arms). The most common and significant AE with lenalidomide were neutropenia, and to a lesser extent thrombocytopenia, and anemia; the only other significantly higher AE in the lenalidomide arm was documented infection. Discontinuation due to AE was 13% for lenalidomide vs. 2% for placebo, and 12% vs. 7% for other reasons.

From day 0 of ASCT, 29 of the 210 patients on lenalidomide and 58 of the 208 patients on placebo experienced disease progression or death (an event), a difference which is statistically significant. At a median follow-up of 12 months, there was a 58% reduction in TTP with lenalidomide. TTP was not reached with lenalidomide vs. a TTP of 25.5 months with placebo. The follow-up is not long enough to determine a difference in OS. The study was unblinded in December, 2009, to allow cross-over with physician support to open-label lenalidomide. Patients were stratified by B2M and prior thalidomide and lenalidomide; patients in each stratification who received lenalidomide maintenance fared better. For patients who received prior thalidomide, the benefit of lenalidomide maintenance was not seen early on, but developed 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 within stratification by high B2M, and prior thalidomide or lenalidomide induction therapy. Lenalidomide maintenance therapy produced some hematologic toxicity but this was not severe, given that the discontinuation due to AE was 13%.

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

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

Residual disease is always present after single or double ASCT, and is responsible for relapse. The ideal maintenance regimen is not known, but what is known is that maintenance with conventional chemotherapy, interferon, or

corticosteroids is not effective. Thalidomide maintenance after ASCT increases the CR rate, event-free survival (EFS) or PFS, and OS. In the IFM 99-02 trial, no benefit for thalidomide was seen if deletion 13 (del 13) was present or if the response was a very good partial response (VGPR) or better after ASCT, suggesting 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. So the rationale for the IFM 2005-02 phase III randomized trial was to determine if lenalidomide could be safe and effective when administered for a long time, given its convenience as an oral agent known to be active in patients for whom HD therapy had failed, and its lack of strong association with PN.

IFM 2005-02 enrolled 614 patients younger than age 65 years with non-progressive disease within 6 months of ASCT as frontline therapy. After stratification according to risk factors and response, patients received 2 months of consolidation with 25 mg/day of lenalidomide, then were randomly assigned to either placebo or 10 to 15 mg/day lenalidomide (n=307 in each arm). The primary endpoint was PFS; the secondary endpoints were CR rate, TTP, OS, and feasibility of long-term lenalidomide therapy. Of the 614 patients, 572 received consolidation. The first interim analysis was in December, 2009, with a median follow-up of 24 months (34 months post-diagnosis and random assignment), after which the independent data monitoring committee recommended unblinding of the study. The median age for both groups was 55 years, and the two arms were comparable in all demographic and disease characteristics.

There was a significant increase in response after lenalidomide consolidation in the CR rates (from 13% to 19%) and VGPR (from 58% to 68%) for the 572 patients. For the intent-to-treat (ITT) population, the best response improved for patients receiving lenalidomide maintenance, but the change was not statistically significant. Lenalidomide maintenance did improve the median PFS, which was 24 months for the placebo arm but was not reached in the lenalidomide arm. Three years post-random assignment (which equals 4 years post-diagnosis), the PFS was 34% in the placebo arm vs. 68% in the lenalidomide arm, which is statistically significant. The benefit of lenalidomide maintenance was observed in all stratified subgroups of patients, including pre-consolidation response, whether partial response (PR) or SD, or VGPR or better; high or low B2M levels; presence

or not of del 13; and VAD (vincristine Adriamycin dexamethasone) vs. VD [bortezomib (VELCADE) dexamethasone] induction regimen. Two prognostic factors were associated with longer PFS in a multivariate analysis: lenalidomide maintenance, and a response of VGPR or better after ASCT or consolidation. Therefore, a response of VGPR or better remains an important prognostic factor even with effective maintenance therapy.

Lenalidomide maintenance was well tolerated. The discontinuation rates and AE were similar between arms during maintenance. Neutropenia was higher with lenalidomide but there was no increased risk of febrile neutropenia. The rates of deep vein thrombosis (DVT) and PN were similar in both arms and were low. The OS at 3 years from random assignment (4 years post-diagnosis) was 80% for placebo vs. 88% for lenalidomide, which is not significant. Dr. Attal said these survival rates are unprecedented compared with results from all previous IFM trials.

Dr. Attal concluded that maintenance with lenalidomide was well tolerated, resulted in a low discontinuation rate due to severe AE, and caused no increased risk of DVT or PN. Lenalidomide maintenance is highly effective in reducing the risk of progression in all stratification subgroups, with an overall 54% reduced risk, although longer follow-up is required to appreciate the impact of lenalidomide on OS. The final analysis of this trial is expected in August, 2010.

Discussion

Post-presentation Q&A

Dr. Antonio Palumbo, University of Turin, Ospedale Molinette, Turin, Italy, observed that in the CALGB trial, the grade 3 and 4 neutropenia was 50% and thrombocytopenia was 10%. In the IFM trial, the AE profile was much better, and he asked why there was a discrepancy. Dr. Attal said he didn't know and would have expected neutropenia to be higher than in the CALGB trial because of the 2-month consolidation phase, and neutropenia occurs in the first month of maintenance mainly due to consolidation. He has no explanation for why it is 31% (7% grade 4) in the IFM trial. The rate of grade 3 and 4 thrombocytopenia is 8% (3% grade 4).

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 practice-changing presentations in myeloma in the last couple of years. The question is now what to do in the clinic based on the data 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 cytoreduce but not cure most myeloma. He thinks maintenance therapy should be called "post-transplant continuous therapy." Post-transplant therapy is active treatment, as it implies further reduction of disease burden, may involve more effective drugs, and is not envisioned 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 toxicity is 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 in the subset analysis is that the benefit of lenalidomide is seen regardless of the response to transplant. Lenalidomide maintenance abrogates the effects of del 13. The response after consolidation is the most important prognostic factor. The most important side effect is neutropenia, and it will be interesting to see why this was significantly lower than in the CALGB trial results 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 observation.

The CALGB study also showed that the PFS was better with lenalidomide maintenance, with no benefit for OS. The important subanalysis from this trial showed that the benefit of lenalidomide is seen regardless of the use for induction of thalidomide or lenalidomide, which is becoming the standard in the U.S.. Neutropenia was a significant side effect, occurring in 42% of patients (grade 3 to 5). Because there

was a significant increase in febrile neutropenia, this therapy should be monitored when it is used in the community to prevent severe toxicities, such as sepsis.

If the goal of treatment is to delay progression, patients should probably receive lenalidomide maintenance whether they are in stringent CR after ASCT, or show residual disease after ASCT, although they may not live longer with maintenance. Other important questions to answer include what is the role of consolidation post-transplant, given the good responses seen after Total Therapy 2 (TT2) and TT3; how long should maintenance be given; and what is the role of transplantation in the era of novel therapies?

The next trial after CALGB 100104 has been planned. BMT CTN 0702 StAMINA is a trial of single ASCT with or without RVD consolidation vs. tandem transplant and maintenance therapy in 750 patients. It has been designed 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 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 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, and an OS benefit may not be seen due to cross over. There is a lenalidomide benefit regardless of B2M, cytogenetics, 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 intervention, 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. Andrzej J. Jakubowiak, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan suggested two additional questions: how to view previously published results of thalidomide maintenance, and how to view bortezomib (VELCADE) plus thalidomide (VT) maintenance vs. maintenance with an immunomodulatory drug (IMiD) alone. Dr. Giralt said consideration of thalidomide maintenance is essential for the global community, because thalidomide is what will be accessible in the developing world. The role of VT, which could be a better treatment, should be answered in the context of a randomized trial. The best

post-transplant therapy is an open question. There are at least two agents that have been shown to improve PFS, and both are IMiDs. Bortezomib data suggest it plays a role in further reduction of tumor burden and PFS improvement. A good measure for tumor burden, e.g., PCR (polymerase chain reaction – do we need to clarify this, or will physicians know without explanation?), would be helpful, and disease reduction could then be quantified as a threshold to determine rationally whether to administer maintenance therapy or not.

Someone asked what Dr. Giralt would do in his practice following this meeting. Dr. Giralt said that when the study report came out, they had to contact patients on placebo. If those patients had low-risk disease and were in CR, he recommended they not go on lenalidomide maintenance. If they had high-risk disease and were on placebo and their disease had not relapsed, he recommended they go on lenalidomide maintenance. Most patients are on study, so they follow the protocol. For those patients off study, if there is any evidence of residual disease post-ASCT, he recommends they go on lenalidomide 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 tumor mass and low-risk disease, the possibility of maintenance or not can be discussed. For patients on thalidomide maintenance who tolerate it well, he wouldn't switch IMiDs.

Additional Discussion of Maintenance Therapy

Dr. Jean-Luc Harousseau, MD, Rene Gauducheau Cancer Center, Nantes, France, discussed the CALGB and IFM studies during one of the Highlights of the Day sessions.

Four published randomized studies show a benefit for thalidomide after ASCT, including an increase in CR/VGPR rates and prolongation of PFS in all four, and prolongation of OS in three. However, thalidomide maintenance has never been considered the standard of care because the optimal dose and duration of therapy are not known, nor is the ability to determine which patients would benefit, and prolonged treatment results in toxicity, especially PN.

In both the CALGB and IFM trials, lenalidomide maintenance improves PFS when compared with placebo across different prognostic subgroups, including beta 2 microglobulin for both; del 13 in the IFM trial, the type of induction therapy (VAD/VD for IFM, prior thalidomide or lenalidomide or not

for CALGB), and response to induction (CR or VGPR/PR) for IFM. There was a significantly prolonged PFS in both trials across different prognostic subgroups. Except for neutropenia (with very rare incidence of infections) low-dose lenalidomide was well tolerated. Due to the short follow-up there is no difference as yet in OS curves between maintenance therapy and placebo. We also know that low-dose lenalidomide also prolongs PFS after induction treatment in elderly patients, who are not transplant eligible, as shown in the MM015 study presented by Dr. Palumbo at ASH and also discussed at this meeting by Dr. Raje at the joint ASCO/ASH session (which is summarized in the section below on therapy for non-transplant eligible patients). He concluded that lenalidomide maintenance might become a new standard of care.

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 of anti-myeloma agents, e.g., proteasome inhibitor and IMiD, and others represent classes that may have been approved in other malignancies, e.g., histone deacetylase (HDAC) inhibitors, mTOR (mammalian target of rapamycin) inhibitors, and monoclonal antibodies (mAbs).

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 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) assessed response rates (RR) and toxicity. Patients received 2 mg pomalidomide continuously every day, 40 mg dexamethasone once a week, and 325 mg aspirin daily, although investigators could administer full-dose anticoagulant at their discretion. 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 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 AE, primarily neutropenia. The median follow-up was 5 months, at which time 66% of patients experienced no progression.

Neutropenia was the major grade 3 or 4 hematologic toxicity in 34% of patients; non-hematologic toxicities were not common, and included one thromboembolic event. Neuropathy occurred in 5 patients (14%) with 3% grade 1 and 11% grade 2. Four of the five patients had neuropathy at baseline that worsened with treatment.

The RR of confirmed PR or better was 26%, and of minimal response (MR) or better was 54%. Best response by mSMART was 47% in the high-risk group vs. 54% in the whole cohort, which was not significant. Nine patients received an increased dose per protocol; of these, one had an increased response from SD to MR, and the rest had SD. 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, and 58% of patients had a PFS of 6 months. The OS at 6 months was 86%.

Dr. Lacy concluded that the pomalidomide plus dexamethasone regimen had significant activity in lenalidomide- and bortezomib-refractory myeloma. Responses were rapid. Toxicity was manageable and consisted primarily of neutropenia. 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. standard-risk disease. Dr. Harousseau asked if they looked for deletion 17p. Dr. Lacy said that they don't have data on that, but in the initial cohort, the response was high, about 70% to 80%.

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 pre-clinical studies.

PX-171-004 enrolled 155 patients with relapsed or refractory myeloma following 1 to 3 prior treatment regimens. Cohort 1 received a dose of carfilzomib of 20 mg/m²; this cohort was divided into bortezomib-treated (n=36) vs. naïve (n=59) patients; cohort 2 (n=60) received a dose of 20 mg/m² in cycle 1 that was escalated to 27 mg/m² in subsequent cycles, and included only bortezomib-naïve patients. In all, 140 patients were evaluable for efficacy. At baseline,

most patients had anemia and neutropenia and nearly half had thrombocytopenia and PN. The results are summarized in Table 1. ORR = overall response rate; clinical benefit response (CBR) was defined as at least MR.

There was grade 1 to 2 neuropathy at baseline in nearly half of the patients. Treatment-emergent neuropathy grade 1 and 2 occurred in 12% to 17% of patients, grade 3 was 0 to 3%, depending on treatment group, and there was no grade 4 PN. PN rates were highest in the bortezomib-treated patients. One of the patients in the bortezomib-treated arm discontinued due to PN. Fatigue, nausea, dyspnea, and cytopenias were among the common AE, were mostly grade 1 or 2, and were manageable. 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 bortezomib-naïve patients, with durable responses in all three treatment groups. Preliminary data suggest higher response rates with higher doses. AE 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 toxicities suggests that carfilzomib is suitable for use in combination therapy regimens, and combinations are being tested. The 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.

Table 1. Results of PX-171-004, single agent carfilzomib

	cohort 1 bortezomib-treated (n=34)	cohort 1 bortezomib-naïve (n=53), 20 mg/m ²	cohort 2 bortezomib-naïve (n=53) 20/27 mg/m ²
ORR	21%	45%	55%
CBR	33%	58%	62%
median TTP	8.1 months	8.3 months	11.2 months
median DOR for patients with at least MR	8.5 months	8.3 months	11.5 months
median DOR for patients with at least PR	11.5 months	10.2 months	11.5 months

Discussion

A participant pointed out that in bortezomib-resistant disease, the responses are lower but the TTP is equal to that in bortezomib-responsive disease, and asked why there was a discrepancy. 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. As a follow-up, a participant asked if the discrepancy was due to definitions responses. Dr. Vij pointed out that the time to next therapy (TTNT) is a more valuable endpoint, and the requirement for salvage treatment is prolonged whether the response was MR or PR. Patients with MR have a survival advantage over patients who don't respond at all based on APEX trial data.

Someone asked why, given the mild toxicity profile and the escalating responses observed with increasing doses, the dose was not increased beyond 27 mg/m². Dr. Vij said that in phase I trials, two different regimens were tested. What was thought to have been associated renal toxicity could also have been toxicity associated with tumor lysis syndrome, sepsis, 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 toxicity profile that is no different from that associated 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, an 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 treatment-related deaths and no maximum tolerated dose (MTD) reported. A phase II study is planned.

Discussion

Dr. Robert Orłowski, 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 Mateos study of combination panobinostat, which is discussed below. Of the 31 patients, 84% had prior thalidomide and/or lenalidomide, 87% demonstrated at least SD, i.e., clinical benefit, and the ITT response rate of at least PR in 52% of patients is encouraging. Responses in lenalidomide-exposed patients and in lenalidomide-refractory disease 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 has limited activity as a single agent, so it is being tested in combination regimens.

The LBH589B2207 dose escalation study enrolled 47 patients with relapsed or relapsed and refractory myeloma. Panobinostat was administered three times a week every week, bortezomib was administered on the "classic" schedule for 2 weeks on and 1 week off, and dexamethasone was administered on the day of and the day after bortezomib. The MTD was considered to be 20 mg panobinostat 3 times a week with 1.3 mg/m² bortezomib. Cohort 3 (n=8) and an expansion cohort 6 (n=9) received these doses.

AE included a high rate of grade 3 and 4 thrombocytopenia that was manageable with dose modification and/or platelet transfusions, and other cytopenias. The non-hematologic AE were primarily GI-related, as well as fatigue and asthenia, and were mostly grade 1 and 2. The combination was associated with minimal grade 3 and 4 PN (4%), and there was no dose-related QT prolongation, which has been reported with HDACs.

Responses were seen even at the lowest doses, with a CR in cohort 2. CBR was seen in 76% of the combined cohort 3 and expansion cohort 6. For all 47 patients the ORR was 70%; in bortezomib-refractory disease (n=15) the ORR was 60%. Median duration on study because of HDAC inhibitor side effects for cohort 3 and 6 was an average of 3 months (it was less for all other cohorts), although one patient has been on therapy for 1.5 years.

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 MTD (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 every-other-day schedule to the 46 patients enrolled. Patients with primary refractory myeloma were excluded, although 54% of patients were refractory to last line of therapy; only 17% of them had prior lenalidomide. There was a 48% response of at least MR, which includes 7 VGPR, 2 CR, and 1 sCR, but none of these were in patients in the lenalidomide-refractory group.

Hematologic AE were commonly observed, with about half of patients experiencing grade 3 or 4 neutropenia and thrombocytopenia. There were 7 deaths, three of which were suspected of being treatment-related; 10 patients discontinued due to AE. 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 BTZ-refractory 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 humanized IgG1 mAb targeting CS1, a cell surface glycoprotein that is highly and uniformly expressed on myeloma cells, with restricted expression on natural killer (NK) cells, and little or no expression on normal tissues. Preclinical data suggest the mechanism of action (MOA) is mainly through NK-mediated antibody-dependent cell-mediated cytotoxicity. As a single agent it has a safety profile not dissimilar to that of other mAbs, with AE being primarily infusion-related reactions, and with responses mostly SD. Preclinical combination studies showed synergism with lenalidomide.

The study objectives for the phase Ib portion were to determine the MTD 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 optimize the premedication regimen in 60 additional patients with advanced disease; 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 low-dose dexamethasone. For the first 2 weeks, elotuzumab was dosed weekly; subsequently it was dosed every other week until progression. 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 dose-limiting toxicities (DLT). The AE were similar to those seen in lenalidomide trials except for infusion reactions thought to be attributable to elotuzumab, which occurred in 2 patients. The ORR was 82% for all 28 evaluable patients and 95% for the 21 lenalidomide-naïve patients; VGPR rates were 25% and 27%. Responses are improved over those reported at ASH, and are relatively independent of prior exposure to lenalidomide, thalidomide or bortezomib. TTP was not reached

at a follow-up of a median of 8 months. After initiation of a new premedication regimen including H2 blockers and other agents, 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 cohort show complete target saturation of CS1 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 toxicities over what is seen with lenalidomide and low-dose dexamethasone other than infusion reactions. The phase II expansion is ongoing to identify the optimal dose of elotuzumab in this combination.

Discussion

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

Dr. Michael Bishop (NCI) asked why dexamethasone was included if steroids inhibit the immune response by reducing NK cells, and part of the MOA of elotuzumab is to enhance NK activity. Dr. Lonial replied that inclusion of dexamethasone was due to practical issues. There is concern about down-regulation of NK cell number in the context of lenalidomide plus dexamethasone. Dexamethasone was not incorporated in the preclinical model, as Dr. Bishop noted. The effects on NK cells in the phase II expansion trial are being evaluated, but data 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 MTD

of elotuzumab in combination with bortezomib, determining safety and tolerability, and evaluating efficacy and immunogenicity. Elotuzumab was infused on days 1 and 11, bortezomib was given at the standard dose and regimen. DLT were assessed after cycle 1; elotuzumab only was dose escalated 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 escalation phase, and there were no DLTs in the dose-escalation phase; 13 patients were added at the expansion phase at an MTD of 20 mg/kg for elotuzumab.

The AE were mostly mild, with the most common grade 3 and 4 events being lymphopenia, fatigue, thrombocytopenia, hyperglycemia, neutropenia, pneumonia, and anemia. The elotuzumab-related AE were mostly mild and were mostly infusion-related reactions. There were two elotuzumab-related serious AE, chest pain and gastroenteritis. The best confirmed responses in 27 evaluable patients by EBMT criteria (with which the study was designed) were PR or better of 48% and MR or better of 63%. The responses using modified Uniform Modified Criteria were slightly higher. There were responses seen 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 bortezomib-naïve patients (n=16).

Dr. Jakubowiak concluded that the combination was well tolerated. MTD was not reached at doses up to the planned maximum dose of 20 mg/kg, and the key toxicities attributable to elotuzumab were infusion reactions. The RR, including responses in bortezomib-refractory disease, and the median TTP of 9.5 months are encouraging. Saturation of the CS1 target on myeloma cells occurs at doses of 10 mg/kg and 20 mg/kg. There may be synergism between elotuzumab and bortezomib that will be investigated in further studies.

Discussion

A participant noted that given that bortezomib is at least additive to or synergistic with anti-CD20 mAb 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.

Someone asked if they looked at the kinetics in combination with bortezomib. Dr. Jakubowiak answered that one objective in this study was to look at NK cells from the bone marrow of these patients, which is still ongoing. Synergy was very clear in preclinical studies, more so than what has been seen in this clinical study, so they may find reasons for the additive effect not being as pronounced in these patients.

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 inhibitor that does not have single-agent activity in myeloma, to create a non-steroid-containing regimen. The phase I trial was conducted to assess toxicity and determine the MTD as primary objectives, and to determine activity of the combination as a secondary objective. Both drugs were dose-escalated and given for 21 days of a 28-day cycle until disease progression or DLT. Data are available for 26 patients who had a median of 4 prior lines therapy; 50% had prior lenalidomide; of those, 10 patients relapsed and 3 were refractory. DLT included grade 4 neutropenia and thrombocytopenia at 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 MTD. Common grade 1 and 2 AE, which were manageable with supportive care, included nausea, fatigue, dyspnea, diarrhea, constipation, neuropathy, and muscle cramps. One patient discontinued due to RAD001-related non-infectious pneumonitis. Of 19 patients evaluable for response, 12 received the MTD. 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 was the discussant of abstracts 8002 and 8003, and called his presentation “The Death and Rebirth of Immunotherapy in Myeloma.”

IMiD agents (thalidomide and especially lenalidomide) demonstrate significant single-agent and combination efficacy in all phases of myeloma therapy; this activity is

likely associated with enhancement of immune function and allowing innate anti-tumor activity to contribute to responses. The use of IMiDs and mAbs in concert may have enhanced efficacy, likely as a result of augmented immune function, and has been demonstrated in other malignancies. Pomalidomide in myeloma has a MOA similar to those of lenalidomide and thalidomide; lenalidomide and pomalidomide might have more immune-enhancing activity, but this has not been formally demonstrated. Thalidomide is useful as the first novel agent in myeloma; lenalidomide is able to overcome thalidomide resistance; can pomalidomide overcome lenalidomide resistance?

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, directed against myeloma cell surface antigens or growth factors and myeloma-bone marrow microenvironment interaction.

However, he believes there is cause for celebration: refractory is the new relapsed; both elotuzumab studies 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 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 Jakubowiak and 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 saturates receptors, does over-saturation increase toxicity or enhance response? Pomalidomide responses have been seen with 1, 2, or 4 mg in different studies, so is there a dose-response curve? There may need to be a patient-specific dose or trial-specific 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 high-risk disease. Identifying the intracellular mechanism for synergy should be a high priority in order to best define 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.

NCCN practice guidelines for myeloma show that the first-generation novel agents are now used throughout the treatment course of myeloma, and augment the outcome of ASCT. But there is a thorny issue concerning the management of patients with myeloma that has relapsed on, or is refractory to, novel agents, portending short survival. According to Dr. Shaji Kumar, updated data from the International Myeloma Working Group (IMWG) suggest an average survival in this group of 6 to 9 months, which is dismal and an area of unmet need.

Carfilzomib is the lead second-generation proteasome inhibitor, in the epoxyketone class, that binds to the proteasome irreversibly. Bortezomib is a boronate peptide, and the two agents have different toxicity profiles. Hydration and low-dose dexamethasone, particularly in the first cycle, have helped reduce renal toxicity seen in early trials with carfilzomib. The ORR and TTP in the trial presented by Dr. Vij

are encouraging. The ongoing trial of the 27 mg/m² dose is critical, as is increasing the dose judiciously to improve the quality of the response. Low toxicity has allowed carfilzomib to be combined with other agents, including lenalidomide. It is controversial whether PN is a class effect of proteasome inhibitors. There may be important differences between the drugs at different sites in nervous tissue. Other second-generation proteasome inhibitors include NPI-0052, a non-peptide-based natural compound with a unique toxicity profile that has been shown to be active against bortezomib-resistant cells. A phase I trial is ongoing and has shown both tolerability, particularly 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 paradigm 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 extramedullary disease. Tailored approaches are now feasible to provide for new, more specific, and less toxic combinations therapies. Challenges include optimal sequencing, drug resistance, and side effect management to optimize the therapeutic index and further improve patient outcome. Myeloma remains incurable and the need for new agents and continued studies is paramount.

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 use of ASCT for younger patients with the introduction of newer drugs. The aims of the study were safety and efficacy of 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 data on maintenance 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 MPR for six 28-day cycles (n=202) or to 2 courses of MEL200 ASCT (n=200). There was then a second random assignment to either no maintenance or maintenance with 10 mg per day of lenalidomide until progression. The median age was 58 years for both groups.

The best response to Rd after 4 cycles (n=370) was: CR 6%, VGPR 31%, and PR 49%. Rd had a good safety profile, with less than 10% neutropenia, 3% thrombocytopenia, and less than 2% DVT. This is one of the best safely profiles for combinations containing novel agents. Within this study, a sub-study compared the use of low-molecular-weight heparin (LMWH; enoxaparin 40 mg per day) vs. aspirin (100 mg per day) for prophylaxis of thromboembolic events (TE). Prophylaxis was continued for patients assigned to the MPR arm, and discontinued for patients assigned to the MP arm. The incidence of DVT was slightly greater than 1% with LMWH; with aspirin, the combined risk of DVT plus PE was about 2.5%. PE was not observed in patients receiving LMWH. Stem cell mobilization was adequate using cyclophosphamide plus G-CSF.

The response rate after 3 cycles of MPR (n=117) vs. one cycle of MEL200 (n=122) was: CR 13% vs. 16%, VGPR 42% vs. 37%, and PR 36% vs. 38%, with no bone marrow confirmation. There was no difference in PFS after a median follow-up of 14 months. PFS was projected to be 91% at 1 year for both arms, with an OS of 97% to 98%, but this is a short follow-up time. Combination therapy with new agents appears to reduce the difference between standard treatment and ASCT. By ISS stage, patients with stage 1 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 AE, with much less hematologic toxicity, and fewer infections and GI toxicities. The 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.

This is an updated analysis of the phase I/II study. The first prospective study of RVD was published in Blood online in April. It was the first regimen with a 100% response rate. Data presented here update results with a longer follow-up, a median of over 27 months. Phase I was to determine the MTD/maximum planned dose (MPD); phase II was to determine the response rates at the MTD/MPD, DOR, PFS, OS, and toxicity. For patients going on to ASCT, data were collected on stem cell collection and engraftment. Important characteristics of the study design include administration of bortezomib twice weekly, dexamethasone administration on the day of bortezomib administration and the day after, and lenalidomide administration daily for 14 days followed by 7 days off. Aspirin prophylaxis (81 or 325 mg daily) was required, anti-zoster therapy was required, an algorithm for dose reduction for neurotoxicity and the use of supplements was used, and bisphosphonates were permitted. 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 bone marrow aspiration and biopsy and radiologic assessments to determine response.

Toxicity was related to high-dose (HD) dexamethasone; HD dexamethasone with lenalidomide is problematic, as has been seen in the ECOG trial. In the phase II portion of the 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. Of the 68 enrolled, 2 patients with rapidly progressing disease were removed from the study, so 66 patients were treated, with a median age of 58 years, age range 22 to 86 years. 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 AE were PN in most patients, which was primarily grades 1 and 2, reversible in most, and manageable. Hematologic toxicities were manageable. The rate of DVT/PE was 6%. Only 1 patient died, unrelated to drug treatment.

Best responses in all 66 patients were CRn/CR 39%, VGPR or better 67%, at least PR 100%; for the phase II portion

(n=35) the rates were 57%, 74%, 100% respectively. 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. The estimated 2-year PFS is 68%, and the OS is 95%. The one-year landmark analysis of survival by ASCT status showed no difference between those who received ASCT vs. those who did not for PFS. 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 cytogenetic abnormalities. There is a difference by ISS: patients with stage 1 disease do very well, those with stage 2 and 3 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 regimen to yield 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 plus dexamethasone 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 toxicity 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 the rationale for the use of 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 toxicity of bortezomib. PN may have an inflammatory component that dexamethasone may modify, so the lower doses of dexamethasone matter, not just for toxicity in general, but for neurotoxicity. 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 alternate-day dosing may be better tolerated but 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 platform was to avoid overlapping toxicities and allow a period of rest. So he thinks lenalidomide dosing is highly flexible in this context, but daily dosing for a period of time matters, and he doesn't want clinicians 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 in the maintenance setting.

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 (the data reflects some patients who received ASCT after relapse from conventional chemotherapy). Novel agents used as frontline therapy in the last few years have completely changed the prognosis of 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 3-drug 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 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 be underpowered 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 prognostic subgroups. The follow-up is short at a median of 14 months, which is too early for OS (and because effective salvage treatments exist), and it is also too early to determine PFS because lenalidomide maintenance prolongs PFS after either ASCT or non-intensive 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 by intent-to-treat population are needed.

Is lenalidomide plus dexamethasone the best induction treatment prior to ASCT? In the ECOG study, after 4 cycles, lenalidomide plus low-dose dexamethasone was inferior to lenalidomide plus high-dose dexamethasone, which was not the case 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 control given the response rates and PFS as reported here by Dr. Richardson. So is RVD the best non-intensive frontline treatment? This question can't be answered without a randomized trial to compare non-intensive upfront treatments. The response rates with RVD are unprecedented, treatment was generally well tolerated except for PN, and the results look better than those achieved 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 subgroups of patients, and a large number of patients is needed to assess differences across prognostic subgroups. The IFM/DFCI trial to start in July will study VRD induction, SC collection, 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 them to look at prognostic subgroups. He 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.

The rationale of this study was 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 (median age about 58 years) who were randomly assigned to VD (n=99) for four 21-day cycles, or to reduced-dose bortezomib (v)TD (n=100). ASCT MEL200 followed 4 cycles of induction. There were more patients with del 17 or t(4;14) in the vTD arm despite stratification by del 13.

After 2 cycles, vTD resulted in 90% at least PR vs. 78% for the VD arm, which was significantly higher. 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 higher in vTD, 73% vs. 59% with VD, which is significant. Again, there was no difference in the CR rate between arms. In previous studies the \geq VGPR rate 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 G-CSF alone as planned (vs. 6% with VD). Therefore 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. Toxicity during induc-

tion was similar between the arms except for AE leading to discontinuations related to PN, which occurred only in the VD arm. There were low rates of other grade 3 and 4 toxicities. One study goal was to reduce the PN rate, and they did see significantly lower rates of at least grade 2 PN in the vTD arm (28%) vs. the VD arm (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 grade 3 and 4 AE is low and the rate of grade 2 and 3 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 dose reduction of bortezomib with twice-weekly administration of 1.0 mg/m², which gives a total dose of 4 mg/m² (vs. 5.3 mg/m² with 1.3 mg/m²), or once-weekly bortezomib, as in the GIMEMA 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 vs. planned? 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 toxicity, so weekly bortezomib is favored. For patients going to ASCT, the goal is to lower the tumor burden with induction as fast as possible, so twice-weekly bortezomib is preferable. Nearly all patients in this study received the planned dose of bortezomib in both arms, 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-transplant-eligible patients).

The goals of frontline therapy for HD chemotherapy programs in the younger population are induction, consolidation, maintenance. This approach has been able to reverse comorbidities, providing drugs in a non-cross resistant fashion to maximize response. In the older population this approach has also been effective for long-term treatment with induction followed by maintenance therapy using combination treatments. Achieving a meaningful sustained response of at least VGPR has been shown to contribute to long-term survival in various phase II and III trials. A new bar for induction therapy in the last several years has been set at 40% CR and over 70% VGPR for comparing future studies. The Arkansas group has shown that in addition to high response rates, DOR 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 suboptimal prior to ASCT. There is a need to address the effect of IMiDs on SC harvest; Dr. Niesvizky suggested an alternative mobilization regimen, e.g. Mozobil (plerixafor). The impact of dose reduction of bortezomib is reduced PN, but the question remains whether the response rate can be improved for the 10% of patients with less than PR before ASCT. Dr. Niesvizky concluded that induction therapy must be optimized to offer a VGPR or better of 70%. It is unclear if the optimal approach is combination therapy or sequential therapy. He cautioned about the benefit of weekly bortezomib; it is always used in combination, and the results should not be extrapolated to all settings. If a patient has high-risk disease, he hopes clinicians would use higher doses in a more intense fashion, i.e., 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, the four-drug approach of VMPT followed by VT maintenance, and what has been considered the best standard of care for elderly patients, the three-drug combination VMP with no maintenance. The study also investigated the safety and efficacy of weekly bortezomib. The study included 511 patients older than age 65 years (or younger if they were not transplant eligible), n=257 for VMP, n= 254 for VMPT to VT. The median age was 71 years in both groups. The study began with twice-weekly bortezomib, but because the first 139 patients experienced neurotoxicity, the schedule was modified to weekly bortezomib for both arms and 50 mg per day thalidomide for the VMPT arm. For VT maintenance, bortezomib was administered every other week. The results are presented in Table 2.

The improvement was mostly in 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.

Grade 3 and 4 hematologic AE included 30% to 35% severe neutropenia (higher for VMPT), 20% thrombocytopenia, and 10% anemia, all of which are expected for a combination containing an alkylating agent and novel agents. Non-hematologic AE included 5% PN, 10% infections, and a higher risk of cardiac complications and TE in the VMPT arm. Aspirin prophylaxis was used. In previous studies in

this population, the discontinuation rate has been 30% to 40%; here, it was about 15% for VMP and about 20% for VMPT. The discontinuation rate for PN was about 7% for both arms. 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; thus efficacy was maintained because the cumulative dose was similar.

Dr. Palumbo concluded that today the best available treatment option for elderly patients is VMPT followed by VT maintenance. This regimen 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 distinguishing between the effects of induction and maintenance. Dr. Palumbo replied that there is a question about how long to treat to increase the response rate. Maintenance does look important to increase DOR. There is a window within a given schema to maximize the CR rate; in this setting 9 cycles 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 MPR followed by lenalidomide maintenance also gave good results, and wondered how to compare his study with VMPT

Table 2. Results of VMPT followed by VT vs. VMP

	VMPT to VT 250 evaluable	VMP 253 evaluable
CR	38%	24%
at least VGPR	59%	50%
at least PR	89%	81%
TTNT (median follow-up 26.5 months)	69%*	55%*
PFS (estimated)	54%*	40%*

* differences are significant

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 MPR-R study is as maintenance; if lenalidomide were substituted for thalidomide, he would be afraid that neutropenia toxicity would lower the efficacy of the four-drug combination, which he also saw with MPR. This might explain the results in the EVOLUTION study in which the four-drug combination (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 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. When response is measured by MRI, the disappearance of focal lesions may take 3 or 4 years; the proper techniques, e.g. MRI and PET, should be used to measure CR, particularly MRI over time. He proposed that a new yardstick, MRI-defined CR, should be developed. This lags 8 to 12 months behind immunofixation-negative CR. Dr. Palumbo agreed that CR in this study is defined by M-protein and plasma cell infiltration, 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. MP, and a secondary comparison done at the behest of 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 non-transplant eligible. At the interim analysis, presented at ASH, there was a statistically significant difference between MPR-R vs. MP ($p < .001$). The authors concluded that continuous lenalidomide is superior to regimens of limited 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 the MM-015 study. The strengths included that the regimen is orally administered and fairly well tolerated, which is important for older patients, and those who, being ineligible for transplant, may have co-morbidities. MPR-R offers a significant PFS advantage over MP, contributing to the emerging theme that lenalidomide maintenance may be a new standard. Limitations of the study include a short follow-up time, and the lack of difference seen between all three arms at 9.4 months for PFS. There is no difference in PFS between MP vs. MPR, and no OS advantage to date.

The landscape of therapy for non-transplant-eligible patients with myeloma currently includes combinations of thalidomide, bortezomib, and lenalidomide, as MPT, MPV, MPV-VT, Rd, 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 a meta-analysis. Dr. Raje's overall conclusions are that MPR-R is certainly one additional strategy in the treatment of newly diagnosed patients with myeloma who are not candidates for transplant. The choice of therapy should be based on patient profile and emergent therapy-related toxicities such as neuropathy, risk of TE, and renal dysfunction. An emerging theme is that maintenance therapies are an important adjunct to anti-myeloma therapy.

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 emerg-

ing 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 initially crossed over and then did receive some of these new drugs; in myeloma it's become incredibly difficult to see a survival benefit 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 fulminant renal failure who needs rapid myeloma control, bortezomib makes sense. For maintenance therapy, data support maintenance strategies even though there is no OS advantage. What will need to be done in the future is to risk-stratify patients 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 vs. clodronate. An important biologic concept in myeloma is that the myeloma cells are in close interaction with stromal cells. An additional loop that is important is the interaction between osteoclasts and osteoblasts, which feeds a pro-survival loop; treatment that could break the loop might be beneficial. The objective of the trial was to ask the question, "Can bone-targeted therapy improve survival in patients with multiple myeloma?" There is preclinical indirect evidence (inhibition of bone resorption and angiogenesis, stimulation of gamma-delta T cell cytotoxicity) and direct evidence (induction of plasma cell apoptosis, modulation of adhesion molecules, reduced tumor burden in mouse models for zoledronic acid, but not clodronate) for the potential anticancer effects of aminobisphosphonates. There has also been some clinical evidence for the anticancer effects of zoledronic acid and clodronate in myeloma.

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 (n=981) or clodronate (n=979) until disease progression. The primary endpoints were OS, PFS, and ORR. The secondary endpoints

were skeletal related events (SRE) and safety. The median follow-up was almost 4 years. The basic conclusion is that zoledronic acid improved OS by about 5.5 months, which is both clinically and statistically significant. There was a reduction in the hazard ratio for OS and PFS. Zoledronic acid significantly reduced the relative risk of death by 16% vs. clodronate, and significantly reduced SREs (24% relative reduction, from 35% to 27%). Is the survival benefit due to an anti-myeloma effect or because of reduced SRE? When analyzed in a Cox model with SRE as a time-dependent covariant, the survival benefit was not due to prevention of SREs, but is an anti-myeloma effect.

In analyzing AE in the safety population over both intensive and non-intensive regimens, there were no differences between the two bisphosphonates for acute renal failure, thromboembolic events, 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%, was generally not acute, and was self-resolving with no surgical intervention (vs. 0.3% rate of ONJ with clodronate). 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 safety profiles. Zoledronic acid might work by directly inducing apoptosis in myeloma cells, synergizing with chemotherapy, breaking feed-back loop between osteoblasts and stromal cells, and up-regulating the gamma-delta T cell effect. This is not isolated to myeloma, because there is evidence in other cancer settings that it 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 data further support the anti-cancer activity of zoledronic acid and provide evidence that it should be considered for early integration into treatment regimens in patients with newly diagnosed myeloma.

Discussion

In response to questions, Dr. Morgan said that 70% of patients had bone disease at baseline, and the benefit of zoledronic acid on SRE and OS was seen in patients with or without bone disease. They will present subgroup analysis, e.g., differences between the older and younger patients or

between patients in CR vs. those not in CR, at ASH when they have a clean data set. 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 progression, but they didn't collect those data. The doses 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 on safety grounds. 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 Pittsburgh, Pittsburgh, Pennsylvania, who reviewed myeloma bone disease, about the MRC IX trial that included patients with non-lytic bone disease. Treatment of patients with non-lytic 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 but not overt lytic bone disease. Dr. Roodman replied that previously the ASCO guidelines were clear on not administering 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 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 toxicity, 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 the underappreciated fact 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 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? This fall the NIH will 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 they are hypercalcemic. 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. Retrospective data in other malignant diseases suggest 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 is an infinite sink for bisphosphonates. Although it appears that bone can't be saturated, there is now a concern about atypical fractures, the cause of which is unclear. 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. 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 of that data. He thinks that the more potent the activity of the bisphosphonate, the higher the risk of ONJ. However, the incidence has fallen dramatically with current recommendations for dental prophylaxis, dental hygiene, and follow-up at least in patients with breast cancer, and anecdotally 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 associated with the more widespread use of bortezomib, which activates osteoblasts. This hypothesis needs to be proven, but it is interesting nonetheless. Dr. Roodman replied that the change in incidence in patients

with breast cancer, who don't receive bortezomib, is the same, and probably attributable to better dental hygiene.

A participant pointed out that data 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 data 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 other tangential 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) 70-gene 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 abrogates 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 biomarker for 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, SCT-eligible patients. 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 re-identified 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 Kaplan-Meier curves of OS and EFS 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 (which is the majority of the patients in TT3), if EF and SC subsets can be distinguished at baseline by either standard prognostic factors or GEP of plasma cells. Biopsy samples are also available to look at the bone marrow microenvironment. The ultimate goal is to define genes to distinguish EF and SC and find new targets of therapy.

There were 123 patients with high-risk disease in TT2 and TT3. SC was distinguished from EF by at least a 3-year OS and, more stringently, at least a 3-year sustained CR vs. an event within 1 year. A logistic regression analysis was

performed to segregate EF from SC based on GEP and standard variables. For the two subgroups within the high-risk population, there are no differences in standard variables with more challenging cut-offs, e.g., B2M, albumin, lactate dehydrogenase (LDH), and cytogenetic abnormalities. However, there were differences between EF and SC subgroups in the GEP median score, which was significantly higher in the EF subgroup, for both the survival and CR DOR model, with the shift to an increased score in the EF subgroup indicating very high risk. The presence of delTP53 was significantly more likely in the EF subgroup for the survival model, but not for the CR model. This is supported by the results of the multivariate logistic regression analysis of variables linked to EF vs. SC.

There are 14 genes that distinguish the EF and SC subgroups; 6 are upregulated and 8 are down-regulated. Among the down-regulated genes are a Wnt suppressor, a kinase that regulates cell division, and a transcription factor involved in B-cell development. Among the upregulated genes is TP53INP1, which induces TP53-phosphorylation and TP53-mediated apoptosis, and is located on chromosome 8q22. The Arkansas group has performed GEP analysis at baseline, 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 MEL in TT4 and TT5. TP53INP1, when low before treatment, was upregulated 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”), and lower delTP53 scores. Among 14 EF- vs. SC-discriminating genes, TP53INP1 is of particular interest, because over-expression in SC is linked to apoptosis and better clinical outcome. TP53INP1 is rapidly inducible by melphalan and bortezomib in patients with low levels of expression. Therefore, it is not only a biomarker, but a therapeutic target. Issues under study include the development of a “super high-risk” model; examination of the potential for super high risk among poorly performing outliers in low-risk myeloma; and the role of the model in predicting post-relapse survival. They are also planning to examine the super high-risk-associated genes in the context of molecular subgroups; and to determine the bone marrow microenvironment-unique genomic features of EF vs. SC. In addition, they want to examine modulation of super high-risk genes

by anti-myeloma agents, e.g., MEL and bortezomib, as rapid inducers of TP53INP1 to restore myeloma cell sensitivity.

Erythropoietin Receptors on Myeloma Cells

Dr. Pamela S. Becker, University of Washington, Seattle, Washington, was first author of a poster, Abstract 8124, entitled Plasma cells from patients with multiple myeloma express erythropoietin receptors: potential relevance to pharmacological use of erythropoietin.

A retrospective study of patients with myeloma showed that the use of erythropoiesis-stimulating agents (ESAs) was an independent risk factor for reduced survival, even after controlling for other prognostic indicators in myeloma, with a significant reduction in median survival from 67 months for no ESAs to 31 months with ESAs. (Katodritou E, et al., *Am J Hematol* 2008; 83:697-701).

This study used flow cytometry to analyze patient bone marrow mononuclear cells for the presence of myeloma markers and the extracellular domain of the human erythropoietin (Epo) receptor (EpoR). Non-erythroid cancer cell lines were also tested for Epo-R expression. The highest expression of EpoR was seen among myeloma cell lines. The expression of EpoR was detected in 40% of patient myeloma cell samples (n=32), but was not detected on lymphocytes from the same patients. Expression studies are in progress in bone marrow cells from patients with other hematologic malignancies and in normal bone marrow samples. Signal transduction could be detected through the EpoR in the U266 myeloma cell line within 5 minutes of stimulation, and will be studied in primary patient myeloma cells. They also want to look at RNA expression and correlate that to cytogenetics in newly diagnosed vs. relapsed, refractory myeloma. These studies may elucidate the tumor progression associated with ESA administration to patients with cancer.

International Myeloma Foundation

12650 Riverside Drive, Suite 206
North Hollywood, CA 91607 USA

Telephone:

800-452-CURE (2873)
(USA & Canada)

818-487-7455

Fax: 818-487-7454

TheIMF@myeloma.org

www.myeloma.org

