

ASCO 2011 Highlights for Patients



ASCO 2011 Annual Meeting Highlights for Patients

The 2011 Annual Meeting of ASCO (American Society of Clinical Oncology) was held in Chicago, Illinois, USA, from June 3 to 7, 2011.

Summary

- Strategies are being developed to define risk factors in the progression of smoldering multiple myeloma (SMM) to myeloma, and to develop therapies to slow or prevent this progression.
- Administration of zoledronic acid shows anti-myeloma activity in addition to reduction of skeletal related events (SRE) such as fractures; however, additional agents active against myeloma bone disease are needed, and some are in clinical trials.
- Most cases of lenalidomide-related second primary malignancies (SPM) appear to be associated with melphalan-based therapies. The low incidence of SPM must be considered within the context of the greater clinical benefit of treatment vs. no treatment of myeloma. Longer follow-up is needed to better identify the risk factors for SPM.
- Promising agents in development for myeloma include the proteasome inhibitor carfilzomib and monoclonal antibodies, including elotuzumab.

Diagnosis, Prognosis, Risk Assessment

Smoldering multiple myeloma (SMM)

Ivan Borello, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, discussed **Smoldering and Asymptomatic Myeloma as part of the Education session entitled Clinical Problems in the Management of Multiple Myeloma** (eQuestions session). Smoldering multiple myeloma (SMM) is defined by a serum monoclonal protein (M-protein) of at least 3 g/dL and/or at least 10% clonal bone marrow plasma cells (BMPC) in the absence of CRAB criteria (end-organ damage such as hyperCalcemia, Renal insufficiency, Anemia, or Bone lesions) attributable to the plasma cell disorder. There are about 5000 new cases of SMM per year in the US. The International Myeloma Working Group (IMWG) recommends a baseline bone marrow biopsy and skeletal survey, plus follow-up laboratory tests (in 2 to 3 months to determine rate of progression, then if stable every 4 to 6 months for a year, then if stable every 6 to 12 months). Treatment of SMM is not recommended outside of a clinical trial. Treatment in the context of clinical trials to delay or prevent progression to symptomatic myeloma may be considered for selected patients.

Risk of progression. The risk of progression of SMM (Mayo Clinic data) is 10% per year over the first 5 years, 3% per year over the next 5 years, then 1% per year over the following 10 years. For comparison, the rate of progression of MGUS (monoclonal gammopathy of undetermined significance) is 1% per year. This suggests that there are subpopulations within SMM, including those with either slower or more rapidly progressing disease. Therefore, it would be useful to be able to stratify the risk of progression. Two risk stratification studies have been performed. A Mayo Clinic study of 273 patients identified the following risk factors:

- BMPC greater than 10%.
- M-protein greater than 3 g/dL.
- Free light chain (FLC) ratio less than 0.125 or greater than 8 (that is, abnormal).

The overall risk of progression at 5 years was 25% vs. 51% vs. 76% if 1, 2, or 3 of these risk factors were present.

A PETHEMA (Spanish) study of 89 patients identified two risk factors:

- 95% or more abnormal vs. normal plasma cells based on the presence of certain proteins on the surface of cells
- Immunoparesis (suppression of non-involved immunoglobulins)

The risk of progression at 5 years is 8%, 42%, or 82% with the presence of 0, 1, or 2 of these factors. It is not known if the progression from MGUS to SMM to myeloma to plasma cell leukemia (PCL) is linear. However, myeloma has been shown to have been preceded by MGUS up to 8 years before diagnosis of myeloma in a retrospective study. The FLC ratio becomes abnormal closer to the diagnosis of myeloma. There is also a linear increase of M-protein spike approaching the time to diagnosis of myeloma.

SMM trial results and ongoing trials. Previously published trial results have not shown a survival benefit of early vs. late melphalan plus prednisone or of zoledronic acid in SMM.

- Preliminary results of an ongoing trial of lenalidomide plus dexamethasone followed by lenalidomide maintenance suggest treatment slows progression and may provide a survival advantage.

- A SWOG (Southwest Oncology Group) study is looking at clinical staging using MRI (magnetic resonance imaging) and PET (positron emission tomography), genetics, genomics, and immune response from asymptomatic myeloma until disease progression requiring therapy.

Conclusions. Standard treatment for SMM is observation until disease progression. Patients with SMM should be considered for treatment in the context of clinical trials. SMM appears to have some subpopulations with a higher risk that could be identified. Early treatment may reduce the risk of progression but could be associated with an increased risk of side effects and disease progression.

Risk factor assessment and stratification

High-Risk Myeloma was presented by Rafael Fonseca, Mayo Clinic, Scottsdale, Arizona, USA, as part of the Education Session: **Identification and Treatment of the “High Risk Patient” with Non-Hodgkin Lymphoma and Myeloma.** Dr. Fonseca reviewed publications on risk stratification and treatments associated with differential survival in various risk groups. He pointed out that although many publications suggest identifying higher-risk populations as candidates for more intensive therapies with the goal of reaching a complete response (CR), this is not necessarily being done in practice, and there are no data to support this approach yet. One strategy being tested is the University of Arkansas Total Therapy (TT) modifications based on gene expression profile (GEP) signature. However, previously defined risks may be overcome by newer therapies, e.g., the translocation t(4;14) may be overcome at least in part by use of bortezomib. There may be risk factors that have different significances at different stages of disease along the spectrum from MGUS to SMM to newly diagnosed myeloma to first relapse to second relapse to refractory disease to plasma cell leukemia. The recent initial sequencing of myeloma genomes has shown that a large number of mutations are not present in all patients. This, Dr. Fonseca says, at the end of the day could mean that myeloma is an “n of one,” that is, each individual patient may be unique in risk and response to therapy. Analyses of subclones from individual patients by comparative genomic hybridization (CGH) show changes over time, with new clones appearing and the proportion of clones changing with different treatments during the course of disease. The challenge is to address all the clones to cure the disease.

Other key points are:

- FISH (fluorescence in situ hybridization) is currently the gold standard for identification of high-risk myeloma.

- GEP-based risk stratification correlates moderately with FISH.

Newly Diagnosed Myeloma

Treatment without Transplant

Survival outcomes in elderly patients with plasma cell myeloma: the three-decade Eastern Cooperative Oncology Group (ECOG) experience (Abstract 8021) was presented by Erica Campagnaro, University Hospitals Case Medical Center, Cleveland, Ohio, USA, in a poster session. This study was a retrospective review of data from 4 phase III ECOG trials in newly diagnosed myeloma (total of 1528 patients) studying treatments other than autologous stem cell transplant (ASCT). The analysis divided patients into three groups based on the dates they entered the study (1988 to 1993; 1994 to 2000; and 2001 to 2006). Only patients in the most recent group received novel agents (thalidomide plus dexamethasone or lenalidomide plus high- or low-dose dexamethasone), and these patients had a significantly better 5-year overall survival (OS) than patients in either earlier group. This difference was greater for patients who were less than age 65 years. Progression-free survival (PFS) was longer for patients younger than age 65 years who were treated with novel agents in the most recent group, although follow-up time is shorter. PFS for patients older than age 65 years was similar in all three groups, that is, novel agents did not appear to contribute to PFS in the older patients. Patients older than age 65 years were more likely to have worse performance status and higher creatinine and beta-2-microglobulin (B2M) than younger patients, but there was no difference between age groups in other prognostic factors such as Durie-Salmon stage, C-reactive protein, or hemoglobin.

This poster was discussed by Suzanne Lentzsch, University of Pittsburgh, Pittsburgh, Pennsylvania, USA. She noted that this is an important analysis of only large, randomized trials, and asks an important question about the outcome of older patients. Weaknesses include the lack of analysis of the cause of death (whether due to myeloma or other causes), which would be helpful in determining whether the marginal increase in OS in older patients is due to novel agents or better medical care, e.g., better cardiac care. It is not clear if the difference is due to reduced dosages or less transplant for older patients or unfavorable cytogenetics. It also isn't known if increased OS might be attributed to salvage therapy with bortezomib, and if bortezomib should be given upfront to older patients with adverse cytogenetics. Unresolved issues include:

- Despite more aggressive treatment, ASCT up to age 75 years, and the use of novel agents, there has been only a marginal

increase in OS in patients over age 65 years.

- PFS has not improved since 2001 in older patients, questioning the effect of improved anti-myeloma treatment.
- Is increased OS in older patients due to better medical care?
- Is the increased risk of adverse cytogenetics associated with worse outcome in older patients?
- Due to the biologic heterogeneity of patients age 65 to 75 years, outcome evaluation should be based on treatment, not on age.
- More information is needed on the biology of myeloma in older patients.

Treatment with Transplant

Melphalan, prednisone, lenalidomide (MPR) versus high-dose melphalan and autologous stem cell transplantation (MEL200) in newly diagnosed multiple myeloma (MM) patients: a phase III trial (Abstract 8020) was presented by Mario Boccadoro, University of Torino, Torino, Italy, in a poster session. This study was conducted in patients with newly diagnosed myeloma who were younger than age 65 years. After four induction cycles of lenalidomide plus low-dose dexamethasone, patients were randomly assigned to either MPR (202 patients) or MEL 200 with ASCT (200 patients). A second random assignment was to either no maintenance or lenalidomide maintenance. **Results.** MEL200 was superior to MPR for PFS at 24 months, although side effects were significantly higher. This is the first study to show a PFS advantage for ASCT compared with combination chemotherapy containing a novel agent, although at this time, OS is similar for both treatments, and longer follow-up is needed.

Supportive Care

Bone Disease Overview

David Roodman, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA, presented **Bone Disease and its Management in Multiple Myeloma** as part of the Education Session, **Clinical Problems in the Management of Multiple Myeloma** (eQuestions session). Bone involvement is most frequent in myeloma vs. other cancers, occurring in up to 84% of patients with advanced disease. Any bone can be affected, but bones with higher red marrow content are most often affected, with pathologic fractures occurring most often in vertebrae (70%), followed by ribs (14%), thigh bones (5%), and other bones. At the time of diagnosis 20% of patients have pathologic fractures, and 60% will have them over the course of their disease. Pathologic fractures in myeloma are associated

with decreased survival and increased cost of treatment.

Management strategies include the following:

- Lifestyle modifications such as movement and avoidance of bed rest (although movement may cause pain), calcium supplements, precautions to reduce falls
- Radiation therapy to treat painful lesions (should be used sparingly because overuse can compromise the use of systemic therapy)
- Surgical interventions: vertebroplasty (no benefit in osteoporosis); kyphoplasty (benefit in patients with cancer, including myeloma)
- Pharmacologic management: vitamin D supplementation (many patients have insufficient vitamin D, but appropriate levels and dosing are unclear and trials are ongoing); bisphosphonates (inhibit osteoclast activity); treatment of myeloma (bone disease can progress in patients in complete remission)

Bisphosphonates. Pamidronate and zoledronic acid are equally active in reducing skeletal related events (SRE), including fractures, radiation to bone, vertebral compression fractures, and hypercalcemia. Issues include:

- Kidney (renal) toxicity (kidney function must be monitored).
- Osteonecrosis of the jaw (ONJ), although good preventative dental care has reduced the incidence.
- SRE (skeletal-related events) are decreased by 50% and progression of bone disease still occurs, although at a slower rate.
- Anti-myeloma activity of zoledronic acid has been demonstrated in the MRC Myeloma IX trial (updated results are summarized below). This was seen in patients without as well as with bone disease, but the anti-myeloma therapy used was not as intensive as current therapy, and newer agents are active in bone. Therefore, Dr. Roodman believes that it isn't clear that all patients should be treated with bisphosphonates.

Discussion. Dr. Roodman pointed out that there are no data about stopping bisphosphonates before dental procedures. He said it is not necessary to stop bisphosphonates for routine cleaning or other procedures such as fillings or root canals, but bisphosphonates should be stopped for 2 to 3 months for planned procedures like extractions or surgery. If there is an emergency condition, the procedure should be performed and bisphosphonates stopped until the tooth socket heals. Bisphosphonates may inhibit healing after surgery

or extraction. He noted that in the MRC Myeloma IX trial, there was a benefit of bisphosphonates for 1 to 4 years, but ONJ increases with the cumulative dose of zoledronic acid. This group had preventative dental care over the follow-up period of thalidomide vs. placebo maintenance, suggesting that if there is good dental prophylaxis, bisphosphonates can be administered past 2 years. ASCO guidelines recommend administration for 2 years. Dr. Roodman says that his personal practice, which is not based on data, is to extend the interval of bisphosphonate administration for patients with CR or plateau, but if they have active disease, then he treats with bisphosphonates.

Bisphosphonates in the MRC Myeloma IX Clinical Trial

There were two oral presentations and one poster presentation discussing the use of the bisphosphonates zoledronic acid vs. clodronate in the MRC Myeloma IX clinical trial. These presentations were updates on the data reported at ASCO 2010 of 1960 patients with newly diagnosed myeloma treated in either an intensive or non-intensive pathway. Within each pathway, 981 patients were randomly assigned to zoledronic acid and 970 patients to clodronate. Patients were further randomly assigned within each treatment group either to maintenance therapy with thalidomide or to no maintenance. Note that although clodronate is not currently approved in the US, it is used in other countries, including Canada and the UK.

The presentations were:

- **Does zoledronic acid (ZOL) reduce skeletal-related events (SREs) and improve progression-free survival (PFS) in patients (Pts) with multiple myeloma (MM) with or without bone disease? MRC myeloma IX study results** (Abstract 8010) presented by Gareth Morgan, Royal Marsden Hospital, Leeds, UK for Kevin Boyd.
- **Are there benefits to long-term bisphosphonate treatment in multiple myeloma (MM)? Insights from temporal analyses of zoledronic acid (ZOL) versus clodronate (CLO) in the MRC Myeloma IX Trial** (Abstract 8011) presented by Faith Davies, Institute of Cancer Research, London, UK.
- **Defining the biological subgroup of multiple myeloma patients which benefits maximally from the overall survival benefit associated with treatment with zoledronic acid** (Abstract 8083, poster) presented by Gareth Morgan, Royal Marsden Hospital, Leeds, UK.

Overall conclusions of these presentations include the following:

- Zoledronic acid significantly reduces the relative risk of SREs vs. clodronate regardless of the presence of bone disease at diagnosis. SRE rates were higher if there were pre-existing bone lesions at presentation.
- Zoledronic acid decreases SREs even when new bone lesions were excluded from the composite definition of SRE. The decrease in SREs with zoledronic acid was seen within the first year independent of bone disease status at presentation.
- Zoledronic acid significantly improved OS and PFS vs. clodronate in the overall population. The OS and PFS benefits appear limited to patients with bone disease at presentation, and were seen in both the intensive and non-intensive pathways.
- Adverse events (AEs) were similar to those previously observed.
- Patients initiating therapy for myeloma have an increased risk for SRE, with prior SRE, osteolytic bone lesions, hypercalcemia, and the use of melphalan plus prednisone increasing this risk. Zoledronic acid significantly decreases SREs vs. clodronate regardless of bone disease status at presentation or of treatment pathway or regimen. The benefits of using zoledronic acid were seen within the first year, supporting early initiation of zoledronic acid.
- The increased OS benefit of zoledronic acid over clodronate is significant within the first 4 months of treatment and increased over time, including during the maintenance portion of the trial, and is seen during each of the first 3 years on study.
- These analyses support the early initiation of zoledronic acid to prevent SREs and prolong survival, and treatment at least until disease progression to provide a long-term benefit.
- The benefit of zoledronic acid on OS vs. clodronate is independent of gender and disease stage.
- Zoledronic acid vs. clodronate:
 - ✓ significantly improved OS in patients with bone disease or other SREs at baseline
 - ✓ more effectively reduced SREs in patients with and without bone disease at baseline
 - ✓ significantly reduced risk of SREs in patients with lower-risk but not high-risk cytogenetics

Discussion. Abstracts 8010 and 8011 were discussed by David Roodman, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA. He reviewed the major findings in the presentations as well as published results on the effect of bisphosphonates in myeloma and other cancers. He noted that that bisphosphonate use will result in additional cases of ONJ, and assuming the rate of occurrence is the same in patients with and without bone disease, the clinical economic cost of treating all patients with bisphosphonates must be considered. The increased incidence of ONJ at 3 years of treatment (seen in patients with breast cancer) was the basis of the ASCO guidelines suggesting 2 years of bisphosphonate therapy. However, good dental prophylaxis (preventive care) has been shown to decrease the incidence of ONJ.

Important remaining questions include whether using other regimens containing agents that may target bone, like bortezomib or lenalidomide, would obscure the benefits of zoledronic acid on OS in patients with bone disease, and the SRE effects of zoledronic acid in patients without bone disease. Do patients without bone disease need less frequent administration of zoledronic acid (or another bisphosphonate) for the same SRE benefit without increased risk of ONJ? Will the lower incidence of ONJ seen with dental prophylaxis remain low with longer periods of treatment with zoledronic acid?

Question and answer discussion. Dr. Morgan pointed out that because the effect of bisphosphonate treatment on high- vs. low-risk disease wasn't part of the original design of MRC Myeloma IX, this effect must be confirmed in a prospective study. Dr. Davies said they are looking at data for the effect of continuous vs. intermittent vs. stopped bisphosphonate administration, but small patient numbers in the subgroups make this analysis difficult. Dr. Morgan said they used skeletal surveys, not DEXA, so they don't know the rates of generalized decreased bone density (osteopenia) in patients. Menopausal status, which is important in the breast cancer studies, is not important in myeloma bone disease.

Taimur Sher, Roswell Park Cancer Institute, Buffalo, New York, USA (session co-chair) asked how long patients should be treated based on response. Dr. Morgan said they are trying to address this in a subsequent analysis. New osteolytic disease is associated with progression, and there is always a period when bone resorption occurs before relapse. Dr. Roodman said that Dr. Raje is using bone markers to decide on treatment, and agrees these should be used, but more selectively. Patients with breast and prostate cancers benefit at each landmark for at least 3 years of bisphosphonate treatment. The risk

of ONJ should be balanced with benefit. Dr. Davies said that the ONJ risk doesn't seem to increase over time.

Other Supportive Care Issues

In the Education session **Clinical Problems in the Management of Multiple Myeloma** (eQuestions session), Sikander Ailawadhi, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, USA, who was a substitute speaker, presented **Complications of Anti-Myeloma Therapies**. He discussed the need to be aware of and appropriately manage hematologic and gastrointestinal side effects, thromboembolism (clots), infections (including zoster reactivation associated with bortezomib), fatigue associated with thalidomide, lightheadedness associated with bortezomib, and ONJ. He mentioned guidelines for the management of side effects of novel therapies and steroids developed by the Nurse Leadership Board of the International Myeloma Foundation (IMF) published in 2008 in the *Clinical Journal of Oncology Nursing* and available through the IMF web site. During the discussion, someone asked if bortezomib once a week or administered subcutaneously was the new standard. Dr. Ailawadhi said that this was an important topic. The standard regimen of I.V. bortezomib is administration on days 1, 4, 8, and 11. There are data supporting the weekly administration of I.V. bortezomib in combination therapy such as modified VMP or modified CyBOR-D. There has been one non-inferiority study of subcutaneous bortezomib administered on days 1, 4, 8, 11, suggesting it is possible to maintain efficacy with reduced adverse events such as PN [a phase III trial reported by Moreau et al. in *Lancet Oncology* 2011, 12:431-440, in which time to progression (TTP) and 1 year OS were similar between the subcutaneous group of 145 patients and the I.V. group of 73 patients, all of whom had relapsed myeloma]. However, subcutaneous bortezomib is not used yet in general practice and is off label, that is, this route of administration has not been approved by regulatory agencies such as the US FDA.

Response Assessment and Monitoring

Secondary Malignancies

There were three oral presentations and one poster presentation discussing the incidence of second primary malignancies (SPM) (other cancers occurring after the diagnosis of myeloma) in patients with myeloma who had been treated with lenalidomide. They were:

- **Incidence of second primary malignancy (SPM) in melphalan-prednisone-lenalidomide combination**

followed by lenalidomide maintenance (MPR-R) in newly diagnosed multiple myeloma patients (pts) age 65 or older (Abstract 8007) presented by Antonio Palumbo, Molinette Hospital, Torino, Italy. This included an analysis of data from patients treated in the MM-015 study with MPR-R vs. MPR vs. MP and data from nine EMN trialist group trials of newly diagnosed patients treated with lenalidomide plus and alkylating agent vs. no lenalidomide.

- **Incidence of second primary malignancies (SPM) after 6-year follow-up of continuous lenalidomide in first-line treatment of multiple myeloma (MM)** (Abstract 8008) presented by Adriana C. Rossi, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, New York, USA of newly diagnosed, transplant-eligible patients in the BiRD phase II study treated with lenalidomide, dexamethasone, and clarithromycin.
- **Lenalidomide and dexamethasone (LEN plus DEX) treatment in relapsed/refractory multiple myeloma (RRMM) patients (pts) and risk of second primary malignancies (SPM): analysis of MM-009/010** (Abstract 8009) presented by Ruben Niesvizky, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, New York, USA (first author: Melitios Dimopoulos) of lenalidomide and dexamethasone vs. placebo and dexamethasone in the MM-009 and -010 trials.
- **Long-term safety of lenalidomide (Len) in relapsed/refractory multiple myeloma patients (Pts): analysis of pooled data** (Abstract 8086) presented by Brain Durie, Aptium Oncology, Inc., Cedars-Sinai Outpatient Cancer Center, Los Angeles, California, USA, a pooled analysis of 11 Celgene-sponsored studies of lenalidomide in patients with relapsed/refractory myeloma (MM-007 to -010, MM-012, MM-016 to -019, MM-022).

Overall conclusions included the following:

- Continuous lenalidomide results in unprecedented PFS improvement. Risk of SPM is increased by use of lenalidomide plus melphalan (not lenalidomide plus dexamethasone). However, the incidence of SPM is low. Benefit to risk ratio strongly favors continuous lenalidomide for patients with newly diagnosed myeloma but current follow-up is about 4 years and longer follow-up is needed. (Palumbo presentation).
- Although the risk of SPM with lenalidomide and alkylating agents is higher than without, the risk of dying of myeloma is lower with lenalidomide and alkylating agents. (Palumbo presentation).

- At 6 years of follow-up BiRD is highly effective in patients with newly diagnosed myeloma. There were no cases of MDS/AML (myelodysplastic syndrome and acute myelogenous leukemia). The frequency of SPMs was low and similar to the incidence reported in the Surveillance, Epidemiology, and End Results (SEER) database of the US National Cancer Institute for the patients' age group. Some patients had invasive cancers before their myeloma diagnosis. All patients should have routine screening for SPMs. (Rossi presentation).
- There was no difference in invasive SPMs for lenalidomide vs. placebo in these trials. SPM incidence rate is low and similar to background among similar age groups in the general population. OS is significantly longer for patients given lenalidomide and dexamethasone. Improvement in OS with lenalidomide is confirmed even with half the patients in the trial switching to lenalidomide from placebo during the course of the trial. The overall benefit-risk ratio for the use of lenalidomide remains strongly positive. (Niesvizky presentation).
- Lenalidomide-based therapy did not significantly increase the rate of SPMs compared with the incidence rate reported by SEER. The rate of SPMs was not significantly increased with increased duration of lenalidomide therapy. The benefit-risk profile of lenalidomide therapy for patients with relapsed, refractory myeloma is strongly positive. (Durie presentation).

Secondary malignancies following multiple myeloma, Abstracts 8007 to 8009, were discussed by Ola Landgren, National Cancer Institute, Bethesda, Maryland, USA. He reviewed the data and observed that the reporting of SPMs is not perfect: there is under-reporting, the retrospective (looking back) study format can introduce bias, survival among treatment arms can be different, and there can be variations in how data are collected. SEER data are not broken down by MDS or other specific malignancies. If a patient develops a cancer common in the ageing population, e.g., prostate cancer, does data collection stop? If a patient develops MDS later, is that information collected? Interest in SPMs after myeloma is not new; AML in patients with myeloma was reported in the 1960s and 1970s. In the 1980s MDS/AML was associated with melphalan- but not cyclophosphamide-containing regimens for myeloma. At last year's American Society of Hematology (ASH) meeting, there were reports of the incidence of SPMs in 3 randomized studies involving lenalidomide maintenance, which renewed interest in the topic.

Mechanisms. Little is known about the mechanisms, in part because the incidence of second cancers in untreated patients is not known. However, a Swedish study presented at the International Myeloma Workshop, Paris, 2011, compared the incidence of SPMs in patients with myeloma and MGUS with that in the general population. The risk of developing AML/MDS is about 11 times higher in patients with myeloma and 8 times higher in patients with MGUS. The isotype of MGUS plays a role, with IgG and IgA associated with AML/MDS. The level of M-spike is also associated with increased risk. Dr. Landgren proposed a model for SPM after myeloma that takes into account treatment, myeloma-related factors, host-related factors that predispose to both myeloma and SPM, environmental and behavioral factors, and the interaction of all of these.

Clinical implications. Based on small numbers, the 3 randomized studies reported at ASH show more hematologic malignancies in the treatment arm. Other studies show a small or no indication of increased risk. As competing causes, the cumulative incidence of development of SPMs is about 7%, and the cumulative probability of death due to myeloma is over 90%. So the risk of dying of myeloma is a much larger problem than SPM on average.

Summary and conclusions. Currently there is a lack of clear answers due to small numbers of patients and study limitations. Benefits vs. risks must be considered. Even with a lack of data, healthcare providers have to discuss the facts with patients. The key point for the future is to determine the mechanisms of SPM development.

Discussion. Dr. Palumbo believes that the risk of SPMs, particularly hematologic malignancies, is slightly increased with the use of lenalidomide, but that the risk of dying of myeloma that isn't treated with lenalidomide is much higher. Dr. Rossi thinks the risk is increased by the use of alkylating agents, and Dr. Niesvizky thinks that alkylators may contribute in the context of the order of agents used in therapy, i.e., induction with lenalidomide followed by alkylators, or the other way around. There is no information on the genetic profile of AML secondary to myeloma, although Drs. Palumbo and Landgren are collecting data on this profile. Dr. Landgren said the NIH is collaborating with CALGB and the Italian group and is inviting everyone to work together because the number of cases is so low. If SPMs are included as events in the trials discussed, PFS does not change. There was a comment about how therapy could cause SPMs in such a short time period, given that most human carcinogens take longer to act. Dr. Landgren agrees latency needs to be taken into account. If AML is associated with treatment, it appears to occur about 4 years out, so longer

follow-up is needed. The 3 studies presented that showed a small increase in SPMs in the treatment arm are suggestive but not definitive. Dr. Palumbo agrees about follow-up, and both he and Dr. Landgren point out the risk of SPM has to be compared with the much greater benefit derived from treatment. Dr. Campagnaro commented about the subset of patients in the BiRD study that presented with prior cancers, noting that it was common. She wondered if there is an enrichment for other prior tumors in patients who subsequently develop myeloma. Dr. Landgren responded that a study published this year reported prior tumors. However, because the average age of patients with myeloma is 71 years, this population can be expected to have other tumors. Men have a 50% chance and women a 30% chance of developing tumors over their lifetime. There must be a study of different cancer types to see if those patients have a higher risk of developing myeloma. There are data suggesting other cancers are more likely to occur prior to myeloma, but the question needs further investigation. Dr. Lentzsch commented that it could be important to look at the development of AML in patients given maintenance with continuous lenalidomide vs. those on a 3 weeks on, 1 week off schedule. Dr. Jakubowiak (session co-chair) asked the presenters if they would recommend maintenance with lenalidomide after transplant or non-transplant treatment outside of clinical trials. Dr. Palumbo said he would absolutely give lenalidomide after ASCT or conventional therapy but would monitor for the risk of SPMs with longer follow-up. Dr. Rossi said she would also definitely give lenalidomide maintenance because the risk of progression and death outweighs the risk of SPMs. Dr. Niesvizky proposed incorporating proteasome inhibition for maintenance in patients with high-risk disease. Dr. Landgren agreed, and stated that they need to be responsible and monitor the patients, and try to understand the mechanisms by which second malignancies develop.

New Therapies

Kenneth Anderson, Dana-Farber Cancer Institute, Boston, Massachusetts, presented **Bench-to-Bedside Translation of Targeted Therapies in Multiple Myeloma** as his David A. Karnofsky Memorial Award and lecture. He reviewed the history of therapy and identification of cell lineages, and emphasized immune-based therapies, discussing monoclonal antibodies (mAbs) for cell depletion, targeted therapies, immunotoxins, and therapeutic vaccines. He also reviewed the role of the microenvironment in myeloma pathophysiology, and discussed new therapies being developed and tested in clinical trials, summarizing recently published results. Some promising therapies or approaches include the following:

- Antibodies
 - ✓ Elotuzumab (anti-CS1 mAb). A phase III registration trial for new drug approval is testing lenalidomide plus dexamethasone with elotuzumab vs. lenalidomide plus dexamethasone. [See mAb presentation summaries in Table 2]
- Proteasome inhibitors
 - ✓ Carfilzomib, an irreversible inhibitor of chymotryptic activity, is in ongoing phase III trials. [see presentation summaries below]
- IMiDs
 - ✓ Pomalidomide is in phase I and phase II trials in relapsed, refractory myeloma. Dr. Anderson is “hopeful for accelerated approval because this agent will meet an unmet medical need.”
- PI3/AKT/mTOR inhibitors
 - ✓ A phase III trial of bortezomib plus the AKT inhibitor perifosine vs. bortezomib in relapsed myeloma is ongoing for FDA approval.
- Histone deacetylase (HDAC) inhibitors
 - ✓ Panobinostat to block the aggresome, plus bortezomib

to inhibit the proteasome, has been shown to be active in a phase I/II trial in refractory myeloma.

Dr. Anderson observed that studying myeloma cells in the context of the bone marrow microenvironment as well as using genomics will help to 1) define functionally important proteins that will target myeloma, 2) further the understanding of myeloma pathogenesis, and 3) identify appropriate patients for given therapies with the goal of developing personalized treatment.

Carfilzomib (Proteasome Inhibitor)

The results of trials of carfilzomib are summarized in Table 1.

Jonathan Kaufman, Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia, USA, discussed the first three carfilzomib posters in the above table during the **Lymphoma and Plasma Cell Disorders Poster Discussion**. He made the following points:

- In PX-171-003, carfilzomib is effective as monotherapy in a heavily pretreated population of patients, is generally well tolerated with minimal treatment-emergent PN, and a subset of patients respond and can remain on therapy for a

Table 1.

Presenter Title Abstract	Study Patients	Conclusions
Michael Wang, MD Anderson Cancer center, Houston, Texas, USA Interim results from PX-171-006, a phase 2 multicenter dose-expansion study of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed and/or refractory multiple myeloma Abstract 8025 (poster)	PX-171-006, phase II Relapsed, refractory myeloma after 1 to 3 prior therapies	Ongoing for PFS, DOR (duration of response) ASPIRE, ongoing phase III open-label trial is comparing CRd to Rd and is actively recruiting (see Moreau poster summary below)
Keith Stewart, Mayo Clinic, Scottsdale, Arizona, USA Carfilzomib produces a high single-agent response rate in patients with bortezomib-naïve relapsed multiple myeloma: updated interim results from the PX-171-004 study Abstract 8026 (poster)	PX-171-004, phase II non-randomized, open-label, single-arm Relapsed or relapsed/refractory myeloma after 1 to 3 prior regimens excluding	Study is ongoing; 22 patients are receiving carfilzomib on extension trial PX-171-010 3-year long-term follow-up OS, DOR, TTP, and safety will be reported when available
David Siegel, John Theurer Cancer center, Hackensack, New Jersey, USA PX-171-003-A1, an open-label, single-arm phase 2 study of carfilzomib in patients with relapsed and refractory multiple myeloma: long-term follow-up and subgroup analysis Abstract 8027 (poster)	PX-171-003-A1, phase II open-label, single-arm Relapsed and refractory myeloma after ≥2 lines of therapy including bortezomib or an IMiD	27 patients continuing on extension protocol PX-171-010 ORR and CBR rates are final; OS data will be updated
Jackie Szymonifka, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA Phase II study of carfilzomib (CFZ) in combination with current agents for relapsed and refractory multiple myeloma (RRMM) Abstract 8028 (poster)	Phase II Relapsed, refractory myeloma	EFS benefit seen in GEP-defined low-risk myeloma Carfilzomib has activity, especially in combination with other agents in this population of patients with advanced disease
Philippe Moreau, University Hospital, Nantes, France A randomized, multicenter, phase 3 study comparing carfilzomib, lenalidomide, and dexamethasone to lenalidomide and dexamethasone in patients with relapsed multiple myeloma Abstract TPS225 (poster)	ASPIRE Phase III, randomized, open-label in relapsed myeloma (1 to 3 prior regimens)	Treatment will continue until disease progression or unacceptable toxicity Primary endpoint is PFS, secondary endpoints include OS, ORR, DOR, safety

long period of time. It is not known what the optimal dose is in patients with refractory disease.

- In PX-171-004, carfilzomib is effective as a single agent in bortezomib-naïve patients. It is not known if there is a dose-response effect or if higher doses should be used. There are no studies asking if there is a PFS or OS advantage vs. best standard care. It is not known how the safety, including the low rate of PN, and the efficacy would compare with what Dr. Kaufman referred to as the “optimal” bortezomib schedule of once-weekly I.V. or subcutaneous administration.
- In PX-171-006, in combination with lenalidomide, no dose-limiting toxicities (DLT) were observed, and AEs were as expected. The combination CRd is very effective in patients with relapsed myeloma and can be administered for prolonged periods of time. However, it is not known if CRd has an advantage over Rd. The ASPIRE ongoing phase III trial will test this.

Elotuzumab (Monoclonal Antibody)

Development of elotuzumab, a humanized monoclonal antibody (mAb) targeting human CS1, a cell surface glycoprotein expressed on myeloma cells, continues. Two presentations on elotuzumab are summarized in Table 2.

Discussion. Abstract 8012 was discussed by Nikhil Munshi, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, who was filling in for Asher Alban Chanan-Khan. He observed

that there are over 10 potential mAb candidates that have entered clinical development. The anti-tumor activity of mAbs as single agents has been modest to date, so combination approaches with immunomodulatory and other drugs are therefore required. The strength of the elotuzumab study is that it involves a large number of patients, and therefore is probably reproducible. Randomized trials are underway to confirm the efficacy of elotuzumab in combination with lenalidomide. It would be interesting to see if elotuzumab has single-agent activity in SMM.

Panobinostat (Histone Deacetylase (HDAC) Inhibitor)

PANORAMA 1: a multicenter, randomized, double-blind, placebo-controlled phase 3 study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma (Abstract TPS227) was presented by Jesús San Miguel, University Hospital of Salamanca, Salamanca, Spain, in the Trials in Progress Poster Session. This trial will enroll 672 patients who have received 1 to 3 prior lines of therapy and whose myeloma is not bortezomib-refractory. The primary endpoint is PFS, and final analysis will be performed when a total of 460 PFS events have been observed. The study will also collect information on biomarkers and quality of life. As of May, 2011, 400 patients had been randomly assigned to treatment.

Table 2.

Presenter Title Abstract	Study Patients	Conclusions
Philippe Moreau, University Hospital, Nantes, France, presented for Paul Richardson. Elotuzumab with lenalidomide and low-dose dexamethasone in patients with relapsed multiple myeloma: a randomized phase II study. Abstract 8014	Phase I/II study of elotuzumab plus lenalidomide plus low dexamethasone in phase I, and efficacy in relapsed, refractory myeloma in phase II. Prior lenalidomide was allowed in phase I but not phase II.	The ORR of 90% in patients with only 1 prior therapy provides the rationale for using this combination earlier in disease. Two phase III trials are being conducted in relapsed myeloma and as frontline therapy.
Sagar Lonial, Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia, USA. Phase I trial of elotuzumab, lenalidomide, and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma. Abstract 8076 (poster)	Phase I data from a phase I/II trial in patients with relapsed/refractory myeloma.	A phase II trial of elotuzumab in combination with lenalidomide and dexamethasone is ongoing.

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