

# ASH 2008

# Multiple Myeloma

# Highlights

# for Physicians

*Highlights from the 50th Annual Meeting  
of the American Society for Hematology (ASH)  
held in San Francisco, California,  
December 5–9, 2008*



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# ASH 2008 Multiple Myeloma Highlights for Physicians

## Continuing Advances in Treatment

The 50th Annual Meeting of the American Society for Hematology (ASH) was held December 5 through 9, 2008 in San Francisco, California. There were 8 simultaneous sessions that included oral presentations of studies related to multiple myeloma, and over 8 poster groupings with presentations concerning myeloma, not including posters on transplantation. In addition, the International Myeloma Foundation sponsored a Satellite Symposium on December 5, Finding Your Way Through the Treatment Maze – Selecting the Best Treatment in the Era of Novel Agents. There was also an Education Program on Plasma Cell Disorders, as well as a session from the newly formed Ad Hoc Scientific Committee on Plasma Cell Biology: High-Risk Myeloma.

Multiple myeloma treatment continues to advance as research results accumulate from trials of conventional, novel, and new therapies. Additional longer-term follow-up data are now available from phase III trials of combination therapies that include the novel agents bortezomib, lenalidomide, and thalidomide, and early results are promising for some even newer agents that have entered phase I/II trials; additional agents are in development and in early stage preclinical and clinical studies.

This write-up summarizes key presentations at the 2008 ASH Annual Meeting, and includes some opinions of presenters and a few comments made during the limited question and answer discussions. Key issues discussed during the meeting include those that have been of continuing concern, as well as emerging issues, such as the role of autologous stem cell transplant (ASCT) in the era of novel therapies; whether the goal of treatment should be cure or management of myeloma as a chronic disease; the necessity for and type of maintenance therapy; and how best to assess for and use information about risk factors.

## Genetic Events in Relationship to Risk Profiling and Pathogenesis

### High-Risk Myeloma

The Ad Hoc Scientific Committee Session on Plasma Cell Biology: High-Risk Myeloma was chaired by Dr. Raymond Powles, Parkside Oncology Clinic, Wimbledon, UK. Dr. Powles pointed out that the High-Risk Multiple Myeloma Ad Hoc Scientific Committee was new to this annual meeting and will be probationary for three years. This committee was convened in part as a response to myeloma being the single most frequently discussed disease at the last ASH Annual Meeting in 2007, and to the number of simultaneous sessions on myeloma.

Dr. Powles emphasized there are many unanswered questions related to high-risk myeloma:

- Does early diagnosis alter risk?
- Which patients progress to bone disease, renal involvement, amyloid, bone marrow failure, and/or clinical immune paresis?
- Which individual patients respond best to which drugs?

- Is early response to treatment an independent risk factor?
- Which patients become operationally “cured” and do these include 10-year survivors?
- What is the best method of risk stratification?

## The Genetic Origin of Myeloma

Dr. Leif Bergsagel, Mayo Clinic, Scottsdale Arizona, began this presentation with a review of the progression of plasma cell neoplasia from a normal B cell to MGUS, SMM, intramedullary myeloma, extramedullary myeloma, and finally a myeloma cell line. This progression is a multi-step process characterized by genetic events including somatic hypermutation, errors in isotype switch recombination, changes in chromosome numbers, IgH and other translocations, and dysregulation of cyclin and other genes. Early in disease progression, ras and myc may be dysregulated. Later events include deletions such as CDKN2C/p18, p53 deletion on 17p, deletion of the glucocorticoid receptor, which may predict resistance to glucocorticoids, and mutations altering the expression of components of the NFkB pathway, TRAF3 (low expression of which may be associated with resistance to dexamethasone and sensitivity to bortezomib), and others. The importance of some genetic alterations may decrease as newer therapies overcome those associated with poor prognosis or drug resistance. Bergsagel noted that interpretation of risk factors among patients who participated in clinical trials should take into account the eligibility of patients with high- vs. low-risk disease.

## Molecular Indicators of High-Risk Disease

In his presentation, Dr. John Shaughnessy, University of Arkansas for Medical Sciences, Little Rock, Arkansas, noted that “genomic chaos” in myeloma has made molecular characterization difficult. His group is asking if genomics can aid in risk assessment and help guide therapy decisions, noting that the common histology of myeloma is associated with variable outcomes. They are exploring the hypothesis that extremes of mRNA expression correlated with treatment failure may point to critical genomic events that may provide insights into the pathogenic mechanisms of therapy failure; these insights may be able to validate prognostic predictive models to support risk-adapted therapy. The 70-gene model from gene expression profiles (GEP) of patients treated with Total Therapy (TT) has been published and validated. Dr. Shaughnessy noted that different models have identified different sets of genes and gene signatures associated with high risk, and correlating these different models remains a problem to be resolved.

## Influence of Targeted Therapy in Redefining High-Risk Myeloma

Dr. William Dalton, Moffitt Cancer Center and Research Institute, Tampa, Florida, observed that a high-risk population can be defined by response to therapy, progression to relapse, and genetic and epigenetic factors. Also of importance are microenvironmental influences that include a network of survival signals,

which are difficult to characterize if myeloma cells are studied in isolation from the bone marrow microenvironment. Some of these influences include interaction with fibronectin, which may be associated with resistance to treatment, and expression of interleukin (IL)-6, a major growth factor constitutively activated in patients with myeloma that in turn activates STAT3, a signal transducer and transcription activator. STAT3 signaling in myeloma cells is also enhanced by adhesion mediated by beta-1 integrin. Questions that must be asked are how interaction with the bone marrow microenvironment influences acquisition of mutations and/or transcription profiles; are there subpopulations of cells with specific mutations and/or transcription profiles that interact differently with the microenvironment; and whether myeloma stem cells exist, and if so, how they might interact with the microenvironment.

Dr. Dalton believes it is possible to target and redefine high-risk myeloma, e.g., by use of combinations of therapies acting on different intracellular pathways. This will require strategic development of combination therapies to improve outcomes. Furthermore, understanding of the precise mechanisms of action of novel target-based therapies will improve rational drug combinations. Models for drug development which include examining the influence of the tumor microenvironment will yield additional new targets for therapy.

## Diagnosis and Management

Dr. Nikhil Munshi, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, chaired the Plasma Cell Disorders Education Session. He reviewed diagnostic advances, including the use of free light chain (FLC), fluorescent in situ hybridization (FISH), magnetic resonance imaging (MRI), and GEP, approaches that have moved from targeting myeloma tumor cells with melphalan-prednisone (MP) to targeting myeloma cells along with their bone marrow environment, and from palliation, to treatment as a chronic illness, to nearing a cure. He then gave a talk entitled Investigative Tools for Diagnosis and Management.

Dr. Munshi noted that analysis of high levels of serum free light chain has helped to predict a higher risk of progression in MGUS and SMM, but that whether stringent complete response (CR) with normal FLC is a predictor of overall survival needs to be validated. Furthermore, although determination of FLC in urine is not indicated, determination of Bence-Jones proteins in a 24-hour urine sample is still important for staging and prognostic work-up, as are albumin, lactic dehydrogenase (LDH), and beta-2-microglobulin levels, bone marrow cytogenetics, and FISH.

Dr. Munshi believes that the International Staging System (ISS) is universally applicable, cytogenetics are informative in about 25% of patients, and the presence of an abnormal karyotype is an independent predictor of poor outcome. The addition of high-density genomic arrays including RNA-based GEP, array comparative genomic hybridization (CGH), and single nucleotide polymorphism (SNP) DNA-based analyses, will improve prognostication. He noted that there are no genes in common between the 70-gene Arkansas model and the 15-gene IFM model, agreeing with Dr. Shaughnessy that this currently complicates using

these data for risk assessment. Groups with different prognoses continue to be defined based on differences in up- and down-regulation of gene expression. However, the importance of genetic markers in defining risk has to be assessed in the context of the particular agent used for treatment.

In response to a question, Dr. Munshi said the best way to evaluate CR was to perform protein electrophoresis and immunofixation on both serum and urine, and determine the percentage of plasma cells in the bone marrow, with confirmation 6 weeks later. Dr. Barlogie suggested assessment should include MRI, and Dr. San Miguel added immunofixation of bone marrow and FLC, although he conceded that neither of these two tests nor MRI is yet an accepted measure of CR.

## Staging

### Improved survival of patients with myeloma after introduction of novel agents and applicability of ISS: an analysis of the Greek myeloma study group (GMSG) (abstract #655)

Dr. Meletios Dimopoulos, Alexandra Hospital, Athens, Greece, presented this study on behalf of Dr. Efstathios Kastritis and colleagues. Most of the patients in this study were treated outside of clinical trials. The aim was to assess applicability of ISS in the era of novel agents because the ISS has not been validated as a prognostic tool in patients who have been treated up front with novel agent-based therapies. Since 1985, 1376 patients with newly diagnosed myeloma have been entered into the GMSG database, 859 before 1999 and 517 after January 1, 2000, when thalidomide (thal) became available in Greece.

Patients in the more recent of the two cohorts were older, had a higher ISS stage and other negative prognostic factors, but also had better response rates. After a multivariate analysis, age, diagnosis before 2000, and ISS stage remained significant adverse survival factors. The Kaplan-Meier survival curves by ISS stage were clearly separated. Novel agents significantly improved survival of patients treated outside tertiary centers, mainly for younger patients in whom median survival doubled. Patients with high ISS, renal disease, high LDH, anemia, and poor performance status (PS) saw improved survival with novel agents; however, median survival for patients with ISS stage III is still less than 3 years.

## Response

### Effect of pre- and post-transplant responses on outcome of patients with myeloma: CR and nCR should not be considered as equivalent prognostic markers: results of a PETHEMA/Gem prospective study (abstract #161)

Dr. Joan Blade, Hospital Clinic, Barcelona, Spain, presented the results of a prospective analysis of the prognostic influence of response in patients in the GEM200 program on behalf of Dr. Juan Jose Laherta, University Hospital, Madrid, Spain, and colleagues. There were 632 patients evaluable after VBMCP/VBAD and BUMEL or MEL 200 ASCT. A median FU of 45 months was available for 968 patients registered; 178 patients did not go on to transplant; there was 2% transplant-related mortality; and 119 patients who received a second transplant were excluded.

CR post-transplant was significantly correlated with response before transplant. Patients with conversion from partial response (PR) to near (n) CR or CR have significantly longer event-free survival (EFS) and overall survival (OS) compared with patients who remain in PR after transplant. Patients who converted to nCR after transplant had significantly improved EFS and OS compared with those who had nCR both pre- and post-transplant. Patients with nCR and stable disease (SD) did better than patients with PR post-transplant, as did patients younger than age 65 years. Patients with SD may not have responded to initial therapy, but also don't have progressive disease. Although they may be considered to have chemoresistant disease, they may have indolent disease. For non-responsive but non-progressive disease, transplantation may not add anything, and the good outcome may be due to the indolent course of the myeloma.

### **90% sustained CR rate projected 4 years after onset of CR in GEP (abstract #162)**

Dr. Bart Barlogie, University of Arkansas Medical Center, Little Rock, Arkansas, conveyed the message that a durable CR can be achieved using current therapies. He described an extension of Total Therapy 3 A (TT3A), n=303, the results of which are published, with the TT3B cohort, n=177 for a total of 480 patients. TT3B involves VRD (bortezomib-lenalidomide-dexamethasone) maintenance for 3 years vs. TT3A with VTD maintenance for 1 year and thal dex (TD) maintenance for 2 years. The group may be considering extending maintenance with lenalidomide (len).

A multivariate analysis of TT3A and TT2B by GEP was used to define a high-risk population in which cytogenetics and LDH are still risk factors, and CR is also a highly significant favorable feature of outcome. TT3A and TT3B vs. TT2 indicates that CR duration is the best surrogate for a "cure." TT3 is of benefit in patients with low-risk disease but is of no benefit for those with high-risk disease.

The addition of btz in TT3 results in translocation 4;14 no longer being an adverse feature, especially in otherwise low-risk disease. A post-bortezomib (btz) pharmacogenomic 80-gene model has been tested and validated as having better prognostic value than the Arkansas GEP 70 score to evaluate patient response to a test dose of bortezomib. For the 85% of patients identified as having baseline low-risk disease, current therapy is difficult to improve upon. A study for low-risk disease randomly assigns patients to standard TT3 vs. "TT light," or TT4, which is expected to have reduced toxicity and sustained efficacy; 20 patients have been enrolled. For high-risk disease, TT5 is being tested in a phase II study in which a dose dense but less dose intense treatment may avoid host exhaustion. So far, there has been high compliance for performing GEP at baseline, 48 hours post btz, 48 hours post MEL, and prior to both transplants 1 and 2 to evaluate the effect of therapy.

## **Front-Line Treatment of Myeloma**

In the last few years the novel therapies (bortezomib, lenalidomide, and thalidomide) moved from approval in the relapsed/refractory setting, to late-phase trials in the front-line setting, to approval for both thalidomide and bortezomib for use in newly

diagnosed patients. Additional data are becoming available for the use of novel therapies in combination with each other as well as with conventional therapies for myeloma.

## **Induction Therapy**

During the Plasma Cell Disorders Education Session, Dr. Jean-Luc Harousseau, University Hospital, Hotel-Dieu, Nantes, France, reviewed induction therapy in multiple myeloma, which usually means remission induction, in contrast to induction in acute leukemias, where the goal is to achieve CR. He observed that until recently, the choice of induction therapy was easy: VAD (vincristine adriamycin dex) followed by high-dose therapy (HDT) plus autologous stem cell transplant (ASCT) for younger patients, and melphalan prednisone (MP) for older patients. The advent of novel therapies has presented more choices of combination therapy, many of which are still in clinical trials. In general, adding a novel agent to MP improves response, e.g., MPT (MP plus thal) is better than MP or Mel 100 for progression-free survival (PFS) and response rate, and in some trials for OS. VMP (MP plus bortezomib) results in better response and longer PFS and OS than MP. MPR (MP plus lenalidomide) is still being studied, as are various other combinations of novel agents with corticosteroids and/or alkylating agents.

Dr. Harousseau emphasized that MP is no longer the standard induction therapy for elderly patients, with either MPT or MPV being a better choice. The combination of len dex is also attractive for this population, with reduced-dose dex offering better tolerability. However, the best induction therapy for elderly patients will be tested in upcoming IFM trials.

For younger patients, CR/very good partial response (VGPR) is achieved after HDT and ASCT. Btz dex prior to ASCT results in better response rates across all cytogenetic risk groups than VAD, which all randomized studies confirm should no longer be used for induction therapy prior to ASCT. Studies are continuing to collect data for len dex and for three-drug combinations, e.g., two novel agents plus dex, or a novel agent with dex plus an alkylating agent.

### **Btz dox (Doxil; pegylated doxorubicin) dex (PAD) as induction prior to reduced intensity ASCT followed by lenalidomide (len) prednisone (LP) for consolidation and len as maintenance in elderly untreated myeloma patients (abstract #159)**

Dr. Antonio Palumbo, Ospedale San Giovanni Battista, Torino, Italy, presented the results of this study to determine if 4 cycles of PAD followed by mobilization with cyclophosphamide and G-CSF (granulocyte colony stimulating factor) then MEL 100 reduced-intensity conditioning (RIC) for 2 cycles was feasible in patients aged 65 to 75 years. LP consolidation was given for 4 cycles, then len alone was used for maintenance. All patients have not yet been treated; responses for the first 77 enrolled patients (per protocol not ITT population) are: 60% VGPR or better after 4 cycles PAD, 87% VGPR or better with 13% CR after PAD Mel 100, CR rising to 59% after consolidation and 73% after maintenance. Median follow-up (FU) is 17.6 months; PFS projected as 80% at 3 years, OS 90% at 2 years. Patients younger than

age 70 years are doing better, so the cut-off for this regimen is probably age 70 years. PAD overcomes the prognostic factors of elevated beta 2-microglobulin and abnormal cytogenetics. Grade 3 to 4 adverse events (AE) include 15% thrombocytopenia, 15% peripheral neuropathy (PN), which may require adjustment of the btz dose, and 15% infections.

### **Phase III Trials in Newly Diagnosed Myeloma**

#### **Superior CR rate and PFS after ASCT with up-front vel thal dex (VTD) compared with thal dex (TD) in newly diagnosed myeloma (abstract #158)**

Dr. Michele Cavo, Istituto Seragnoli, Bologna, Italy, presented preliminary results of a phase III randomized study of three 21-day cycles of induction therapy with btz thal dex compared with thal dex followed by stem cell collection, cyclophosphamide, HD melphalan, and consolidation. 460 evaluable patients after at least ASCT were included in this analysis. The median age was 56 years. Results for the ITT population so far are: VTD n=226 with CR/nCR 32%; TD n=234 with 12% CR/nCR. At least VGPR was 62% vs. 29%; PR or greater was 94% vs. 79%. VTD was superior, at least for the nCR rate, across subgroups including poor prognostic factors such as deletion (del)13, translocation 4;14, and del 17. The response to the first ASCT was: VTD CR/nCR 55% vs. TD 32%; CR 43% vs. 23%, at least VGPR 78% vs. 56%. VTD also gave significantly better response rates than TD after the second ASCT and consolidation.

Serious AE (SAE) that were higher with VTD included grade 3 to 4 PN and skin rash; otherwise SAE were similar. Of patients with grade 3 to 4 PN while on VTD as induction therapy, 95% remained on therapy with no effect on response rate compared with those with lower-grade or no PN. Discontinuations of induction therapy were higher for patients on TD than VTD, mostly due to disease progression. Estimated 2-year PFS is 90% for VTD vs. 80% for TD, which is significant; OS for VTD is 96% vs. 91% for TD, which is not a significant difference.

Dr. Cavo concluded that short-term induction with VTD results in significantly increased rates of at least nCR and VGPR, and overcomes adverse prognostic factors. The significantly increased VGPR or greater rate is seen after both first and second ASCT and consolidation, as is significantly improved time to progression (TTP) and PFS. However, longer follow-up is needed for this trial, which closed this past April with a current median follow-up of only 15 months. Less than half the patients have received their second ASCT, so even fewer have received consolidation therapy.

#### **Final analysis of HOVON-50 randomized phase III trial of thal adria dex (TAD) and HD mel (HDM) in patients with myeloma (abstract #157)**

Dr. Henk Lokhorst, University Hospital Utrecht, Utrecht, Netherlands, presented the results of the study of 556 patients randomized to VAD vs. TAD, followed by all patients receiving CAD (cyclophosphamide adriamycin dex) and G-CSF. Patients then received RIC (n=109) or HDM followed by maintenance with interferon (IFN) or thal. Although response rates, EFS, and PFS were better in the TAD group, there was no difference in OS

between the two arms with a 5-year median OS for both groups. A landmark analysis indicated that patients who had CR as the best response had the best prognosis, with 80% 5-year survival. Patients with ISS stage I disease at diagnosis had a 70% 5-year survival. Patients who received thal maintenance had a reduced OS at relapse compared with patients who didn't receive thal maintenance.

#### **Mel + pred vs Mel + pred + thal in induction therapy for myeloma in elderly patients: final analysis of the Dutch cooperative group HOVON 49 study (abstract #649)**

Dr. Pierre Wijermans, Haga Hospital, The Hague, Netherlands, presented the results of this randomized, phase III study in patients older than age 65 years. The target enrollment was 420 patients but the study was stopped early at MP n=167 and MPT n=165 because doctors in the Netherlands were convinced that thalidomide should be given as frontline therapy for elderly patients. Toxicity was higher in the thal arm, mostly grade 2, with a low thrombosis rate because most patients received DVT prophylaxis, although it was not required. CR+VGPR was 29% for MPT vs. 9% for MP. The quality of response increased with continued therapy. EFS was MPT 53% vs. 35% MP at 1 year, 33% vs. 19% at 2 years, 9% vs. 3% at 4 years. There was no difference in OS; most patients in the control arm got thal at relapse, and its role as maintenance can't be ruled out.

#### **First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing btz, adriamycin, dex (PAD) vs. VAD as induction treatment prior to HD mel in patients with newly diagnosed myeloma (abstract #653)**

Dr. Pieter Sonneveld, University Hospital Rotterdam, Rotterdam, Netherlands, presented results of the first interim analysis on ITT response data for the initial 300 of 825 patients (150 patients per arm) randomized to VAD vs. 3 cycles of PAD. Following randomization, all patients received CAD, stem cell collection, and HDM with autologous peripheral blood (PB) SCT. Patients then received either thal or btz maintenance for 2 years. If patients had HLA identical siblings, they could have an allogeneic transplant in lieu of an autologous transplant. Patients in the Netherlands received 1 HDM/PBSCT vs. 2 for participating patients in Germany. CR/nCR was 5% for PAD (lower than expected) vs. 1% for VAD. VGPR was 42% for PAD, 15% for VAD. HDM and SCT results were CR/nCR 23% for PAD vs. 9% for VAD.

The only significant AE for PAD was 16% grade 3 to 4 PN, vs. 6% for VAD. Deep vein thrombosis (DVT) rates were similar for both arms with no prophylaxis. PAD overcomes the poor prognosis associated with translocation 4;14 and del 13 but these poor-risk patients do not totally account for the improved responses with PAD. Responses continue to improve while patients are on btz maintenance.

#### **Vel-mel-pred (VMP) vs. vel-thal-pred (VTP) in elderly untreated patients with myeloma: which is the best partner for Velcade: an alkylating or an immunomodulator agent? (abstract #651)**

Dr. Maria-Victoria Mateos, University Hospital of Salamanca, Salamanca, Spain, presented the results of this phase III, ran-

domized trial in 260 newly diagnosed patients older than age 65 years. Patients received VMP vs. VTP. The first 6-week cycle was standard btz for both groups. Thereafter patients received bortezomib once a week for 5 cycles plus either oral melphalan and prednisone or thalidomide at 100 mg daily plus prednisone. For both groups, treatment continued for a maximum of 6 cycles (31 weeks) barring disease progression or unacceptable toxicity. The overall response rate (ORR) was 81% for each arm with 22% CR for VMP and 27% for VTP, nCR was 19% vs. 10%; PR 40% vs. 44%. Median FU is 16 months with the 2-year TTP estimated at 72% for VMP vs. 65% for VTP, and the OS estimated to be 88% vs. 93% at 2 years.

There was more neutropenia, thrombocytopenia, and infection with VMP and higher cardiologic toxicity with VTP. Thromboprophylaxis was mandatory but DVT and TE (thromboembolism) was 4% in the VTP arm. SAE were significantly higher with VTP as was the discontinuation rate. There were 4% deaths in both arms. ORR and IF- (immunofixation) negative CR rates were similar. Dr. Mateos concluded that thal may not be the partner of choice with btz for elderly patients and suggested that lenalidomide should be tested. During the discussion, suggestions included testing maintenance therapy due to a precipitous drop in EFS around 20 months when effective therapy ended, as well as a less intense regimen of VMP for more fragile patients.

#### **Prospective, randomized phase III study of btz, mel, pred, and thal (VMPT) vs. btz mel pred (VMP) in elderly newly diagnosed myeloma patients (abstract #652)**

Dr. Antonio Palumbo presented the results of this GIMEMA trial in 393 patients over age 65 years who were not eligible for transplant and who received either VMP with no maintenance, or VMPT and maintenance with btz and thal. The protocol started with a schedule similar to that used in the VISTA trial, which was amended to weekly btz.

VGPR or better was 55% for VMPT vs. 45% for VMP; CR for VMPT was 39% and 21% for VMP. Time to PR for the majority of patients occurred in 1 to 2 cycles of treatment, but CR increased slowly over time, suggesting lower intensity but longer treatment might result in more CR. There was no difference in OS projected at 3 years between the two treatment arms.

Hematologic AE are similar, but non-hematologic AE are significantly different. VMPT is associated with 13% sensory neuropathy vs. 5% for VMP. Infections were higher with VMPT, 13% vs 9%. In a subgroup analysis, weekly vs. biweekly btz did not reduce CR but did reduce PN from 24% to 6% for VMPT, and reduced CR slightly and PN from 14% to 2% for VMP.

Dr. Palumbo concluded that VMPT doubles the response rate of VMP, and increases time to next therapy, but not OS. He suggested longer FU (beyond the current 14 months) is needed to assess PFS and OS. Because of the need for further investigation, VMPT shouldn't be incorporated into the standard of care.

#### **Updated follow-up and results of subsequent therapy in the phase III VISTA trial: btz plus mel-pred (VMP) vs mel-pred (MP) in newly diagnosed myeloma (abstract #650)**

Data for the VISTA trial through April 25, 2008, was presented by Dr. Jesus San Miguel, University Hospital of Salamanca, Salamanca, Spain. This phase III trial, which included 682 patients who were not candidates for transplantation, was stopped at the third interim analysis with a median FU of 16 months. Current median FU is 25.9 months. M-protein determinations, which were done at a centralized lab, were stopped at study end.

There was a 36% reduced risk of death with VMP, although 43% of patients receiving MP also received btz at relapse. There was consistent efficacy in patients with poor prognostic characteristics, including high creatinine clearance (CrCl), or high-risk cytogenetics, e.g., translocations 4;14 and 14;16. Of patients treated with VMP, 38% vs. 57% of those treated with MP required subsequent therapy for progression. The response rate was higher with btz as therapy for progressive disease (PD) in patients in the MP arm vs. patients in the VMP arm; responses to subsequent therapy with thal or len were similar regardless of arm. Patients receiving VMP were not more resistant to subsequent therapy at relapse. Better survival was seen for patients who received VMP upfront than those who received MP and subsequent therapy at relapse. CR was associated with longer TTP but not longer OS, possibly due to the low number of events. Erythropoietin stimulating agent (ESA) use did not adversely affect long-term outcomes with VMP or MP, although ESA use was higher with MP.

There were no differences in hematologic AE between arms. VMP was associated with higher gastrointestinal toxicity (19% vs. MP 5%) and PN (13% vs. none). PN reversed in 79% of patients in a median of 1.9 months and 60% of patients with PN eventually completely recovered. The longer FU confirms a significant benefit for VMP vs. MP, including time to next therapy, in all patients, including those with high-risk cytogenetics, the elderly, and those with renal impairment. Patients who receive VMP will not progress to relapsed disease that is intrinsically more resistant than those who receive MP.

### **Early Trials in Newly Diagnosed Patients**

Dr. Sundar Jagannath, St. Vincent's Comprehensive Cancer Center, New York, and Dr. Antonio Palumbo moderated a session in which early phase trials of therapy of newly diagnosed patients were discussed. These results are summarized in the following table:

See chart "Summary of Early Trial Data in Newly Diagnosed Myeloma" on page 10

### **Relapsed and Refractory Myeloma**

#### **Combination of len, mel pred, and thal (RMPT) in relapsed/refractory: results of a multicenter phase II clinical trial (abstract #868)**

Dr. Antonio Palumbo presented the results of a GIMEMA study. He noted that the CR rate with VMP is 21%, and with VMPT CR is increased to 39%. This study included 44 patients, half receiving 50 mg thal, the other half 100 mg thal, standard dose MP, and len 10 mg for 3 of every 4 weeks for 6 cycles of induction. Low-dose ASA (100 mg) WHAT IS ASA? was mandated. The CR/nCR rate

was 13%, with 20% VGPR. This was a lower response rate than seen in historic controls treated with VMPT, and the hematologic toxicity and infection rate was also greater. The OS projected at 12 months was also lower than that seen with VMP.

## Maintenance Therapy

### Maintenance that may improve progression-free but not overall survival: results from the Myeloma IX maintenance randomization (abstract #656)

Dr. Gareth Morgan, Royal Marsden Hospital, Sutton, Surrey, United Kingdom, presented preliminary results of a maintenance study randomizing patients to thalidomide or no maintenance. This study enrolled 1970 patients, including older, less fit patients treated with MP or CTD, and younger, fitter patients treated with CTD or CVAD then HDM, with 820 randomized to maintenance. The optimum induction regimen isn't known because the study has not been completely unblinded.

CTD with no maintenance seems to be the optimum intensive regimen. For patients receiving non-intensive therapy, the OS with CTD is 40 months vs. 29 months with MP. It appears that the use of thal plus alkylating agent plus steroid as one treatment is superior to alkylating agent plus steroid followed by thal maintenance.

For patients with PR after intensive therapy, thal maintenance improves PFS but not OS, and there was no benefit beyond 6 months of maintenance. This may reflect a continuing therapy rather than maintenance benefit. Thal maintenance had no impact on OS of patients with chromosome 14 translocations associated with poor prognosis, and was associated with reduced PFS and OS for patients with deletion of 17p. Dr. Morgan concluded that rather than defining a maintenance effect for thal, the results might reflect a consolidation effect for poor response after induction. He thinks CTD induction with no maintenance after HDM might be appropriate for younger patients, and suggested looking at len maintenance.

## Skeletal-Related Events

Dr. G. David Roodman, Pittsburgh Healthcare System and University of Pittsburgh, Pennsylvania, presented Skeletal Imaging and Management of Bone Disease during the Plasma Cell Disorders Education Session. Myeloma is the most frequent tumor to involve the skeleton. Dr. Roodman believes that if one were to look closely enough, all patients with myeloma would be found to have skeletal involvement. Fracture increases the risk of mortality. At diagnosis, 20% of patients have pathologic fractures, and up to 60% will have fractures over the course of their disease. In myeloma, bone remodeling absorption and formation are uncoupled.

Dr. Roodman feels that bone scans can underestimate the degree of bone disease, and therefore the diagnostic gold standard should be a metastatic bone survey of the skull, vertebrae, pelvis, and extremities, although lesions will not be seen until there is a 30% loss of trabecular bone. This test is not useful for assessing response to therapy, because in most patients these lesions do not heal. Computed tomography (CT) evaluation is more sensi-

tive than x-ray, and with the development of low-dose whole body CT, this may become the new gold standard. MRI is also more sensitive than x-ray because it detects bone marrow involvement: low T1- and high T2-weighted images are characteristic. MRI is the choice to evaluate vertebral compression. Positron emission tomography (PET)/CT is also more sensitive than x-ray, with the same sensitivity as MRI, although it may miss small lesions, and false positives are seen with inflammatory disease. Another drawback is that PET/CT is very expensive.

Treatments for myeloma bone disease include bisphosphonates, surgical procedures, e.g., vertebroplasty and balloon kyphoplasty, radiation, and, obviously, treatment of the underlying myeloma disease. Kyphoplasty offers good pain relief. Bisphosphonates bind to bone, are taken up by osteoclasts, blocking their activity, and reduce skeletal-related events. However, they have no clear antitumor activity. AE associated with bisphosphonates include an acute-phase inflammatory reaction with zoledronic acid requiring premedication, renal toxicity, a newly identified musculoskeletal pain syndrome, which can occur early or late in treatment, and osteonecrosis of the jaw (ONJ). The mechanism behind ONJ is still unclear, with no direct cause and effect relationship with bisphosphonates. Risk factors include invasive dental procedures, longer time from diagnosis, and infection with actinomycetes. If ONJ occurs, bisphosphonates should be discontinued until lesions heal. Management includes dental evaluation prior to bisphosphonate use, empirical treatment with antibiotics and oral rinses, pain control, and limited debridement. Dr. Roodman notes that hyperbaric oxygen is not effective. ASCO guidelines suggest bisphosphonates should be administered for two years, but there are no clinical data to support this, although two prospective studies are ongoing. Withholding bisphosphonates for a short period of time before dental procedures, as suggested in Canadian guidelines, makes no sense, Roodman explains, because the drugs can remain in bone for a decade. He concludes that as signaling pathways and factors involved in myeloma bone disease are identified, new and more effective targeted therapies may be developed.

## IMF Satellite Symposium

### Finding Your Way Through the Treatment Maze – Selecting the Best Treatment in the Era of Novel Agents

This program was facilitated by Dr. S. Vincent Rajkumar, Mayo Clinic, Rochester, Minnesota, and featured discussions of case studies by Dr. Rajkumar and faculty members Dr. Antonio Palumbo, Dr. Philippe Moreau (IFM, Nantes, France), and Dr. Jesus F. San Miguel. The audience's knowledge of treatment options for each case patient was assessed before and after the presentations and discussions.

Case studies with suggested treatments included the following:

- a newly diagnosed patient with multiple myeloma who was ineligible for transplantation
  - P-T (melphalan-prednisone-thalidomide) or MP-V (MP-bortezomib; btz) are good options; MP-lenalidomide (Revlimid; MPR) is still being investigated

- thalidomide-dexamethasone (thal-dex) is not the standard of care because the results are not superior to those obtained with MP
- for patients over the age of 75 years, dose-reductions should be considered to reduce toxicity
- a newly diagnosed, transplantation-eligible patient with ISS stage III multiple myeloma, who had normal cytogenetics and translocation 4;14 by FISH
  - alkylating agents, which interfere with the collection of stem cells, should not be used
  - thal-dex is FDA approved, but is associated with neurologic side effects
  - btz-dex, VTD (btz-thal-dex), and VRD [btz- Revlimid (lenalidomide)-dex] are being studied
  - choices include the oral regimen lenalidomide + low-dose dex (Rd) for a patient with low-risk disease; a btz-based regimen for a patient with high-risk disease; and VTD for a patient with acute renal failure, to control disease rapidly
  - there were suggestions to add a third drug, e.g., cyclophosphamide or Doxil (pegylated doxorubicin), which needs to be tested in trials, or to use two drugs and save the third one for relapse
- a patient age 64 years, with ISS stage II myeloma, normal cytogenetics, t(4;14) by FISH, for whom transplantation eligibility is uncertain, due to a partial response after 4 cycles of induction therapy
  - for younger patients not being treated in a clinical trials, induction therapy, possibly with a btz-dex-based regimen followed by ASCT prepared by Mel 200, with post-ASCT maintenance with thal (or maybe lenalidomide) for one year would be a reasonable regimen
  - ongoing studies are addressing whether ASCT is needed in the era of novel therapies
- a patient with multiple myeloma who relapsed multiple times after multiple treatments following induction therapy
  - IMiDs (thal, len, and presumably pomalidomide which is in development) with btz should be restricted to well-controlled trials to preserve future options for patients
  - young patients with early relapse (less than one year post-ASCT), intermediate relapse (1 to 3 years post ASCT), and late relapse (more than 3 years) should be distinguished:
    - ◆ early relapse: therapy should address overcoming drug resistance with combinations or alternating non-cross-resistant agents
    - ◆ intermediate relapse: therapy should prolong survival with sequential novel agent combinations until curative treatments are developed
    - ◆ late relapse: re-induction and a second ASCT
  - for elderly patients, their general condition should be taken into account, using a different drug than that used for induction followed by enrollment in a trial for active treatment, and oral cyclophosphamide plus prednisone for patients not candidates for active treatment

New therapies in development to target different points in pathways thought to be important in the development of myeloma include monoclonal antibodies targeting receptors on the surface of myeloma cells and agents affecting intracellular signaling pathways such as:

- new proteasome inhibitors
- histone deacetylase inhibitors
- heat shock protein (HSP) 90 inhibitors
- new immunomodulatory drugs

The issue of maintenance therapy was discussed in the question and answer period. Dr. Moreau felt that maintenance with thalidomide was beneficial mainly in patients who had a response of less than VGPR. Dr. San Miguel noted that thalidomide was not approved for this purpose. Dr. Palumbo said there was no role for maintenance, but adding a third drug for consolidation after a sub-optimal response was appropriate. Ongoing trials may clarify the role of maintenance therapy.

## New Treatments in Early Stage Development

As the natural history of myeloma is better understood, new therapies are being developed to target specific pathways involved in the disease. Targets include the interaction of myeloma cells with the bone marrow microenvironment, cell surface proteins and receptors on myeloma and bone marrow stromal cells, and intracellular molecules in pathways involved in myeloma pathogenesis.

Progress is being made in developing therapies targeted to specific growth factors and other molecules essential for the development and progression of myeloma. Because many of these therapies have limited activity as single agents, they will likely be used in combinations, particularly with the novel therapies bortezomib, lenalidomide, and thalidomide. Combining agents with different mechanisms of action may increase their activity while reducing the likelihood of side effects.

Interesting clinical trial results are summarized in the table “**Clinical Trial Results New Therapies**” on page 11

## Future Directions

New therapies that are targeted to specific pathways in myeloma development continue to enter clinical trials. The novel therapies bortezomib and thalidomide have moved from the relapsed, refractory setting to the frontline setting, and lenalidomide may be expected to do the same. The trend of combining these therapies with conventional chemotherapies, each other, and/or and targeted therapies is continuing, expanding the treatment options for patients with multiple myeloma. Multiple myeloma is becoming more like a chronic, long-term disease as new treatment options continue to become available.

Lynne Lederman, PhD, is a medical writer based in Mamaroneck, New York

## Summary of Early Trial Data in Newly Diagnosed Myeloma

Treatment	First Author (abstract)	Study Design	Results and Conclusions
RCd: lenalidomide (len) with cyclophosphamide (cyclo) and low-dose dexamethasone (dex)	Shaji Kumar (#91)	Phase II feasibility; patients could go on to ASCT; n=34, then cyclophosphamide dose lowered and 19 additional patients enrolled	VGPR+CR 32%, may increase with time for patients not going to transplant and still on study; most AE were hematologic; 20 patients completed therapy, 2 died, 11 PD; median time on study 4.8 months, median FU 12.3 months; 30 patients collected stem cells, 8 failed, 3 salvaged with AMD3100, 1 with cyclo
Len, bortezomib (btz), dex: btz standard dose and schedule; len maintenance after 8 cycles; dex reduced during study	Paul Richardson (#92)	Phase I/II to define maximum tolerated dose (MTD) of combination and response; n=66	46 patients completed 8 cycles, 15 went to ASCT. Most common AE: manageable myelosuppression; 3% TE; low rate PN. 26% CR, 18% nCR, 36% PR. Further phase III studies in progress or planned.
Btz, dex, cyclo, and len (VDCR): standard btz, dex weekly	Shaji Kumar (#93)	Phase I/II multicenter EVOLUTION; n=25, MTD not reached, 2 dose-limiting toxicities (DLT). Phase II recruiting and randomizing to 3 arms: VDR, VDC, and VDCR induction up to 8 cycles, then btz maintenance weekly	Most common AE: PN, cytopenias (not cumulative), no TE. Best unconfirmed response preliminary phase I: 36% CR (20% stringent CR), 68% VGPR or better. 11 patients have collected stem cells.
Btz, cyclo, thal, and dex	William Bensinger (#94)	Phase II; btz cyclo dex cycles 1 to 3; btz, thal, dex cycles 4 to 6; n=44	Best response: 26% CR, 9% nCR, 21% VGPR; OS n=43 86% (12-month estimate); 22 patients transplanted; 11 patients grade 3 to 4 AE requiring dose reduction, 10 patients discontinued; 8 deaths including 4 disease related
Consecutive patients receiving len dex as initial therapy, could pursue ASCT at end of 4th cycle	Prashant Kapoor (#95)	100 patients classified mSMART model as high risk (n=16) or standard risk (n=84)	Median estimated FU 46 months. Similar responses high and standard risk, median OS similar at 2 years: 92% alive, at 3 years: 84% vs. 77%. TTP and PFS high risk inferior to standard risk.
Btz and HD mel (HDM) before ASCT	Murielle Rousell (#160)	Phase II, open label, multicenter study, 2 cycles btz before and 2 after HDT; n=54; choice of induction therapy not specified	Btz HDM might be superior to HDM alone after VAD induction. A phase III study was planned.

## Clinical Trial Results New Therapies

Treatment	First Author (abstract)	Study Design	Results and Conclusions
<b>Perifosine (alkylphospholipid oral AKT inhibitor)</b>			
Perifosine (KRX-0401) + btz	Paul Richardson (#870)	Phase I/II multicenter trial in patients with relapsed/refractory myeloma including btz; btz standard schedule, at progression add dex; n=84	GI toxicity, diarrhea manageable with dose reduction. Manageable hyponatremia, hyperglycemia with dex. Best response in 72 evaluable patients CR 3%, nCR 4%, ORR 38%; dex did contribute to ORR; median TTR: 5 cycles; TTR btz refractory: 6 cycles, TTP (n=72): 6.3 months; in those MR or better 9.4 months; ORR 38%, btz refractory 31%  Randomized phase III trial peri + bz+dex vs. bz+dex+ placebo in relapsed/refractory myeloma planned or ongoing
<b>Vorinostat [Histone Deacetylase (HDAC) Inhibitor]</b>			
Vorinostat plus btz	Donna Weber (#871)	14-day vorinostat dose, from bid to qd schedule; btz dose lower, escalated to standard dose; EBMT response criteria; n=34, median age 64 years	DLT: 1 transient AST grade (gr) 3, thrombocytopenia gr 4; thrombocytopenia, fatigue common; SAE 29%; PR 38%; DOR 5.3 months
Vorinostat plus btz	Donna Weber (#871)	Vorinostat days 4 to 11, dose escalated; btz dose started higher, reduced to standard dose; IMWG response criteria; n=23, median age 54 years	DLT: prolonged QT and fatigue gr 4; increased myelosuppression with increasing cycles; VGPR 10%, PR 33%; DOR not available
<b>Monoclonal Antibodies (mAb)</b>			
CNTO 328 (anti-IL-6 mAb) plus btz	Jean-Francois Rossi (#867)	Phase II study in btz- naïve, relapsed/refractory myeloma, part 1: n=21; part 2: n=270	Part 1: median TTP 8.7 mo, CR 3 patients, VGPR 3 patients, PR 6 patients; CR+VGPR 29%, ORR 57%; hematologic toxicity as expected with btz, mostly neutropenia; 5 patients gr 3 to 4 infections; part 2 ongoing
<b>Pomalidomide [Thalidomide analog (IMiD) CC4047]</b>			
Pomalidomide plus low-dose dex	Martha Lacy (#866)	Phase II relapsed myeloma; n=60, starting dose 2 mg PO daily, dex 40 mg once a week, mandated ASA for DVT prophylaxis	Hematologic toxicity gr 2 neutropenia prominent, non-hematologic toxicity gr 3 fatigue 28%, 1 death neutropenia/pneumonia. No gr 3 to 4 PN, no DVT/PE. Dose reduction pomalidomide 13%, dex 32%. 66% MR or better; best response median FU 4 months: ORR 58%, CR+VGPR 25%.  Future phase II trial of pom dex for len-refractory and btz- refractory myeloma.
<b>Carfilzomib (Proteasome Inhibitor PR-171)</b>			
Carfilzomib (PR-171; CFZ)	Sundar Jagannath (#864)	PX-171-003, open label, single-arm, phase II study in patients with relapsed and refractory myeloma with at least 2 prior therapies that included btz, thal or len; CFZ 20 mg I.V. push 2 consecutive days 3 weeks on, one week off for maximum 12 cycles; trial is ongoing; n=46	39 evaluable patients, PR 13%, MR 13%, SD 41%, PD 28%; 5 btz-refractory pts had MR or better; median DOR: 7 months. Hematologic toxicity primarily anemia and thrombocytopenia, cyclical as for btz, not as much neutropenia. Non-hematologic toxicity gr 3 to 4 events in 3 patients, e.g., fatigue. Creatinine changes generally transient and non-cumulative; 4 patients with acute renal failure, 1 died pneumonia and septic shock. All renal failure reversible off drug. Well tolerated for up to a year, no painful PN. Next stepped up dose escalation from cycle 2, study expanded to n=250, treatment extended beyond a year, potential for accelerated approval within a year as a drug for unmet need.
Carfilzomib (PR-171; CFZ)	Ravi Vij (#865)	PX-171-004, open label, single-arm, phase II study in patients with relapsed myeloma; 12 cycles; dex 4 mg PO first cycle only as premed to reduce cytokine release seen in phase I studies as low-grade fever; results for n=31 reported here	ORR: 35%, CR 3%, VGPR 6.5%, PR 26%; btz-exposed ORR 18%, btz-naïve ORR 57%; 90% response by cycle 4. TTP btz-naïve median FU 108 days no progression, btz- exposed median FU 113 days some progression. Don't have DOR yet. AE hematologic gr 3 to 4 10% or less ; non-hematologic toxicity 2 gr 3 dyspnea, overall fatigue, nausea/vomiting; 2 cases tumor lysis syndrome in btz- naïve patients, 1 possible, 1 documented. Prophylaxis amendment to protocol instituted hydration, allopurinol, no additional instances in next 80 patients. Will extend phase II studies.

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