

A Comprehensive Guide to Kos 2007

Review of the XIth International Myeloma Workshop



Summaries from the workshop sessions in Kos, Greece 5–30 June, 2007

Target Audience:

This activity has been designed to meet the educational needs of hematologists and hematologic oncologists treating patients with multiple myeloma.

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Session 1: Genetics

Chair:

Brian Van Ness, PhD

University of Minnesota Cancer Center, Minneapolis, Minnesota, USA

In virtually all areas of medicine, individualized assessment of risk and response are becoming more and more central to evaluation of clinical trials. Genetic heterogeneity has also taken on a key role in contributing to the understanding of patient variability. Whereas head-to-head comparisons of treatment arms have been the standard for determining the best treatment options, individual variation, associated with chromosomal abnormalities and gene expression profiles (GEP) in the tumor, as well as germline variations that may affect drug efficacy, are defining important subgroups of patients. Thus, it seemed an appropriate lead for the 11th International Myeloma Workshop held in Kos, Greece, June, 2007, to hear discussions of genetic variation, as one might argue it set the stage for other sessions dealing with therapeutic responses.

One recurring theme that was expressed by all presenters was that multiple classification schemes exist for multiple myeloma (MM), yet all describe a heterogeneous condition best described by genetic and cytogenetic markers, with consequent variability of phenotypes and outcomes. The initial presentation by Dr. Leif Bergsagel (Mayo Clinic, Scottsdale, United States) described underlying genetic abnormalities that are present at diagnosis, and continue in MM tumor cells, including immunoglobulin (IgH) gene translocations and hyperdiploidy. The clinical relevance is that these groups identify patients with vastly different prognoses when treated with a variety of standard, high-dose, or novel therapies. The dominance of the chromosomal abnormalities are further affected by secondary events, such as activating mutations in the oncogene Ras, amplifications of 1q, and deletions of 13q [del(13)], all of which modify the course of the disease. Through a combination of comparative chromosomal analysis and gene expression profiling, Dr. Bergsagel and colleagues at the Mayo Clinic have identified a group of mutations that collectively result in activation of nuclear factor-kappa B (NF- κ B) pathways,

long known to be associated with tumor proliferation. One common mutation, TRAF3, appeared to have some profound differences in response to dexamethasone (10% response) versus bortezomib (90% response).

Dr. Mike Kuehl (National Cancer Institute [NCI], United States), a long-time associate of Dr. Bergsagel, continued with detailed discussions of the role of deregulating cyclin D genes as a very early event in both monoclonal gammopathy of uncertain significance (MGUS) and MM. In a nicely collaborative effort among Mayo, NCI, and the University of Arkansas researchers, combining cyclin D expression and chromosomal translocations led to a "TC classification" resulting in eight subgroups that were substantially concordant with the subgroup classification based on gene expression profiles. Deregulated expression of the Myc oncogene by translocation events was described as likely to be a late progression event. Thus, a recurring theme emerged that provides novel cytogenetic and expression classifications that are defining important subgroups of patients, both at diagnosis and during disease progression.

Gene expression profiling has been a dominant genetic classifier of myeloma and MGUS. Dr. John Shaughnessy's studies at the University of Arkansas Medical Center, United States, have been extended to extensive longitudinal studies that are shedding light on molecular characteristics of disease progression and therapeutic response. Comparative gene expression profiling identified 52 genes that may provide distinct clues to the transformation of MGUS to MM. Relative expression of these genes may serve to distinguish myeloma high-risk and low-risk subgroups, which in turn could influence therapeutic options. Notably, a system of analyzing gene expression extremes that reflect gene copy number gains or losses led to a 17-gene expression model of survival. Interestingly, 50% of the genes map to chromosome 1 and were linked to early disease-related death.

Secondary changes in the tumor could be associated with more aggressive disease, and indeed, the gene expression risk score was found to increase at relapse and was able to predict post-relapse survival.

A very comprehensive summary of classification schemes was presented by Dr. Rafael Fonseca (Mayo Clinic, Scottsdale, United States). He provided biologic classification schemes influencing primary and secondary events in disease progression, as well as classifiers that define prognosis. The combination of such classifications is increasingly important for understanding disease response and management. What emerged was a unifying system of disease classification as well as insights into patient subgroups that may benefit from selective therapies.

Cytogenetic abnormalities were further refined by Dr. Hervé Avet-Loiseau's (Nantes, France) description of interphase fluorescent in situ hybridization (FISH). From his presentation it appeared that although del(13) is associated with shorter survival, the prognostic power is almost always related to other chromosomal abnormalities. Moreover, combining cytogenetic definitions with other biologic measures, such as beta-2 microglobulin levels, can distinguish therapeutic outcomes. Dr. Avet-Loiseau contends that by itself, ploidy is not a reliable prognostic marker, as shown by the French Intergroupe Francophone du Myélome (IFM) clinical trials group. His contention is that combining biologic markers with cytogenetic ones (i.e., FISH) can provide strong predictors of survival.

Although initiation, progression, and response in patients with MM is clearly dependent on a variety of genetic deregulation events in the tumor cells, individual patient outcomes are also likely dependent on inherited variations in a wide variety of genes that affect cellular interaction, the immune system, and drug metabolism. Such is the rationale behind the Bank On A Cure[®] (BOAC) concept for detecting germline single nucleotide polymorphisms (SNPs) and their association with outcomes. Dr. Brian Van Ness (University of Minnesota, United States) presented the BOAC SNP panel design and content, which resulted

in a SNP chip assessing 3,404 genetic variations. One early application demonstrated a 6 SNP model in two phase III clinical trials that provided an 81% classification prediction of short (< 1 year) versus long (>3 year) survival. Other presentations in other sessions described the use of the BOAC SNP panel to generate SNP predictors of bone disease (presented by Dr. Brian Durie, Cedars-Sinai Cancer Center, Los Angeles, United States) and SNPs in inflammatory response genes associated with risk for thrombotic events resulting from thalidomide treatment (presented by Dr. Gareth Morgan, Royal Marsden, London, United Kingdom). These emerging studies on inherited variations are likely to enhance the tumor genetic classifiers and provide a more complete understanding of patient variations, which in turn could lead to better individualized therapeutic options.

The associated poster sessions on myeloma genetics provided a strong international contribution to the identification of genetic abnormalities that define important prognostic subgroups. These presentations included Dr. Mario Boccardo's (Torino, Italy) association studies linking chromosomal abnormalities with immunophenotypes, additional FISH studies for prognostic indicators from Dr. San Miguel's group (Salamanca, Spain), cytogenetic abnormalities in Western Australia (Drs. Lee, O'Reilly, and Cooney), FISH studies that showed hyperdiploid and IgH rearrangements from the Korean Myeloma Working Party; and IgH translocations associated with various outcomes from Dr. Cross in the United Kingdom. Transcriptional features of chromosome 1 gains and losses were described by Dr. Neri (Italy), Dr. Cross, and Dr. Shaughnessy (Arkansas, United States). Additional studies on targeted SNP genotypes in inflammatory genes were presented by Dr. Vogel's collaborative group (Denmark and Germany), HAS 1 genes by Dr. Linda Pilarski's lab (Canada), and specific NQ1 genotypes by Dr. Lee (Korea). DNA repair variants showing risk associations were presented by Dr. Cavo (Italy). Two groups (Dr. Meral Beksac, Turkey, and Dr. Chen-Kiang, Weill Medical College of Cornell University, United States) presented findings linking phosphorylation of the retinoblastoma gene product with therapeutic response.

Finally, pharmaceutical companies are interested in the concept of genetic variations as they may affect response, as evidenced by a poster presentation by Millennium Pharmaceuticals (Cambridge, Massachusetts, United States) on pathways that can variably influence response to bortezomib.

The Genetics Session presentations at the 11th International Myeloma Workshop highlighted the results of a rapidly growing technology, that provides detailed and high

throughput analysis of cellular programs that not only lead to malignant transformations, but also tumor heterogeneity and patient variation in outcomes. The combination of cytogenetic analysis of chromosomal abnormalities, gene expression analysis of cellular deregulation, and SNP analysis of inherited variations is now being linked to individualized outcomes. Evidence presented at the meeting clearly demonstrates an emerging application to individualized care that maximizes effectiveness and minimizes adverse events.

Session 2: Pathophysiology – Microenvironment

Chairs:

Dr. Brian G.M. Durie

Cedars-Sinai Cancer Center, Los Angeles, USA

Marie-Christine Kyrtsonis

1st Dept. of Internal Medicine and 1st Dept. of Propedeutic Internal Medicine,
National and Kapodistrian University of Athens Medical School, Laikon General Hospital,
Athens, Greece

Dr. Karin Vanderkerken (Vrije Universiteit Brussel, Belgium) presented an overview of the current animal models of MM. Each model has its advantages and limitations. Whereas *in vitro* studies allow a two-dimensional experimental approach to studying myeloma, *in vivo* models provide a three-dimensional approach. The ideal animal model of myeloma is one that reproduces the key features of the disease, including the presence of myeloma cells in the bone marrow, interactions of myeloma cells with the bone marrow microenvironment, and development of bone disease. Models provide tools to study tumor burden, bone disease, and angiogenesis, and allow isolation of different cellular compartments. Many current models use SCID (severe combined immunodeficiency) mice with xenografts of either human myeloma cells or human or rabbit fetal bone implanted with human myeloma cells. Another model uses myeloma cells in hollow fibers. There are also transgene-based models. Dr. Vanderkerken emphasized that given the advantages and limitations of current models, it is important for researchers to base their selection of animal models on the questions they want to ask.

An important issue in myeloma is that focal lesions are often the site of relapse, and the disease may reappear at sites of focal lesions after complete remission (CR). Dr. Joshua Epstein (University of Arkansas, United States) suggested that these focal lesions retain dormant myeloma cells that cannot be detected by current tests defining CR. Once myeloma-associated osteolytic lesions appear they do not heal; the reasons for this are not known, although it could be that the microenvironment is exhausted or there are undetectable residual tumor cells present. This lack of healing is specific to myeloma; healing is seen in osteolytic

lesions associated with other tumor types. The SCID-hu model of SCID mice implanted with human fetal bone (generally half a tibia or femur) was developed to identify the cell responsible for myeloma growth and relapse and to study the microenvironment. Whole bone marrow or purified plasma cells from patients with myeloma are injected into the implanted bone. In this system only myeloma cells and no other classes of cells proliferate. If two bones are implanted and only one is injected with myeloma cells, the cells will migrate to the non-injected bone, and both bones will display lytic lesions. Dr. Epstein's group has transferred myeloma cells after establishment in one animal to a second, third, and fourth animal. The cells do not change phenotype or mature, and their CD138⁺ phenotype is maintained. No other cell can or is required to produce myeloma in this system. Whether there is a myeloma stem cell or a recycled myeloma cell that gives rise to myeloma in this system is still under debate.

It is not clear whether myeloma that develops after MGUS is identical to myeloma with an unknown prior history. Genetic abnormalities associated with myeloma can be detected in MGUS, and although some of these are associated with poor prognosis in myeloma, they are also associated with MGUS that is stable for years. Dr. Johannes Drach (Medical University of Vienna, Austria) proposed that post-MGUS myeloma appears to be a separate entity with a different outcome than myeloma with an unknown prior history. Those patients with post-MGUS MM with only 13(del) had a much better survival, and those with the translocation between chromosomes 11 and 14 (t[11;14]) had a much poorer survival. Dr. Drach's group is looking at epigenetic changes in plasma cells that might be

associated with development of myeloma, e.g., aberrant methylation of promoter regions in tumor suppressor genes. Demethylating agents such as 5-aza-2-deoxycytidine and/or trichostatin A were used to treat cell lines, and about 470 unique genes were induced in at least one of the lines. Of these, 88% were shown to have CpG islands, and therefore to be genuine methylation targets. Although all chromosomes contained some of these genes, an obvious cluster occurred on chromosome 6 at 6p21. This process selected some genes that have previously been identified in other cancers that were not previously known to be associated with myeloma, including genes involved in the cell cycle, cell adhesion, signaling, and DNA repair. Methylation was higher in an analysis of DNA from 111 patients with myeloma than from 25 patients with MGUS. Methylation seems to be associated with poorer outcome. Analysis of proteins using gel electrophoresis followed by nanoflow liquid chromatography revealed some potentially important methylation targets that might be useful in predicting response, including apoptosis-inducing factor 1, several cell adhesion molecules, serine/threonine protein kinase, adenosine deaminase, estradiol 17-beta dehydrogenase, and NF- κ B inhibitory interacting Ras-like protein 2.

The ability to predict patient response to therapy would allow individualization of therapy; only patients expected to respond well to a particular treatment would then be exposed to the potential toxicity of the treatment. The ability to target therapy to myeloma genetic type does not yet exist. GEP yields a molecular portrait of a large number of genes that may be useful in diagnosis, stratification, prediction of response based on the profile, and an indirect assessment of IgH locus translocations. GEP may provide three types of information related to drug response: the individual genes expressed in responders vs. non-responders, IgH translocations, and the presence of functional pathways. Dr. Shaji Kumar's group (Mayo, Rochester, Minnesota, United States) has done GEP profiling on CD138+ cells isolated from 30 patients receiving thalidomide and dexamethasone as initial therapy on the ECOG phase 2 or 3 trials, and identified 25 genes that separated responders from non-responders; 15 of these genes

were unique and included structural, immune regulation, adhesion, and apoptosis regulatory genes. There was a correlation with lack of IgH translocation and response to therapy. GEP analyses of other patient populations in different studies using different chips and different drugs have identified other sets of genes associated with response to treatment, supporting the use of this approach. Dr. Kumar plans to carry out an analysis to identify genes associated with response to lenalidomide.

Dr. Angelo Vacca (Bari, Italy) discussed mosaicism of blood vessels in patients with myeloma, and therapeutic approaches. Angiogenesis in myeloma appears to be the result of new vessel formation by new mesenchymal cells recruited by the tumor cells. Hematopoietic stem cells from patients with myeloma before therapy as well as macrophages could differentiate into an endothelial cell type when cultured with the appropriate growth factors on a suitable support system. Factors released by myeloma and inflammatory cells appear to contribute to this process. The involvement of the vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) pathways in this process suggest that therapies targeting these two signaling pathways may provide a new, effective way to block the growth of myeloma cells and their associated angiogenesis. One such potential therapy, TKI-204, targets several angiogenic growth factor receptor tyrosine kinases in myeloma.

The presence of T cell clones in myeloma may be related to progression and response. T cell clones other than those normally seen in the elderly were seen in patients in the MM6 study of thalidomide maintenance following autologous transplant, presented by Dr. Douglas Joshua (University of Sydney, Australia). Thalidomide contributed to overall survival (OS) and progression-free survival (PFS), as did the development of T cell clones. The percentage of patients with clones increased from 48% pre transplant to 96% post transplant. However, what these clones do is unknown, although they are expected to be involved in immune stimulation. T regulatory cells (T reg) are involved in immune responses to infections and tumors. There

is disagreement about whether this cell type increases or decreases in myeloma, and whether these cells are functional or not. Dr. Joshua believes that in myeloma, CD4 and CD8 T cells acquire new cell surface antigens, and that this, in combination with dysfunctional T reg cells, may be responsible for the immune defects seen in T cells in myeloma.

Dr. Giovanni Tonon (Dana-Farber Cancer Institute, Boston, Massachusetts, United States) discussed a genetic model of MM on behalf of his colleague, Dr. Ruben Carrasco. X-box Binding Protein-1 (XBP-1) is a differentiation and unfolded protein/ER stress response factor. A transgenic mouse model of myeloma, $E\mu$ -XPB-1s, causes mice to develop either a severe cutaneous disease or MGUS followed by myeloma after a long latency period, mirroring human disease progression. Those developing myeloma also develop renal complications, a monoclonal antibody spike, plasma cells infiltrating the bone marrow, and bony lytic lesions. However, unlike human disease, the monoclonal gammopathy is primarily IgM, which is rare in human patients, not IgG. Nevertheless, this system may allow testing of the role of genes that are upregulated or amplified in human disease.

Dr. Tonon then discussed how an array comparative genomic hybridization (aCGH) platform and GEP were used to analyze cells from newly diagnosed patients with myeloma before and after treatment, revealing at least 4 distinct genomic patterns. These were further divided into subgroups based on chromosomal abnormalities (non-negative matrix factorization or gNMF analysis of aCGH profiles). These subgroups were associated with different prognoses. Additional approaches included Significance Analysis of Microarrays (SAM), Gene-eight measure of RNA expression, and Gene Set Enrichment Analysis (GSEA) in specific myeloma subgroups defined by the gNMF analysis. GSEA comparing myeloma and normal cells identified pathways with increased levels of expression, including some altered in all myeloma cells independent of subgroup. These included the proteasome pathway, suggesting that proteasome inhibitors might be active in all myeloma subgroups, as well as p53, K-ras, and mTOR (mammalian target of rapamycin) pathways. Other pathways altered in some but not all subgroups included those involved with interleukin and growth factors, and the Wnt and Akt pathways.

Session 3: Pathophysiology – Bone Disease

Chair:

Prof. Douglas Joshua
University of Sydney, Australia

This session concentrated on the pathophysiology of myeloma lytic bone disease. Bone disease is characterized by the presence of osteolytic bone lesions and generalized osteoporosis and accounts for much of the morbidity associated with myeloma. Bone disease is present in approximately 75% of patients at diagnosis, and over the next 2 years more than half of all patients with myeloma will experience a skeletal-related event.

Important new advances in the understanding of myeloma bone disease and its therapy were presented during this session. Our understanding of myeloma bone disease has been dramatically changed by experiments that have dissected the cytokine pathways responsible for both osteoclast stimulation and osteoblast inhibition; until recently, the identity of such molecular mechanisms was unknown. In addition, clinical associations with biochemical markers of bone disease and the ability to select patients who are more likely to respond well to bisphosphonates have been documented. Also, the risk factors associated with the development of osteonecrosis of the jaw (ONJ) are becoming clearer. A number of trials evaluating the appropriate dosage of bisphosphonates and, importantly, defining which patients are more likely to get myeloma bone disease on the basis of their genetic makeup are underway. Newer novel therapeutic agents directly inhibit osteoclast differentiation and are now finding a place in the therapy of patients who have bone disease. This represents a new and exciting development in our ability to manage this complication.

Dr. Peter Croucher (University of Sheffield Medical School, United Kingdom) and Dr. David Roodman (University of Pittsburgh, Pennsylvania, United States) reviewed the pathophysiology of myeloma bone disease and discussed the mechanisms responsible for the increased osteoclastic bone absorption. Studies have demonstrated that a num-

ber of molecules play important roles. The ligand for the receptor activator of NF- κ B (RANKL) and its decoy receptor osteoprotegerin (OPG) are abnormally expressed in myeloma. RANKL is a potent inducer of osteoclast formation. RANKL expression is increased in cells of the bone marrow microenvironment and may also be expressed by myeloma cells themselves.

In patients with myeloma, circulating concentrations of soluble RANKL are elevated, whereas levels of the decoy receptor OPG are decreased. Targeting this system with recombinant OPG or soluble RANKL constructs have been shown to prevent the development of osteolytic disease. Furthermore OPG peptidomimetics designed on the basis of the predicted structure of the RANKL/OPG complex prevent the development of bone disease in murine models. These observations have led to the evaluation of novel anti-RANKL strategies in clinical studies.

In addition to RANKL, macrophage inflammatory protein, (MIP)-1 alpha and beta have both been implicated in the development of bone disease. Myeloma cells have been shown to produce MIP-1 alpha and beta. Whether these molecules promote bone resorption by induction of RANKL or do so by a RANKL-independent mechanism remains unclear. Tumor-stromal cell interactions via adhesion molecules (VCAM-1) result in the release of not only RANKL, but also many other cytokines, including interleukin (IL)-6, MIP-1 alpha, and tumor necrosis factor (TNF) alpha, which increase the production of osteoclastic factors and thus progressive lytic disease. Dr. Roodman extended these observations. He showed that P62, a recently described member of the NF- κ B signaling pathway, is activated by RANKL and plays an important role in controlling myeloma cell growth and bone destruction. These findings support the concept of P62 as a potential novel target for the therapy of bone disease.

In addition to molecules that stimulate osteoclasts, molecules that inhibit osteoblast differentiation have also been documented. The Wnt signaling pathway is one system that has been shown to play a key role in normal osteoblast differentiation. An inhibitor of the Wnt signaling pathway, DKK1, is produced by myeloma cells and inhibits osteoblast differentiation. Inhibiting the activity of DKK1 with a monoclonal antibody in the SCID mouse model has been shown to prevent the development of myeloma bone disease. In addition, DKK1 levels are increased in the serum of patients with myeloma, suggesting this factor is of clinical importance. New markers of osteoclast stimulation such as serum levels of RANKL or OPG and the ratio of RANKL/OPG correlate with osteolytic lesions, disease activity, and survival. However, more studies are awaited to finally determine the role of these markers in assessing and monitoring bone disease. In a poster presented by Dr. Rosa Fisac-Herrero (Segovia, Spain), serum DKK1 was shown to be elevated in patients with myeloma, to correlate with levels of RANKL but not other markers of bone resorption, and bear no impact on survival.

Dr. James Berenson (Los Angeles, California, United States) described his pivotal work on the role of bisphosphonates in the therapy of myeloma. Dr. Berenson showed that bisphosphonate treatment both reduced the number of skeletal-related events in patients with myeloma, and possibly may have had some beneficial effect on survival in certain instances. Bisphosphonates are now accepted therapy for patients with myeloma who have active bone disease or are undergoing therapy, but the description of a previously unrecognized complication of bisphosphonate therapy, osteonecrosis of the jaw (ONJ), has caused some concerns about the duration and dose of treatment required. Dr. Berenson reviewed the reports on ONJ in the literature, and pointed out the risk factors for ONJ are multifactorial. They include previous dental work, poor dental hygiene, and tobacco or alcohol abuse. However, no reliable predictable pattern has been clearly identified to allow risk calculations for the development of ONJ in any particular patient. Dr. Berenson pointed out that it is now recommended that patients receiving

bisphosphonates should be evaluated early in their treatment for dental problems and encouraged to maintain excellent dental hygiene. The course of ONJ is variable, but in many patients does not worsen, and may show improvement over time. It is not yet clear whether patients who develop ONJ need to discontinue the use of bisphosphonates, especially if they still have active bone disease. It is also not clear what the duration of bisphosphonate use should be, although a number of guidelines have been published suggesting cessation at either 12 months or 24 months in the absence of active myeloma disease.

Dr. Berenson reviewed data on the incidence of ONJ and presented data on the incidence of ONJ in a cohort of 100 patients. He has demonstrated an incidence of approximately 10% in these patients with long-term use of zoledronic acid. In a recent retrospective analysis of a randomized trial comparing monthly zoledronic acid to pamidronate, patients with elevated bone alkaline phosphate levels had superior survival with zoledronic acid. While this was not a primary aim or endpoint of the study, it may suggest that potent bisphosphonates have anti-myeloma activity and should not be prematurely discontinued in patients who have active bone disease or who are receiving high doses of dexamethasone.

Dr. Terpos (Athens, Greece) addressed whether biochemical markers of bone metabolism in multiple myeloma could be used to predict which patients should have bisphosphonate therapy or to predict which patients will have adverse outcomes with bisphosphonate therapy. Both markers of bone resorption and markers of bone formation have been used in an attempt to answer these questions. Markers of bone resorption seem to be more useful. They are elevated in patients with myeloma, especially the N terminal cross-linking peptide of type 1 collagen (NTX), which shows consistent value in determining disease state, skeletal morbidity, and the subsequent likelihood of a skeletal-related event. NTX has the strongest positive correlation with dynamic histomorphometric indices of bone resorption.

The most favorable marker of bone resorption in determining clinical state is the bone-specific alkaline phosphatase (bALP), which correlates significantly with pain, bone lesions, and fractures. The use of these markers for monitoring bisphosphonate therapy has been studied; bisphosphonate therapy appears to reduce the levels of these markers in patients who have active disease. Patients in whom elevated levels of NTX do not rapidly return to normal after bisphosphonate therapy (in 3 months) have a significantly higher risk of developing a skeletal-related event and a shorter time span to its development.

A number of randomized studies on the dosage of bisphosphonates were presented. Traditionally a dose of 90 mg of pamidronate monthly has been used, but a large Norwegian study did not show any difference in physical function in 12 months when patients were randomized to either 30 mg or 90 mg of pamidronate. Therefore, although bisphosphonates have an important role to play, their exact dose and duration of treatment remains somewhat unclear. Furthermore, the therapeutic assessment of bisphosphonate therapy is now clouded by the fact that the new novel therapies including bortezomib and lenalidomide suppress osteoclast formation. Important data were also presented on the therapy of myeloma bone disease and the influence of novel agents lenalidomide and bortezomib on osteoclastic activity by Drs. I. Breitkreutz, P. Boissy, and E. Terpos in a poster session. Lenalidomide and bortezomib inhibit osteoclast differentiation and activity directly, preventing the development of new osteolytic lesions. In addition, cytokine secretion by osteoclasts is down regulated by these drugs, which leads to subsequent inhibition of myeloma cell survival in the bone marrow micro-environment. Inhibition of osteoclast activity has been demonstrated for lenalidomide and bortezomib, in vitro, and clinical studies have confirmed reductions in markers of bone resorption in vivo. New agents such as resveratrol and AZD 6224, a MEK1/2 inhibitor, appear to inhibit osteoclast differentiation and provide exciting avenues for subsequent therapy of bone disease in myeloma.

Important new data were presented by Dr. Brian Durie (Los Angeles, United States) in a poster on genetic polymorphisms which may predispose patients to the development of bone disease in myeloma. This is the first assessment of genetic polymorphisms linked to myeloma bone disease, and has led to the identification of potential biological targets which may be used for subsequent therapy of myeloma bone disease. In summary, there have been dramatic changes in our understanding and ability to treat bone disease in myeloma. Such changes have had the potential to greatly influence our approach to treatment and have been of significant benefit to patients.

Two important presentations describing the development of new mouse models for myeloma were documented in this session. The first model, presented by Dr. P. Neri (Boston, Massachusetts, United States) in a poster, was specifically developed to study myeloma bone disease, and involves the injection of myeloma cells into a human bone chip in SCID mice. This model reproduces the clinical bone lesions seen in human myeloma, with increased osteoclasts and bone lysis. Studies with this model showed zoledronic acid inhibited the development of bone destruction as well as tumor growth. A second model, presented by Dr. Marta Chesi (Mayo Scottsdale, Arizona, United States), a transgenic model relying on activation of the Myc gene, closely resembles the human disease, including bone disease, and will prove a valuable addition to our experimental models available to study human disease.

Dr. Michio Kawano (Yamaguchi University, Ube, Japan) presented new data describing the loss of the master B cell regulator Pax-5 in some myeloma cells, which confers on them the plasticity to achieve multi lineage differentiation and a stem cell phenotype. He has coined the term "stone cells" (stem cell-like cells dropping out of lineage). This is of great interest in our attempts to study the possible myeloma stem cell and subsequently aim for therapies directly targeted to it.

Session 4: Novel Treatment Approaches

Chair:

Dr. Heinz Ludwig

Wilhelminenspital, Vienna, Austria

Novel agents, such as thalidomide, bortezomib, and lenalidomide, provide significant improvements in the care of difficult-to-treat patients, such as those with relapsed/refractory disease, poor cytogenetic features, advanced age, and/or renal impairment. Further, recent research has led to the development of novel oral proteasome inhibitors with high activity even in bortezomib-resistant MM, and of other novel classes of anti-myeloma drugs, such as inhibitors of heat shock protein (Hsp) 90 and of several tyrosine kinases important for the growth of myeloma cells.

Dr. Paul Richardson (Dana Farber Cancer Institute, Boston, Massachusetts, United States) started his presentation with a short review of factors negatively effecting the outcome of multiple myeloma, and on the multiple mechanisms of bortezomib thought to be important for its anti-myeloma activity. He then updated the results of the important study comparing bortezomib with dexamethasone in patients with relapsing/refractory disease. With longer follow-up, response to bortezomib improved from 38% to 43% (compared with 18% treated with dexamethasone only). Median time to progression with bortezomib therapy was twice as long compared with dexamethasone (6.2 months vs. 3.5 months). The difference in overall survival became even more pronounced, with a 6-month difference in median survival between both groups. This improvement was obtained in spite of 62% of patients being switched from dexamethasone to bortezomib due to progressive disease (PD).

Dr. Richardson presented additional data showing similar activity of bortezomib in elderly patients compared with younger patients, and in patients with renal impairment compared with patients with normal renal function. Bortezomib is active in extramedullary disease and in patients with unfavorable cytogenetics. Another interesting feature of bortezomib is its very specific effect on

bone turnover, with significant stimulation of bone formation. This is reflected by a substantial increase in markers reflecting increased activity of bone formation (bone-specific alkaline phosphatase, osteocalcin) and reduction in markers of bone degradation (collagen degradation products). These data fit well with the finding of Yaccoby et al., who found a substantial increase in bone mass in bortezomib-treated mice.

Among the various activities unique to bortezomib, its capacity to inhibit DNA repair may be particularly important when used in combination with other drugs. This may explain the high anti-myeloma activity seen in various combination regimens. Bortezomib has successfully been combined with a variety of drugs both in relapsed and in previously untreated myeloma. The results of a prospective comparison between patients treated with bortezomib plus pegylated doxorubicin and those treated with single-agent bortezomib are particularly impressive. This large study, which previously was presented by Dr. Robert Orlowski, included 646 pretreated patients. The combination yielded a higher response rate (52% vs. 44%), a significantly increased time to progression, and a lower risk of death in the group treated with the combination. This combination is particularly appealing for patients with poor tolerance of dexamethasone or other corticosteroids.

In the last part of his presentation, Dr. Richardson covered results presented previously by Italian researchers of the highly active MPT (melphalan-prednisone-thalidomide) protocol which has been extended by the addition of bortezomib (V-MPT). This regimen yielded a response rate of 78% as second-line therapy, and of 56% as third-line treatment. Finally, he presented laboratory data suggesting synergistic activity between bortezomib and lenalidomide as well as clinical results obtained with this

combination, showing a response rate of 58% in heavily pretreated patients.

Dr. Donna Weber (MD Anderson Cancer Center, Houston, Texas, United States) reported results of lenalidomide treatment for patients with relapsed or refractory myeloma. She presented updated results of 2 phase III double-blind trials comparing lenalidomide plus dexamethasone with dexamethasone plus placebo in patients with relapsed/refractory MM. Because of the similar design of both trials, one of which had been conducted in North America and one in Europe, Australia, and Israel, data were pooled for analysis. The lenalidomide-dexamethasone regimen resulted in significantly increased time to progression (11.2 months vs. 4.7 months) and overall survival (29.6 months vs. 20.5 months). The combination was generally well tolerated, but grade 3 and 4 neutropenia occurred more commonly in patients treated with lenalidomide-dexamethasone, particularly in the subgroup that had prior autologous stem cell transplant. Patients receiving erythropoietin or darbepoetin were more likely to develop thromboembolic complications. Aspirin prophylaxis reduced the incidence of thromboembolic complications, but these complications remained increased in patients taking aspirin. The increased side effect profile observed in patients with renal dysfunction suggests the need for dose reduction, e.g., from 25 mg daily to 10 mg daily, and to 15 mg every 48 hours in patients with end-stage renal disease.

Dr. Weber mentioned several phase I and II studies combining lenalidomide with several agents. Data from a small study conducted by Dr. Stephen Knop et al. (University Hospital, Würzburg, Germany), in which lenalidomide was administered with doxorubicin and dexamethasone, showed an overall response rate of 84% with a 3% CR rate. Another regimen previously presented by Dr. Baz et al., included lenalidomide with liposomal doxorubicin and dexamethasone. Overall response rate was 75%, with a 15% CR rate and a median progression-free survival of 12 months. Although all patients received antibiotic and antiviral prophylaxis, the dose-limiting toxicity was non-neutropenic sepsis. Grade 3 to 4 neutropenia occurred

in 32% of patients. Despite aspirin prophylaxis, thromboembolic complications occurred in 9% of patients. A further trial conducted by Dr. Morgan et al. administered lenalidomide with cyclophosphamide. Among 17 evaluable patients, the PR rate was 65% and the CR rate was 6%. Two-thirds of patients received G-CSF prophylaxis to maintain neutrophil counts, but neutropenic fever was seen in 22% of patients. An interesting combination of lenalidomide with bortezomib has been studied by Richardson et al. Patients who developed progressive disease received dexamethasone in addition. Limiting toxicity was reached at a lenalidomide dose of 15 mg given on days 1 through 14 and of bortezomib 1.0 mg/m² given in the conventional 21-day cycle. The overall response rate was 39%, and responses were observed even in patients with prior resistance to bortezomib. These studies illustrate the significant clinical activity of bortezomib, which also has been shown in patients with unfavorable cytogenetic abnormalities including del(13) and t(4:14). Dr. Weber expects the future to bring more trials combining lenalidomide with both conventional and novel drugs in different phases of myeloma therapy. Due to the high rates of CR obtained with lenalidomide combinations in first-line treatment, one of the important questions to resolve in the future will be whether transplantation can be omitted in those patients with very good results up front.

Dr. Heinz Ludwig presented various aspects of the treatment of disease with unfavorable features, such as adverse cytogenetic abnormalities, renal impairment, and old age. Response to bortezomib was studied in 62 heavily pretreated patients analyzed for del(13) status. Bortezomib was able to overcome the negative impact of del(13) and induced responses in 45% of the 33 patients with this abnormality; however, this was not significantly different from the response rate of 55% obtained in 23 patients without del(13). Duration of response and survival likewise were similar in both groups. The activity of bortezomib or bortezomib combination therapy was studied in another cohort of 74 patients analyzed for 1q21 status. Patients with gain of 1q21 presented more frequently with IgA or light chain myeloma and had inferior response

rates to single agent bortezomib compared with those with normal 1q21 status (30% vs. 58%). When bortezomib was used in combination with dexamethasone, and in some patients with either doxorubicin or melphalan as well, response rates were independent of 1q21 status (54% in patients with, and 64% in those without, gain of 1q21). Survival was similar in both groups, but was significantly shorter in those with gain of 1q21 treated with single agent bortezomib only.

The next topic concerned patients with acute renal failure treated with bortezomib or bortezomib combinations. In a pilot study, 5 of 8 patients with acute renal failure (median serum creatinine of 9.0 mg/mL) treated with bortezomib plus dexamethasone with or without the addition of doxorubicin had a significant reduction of myeloma protein and improvement in renal function (median creatinine: 2.1 mg/mL). These encouraging results supported a phase II trial treating patients with acute myeloma-induced renal failure with bortezomib-doxorubicin-dexamethasone. Of 30 patients enrolled at the time of reporting, 15 had been treated with ≥ 3 cycles and therefore were evaluable for response. Nine had a tumor response (CR/nCR: 3, PR: 6) and 7 of them had significant improvement in renal function. As the initial regimen was associated with high toxicity, a reduction in the dose of bortezomib to 1.0 mg/m² and of the administration frequency of doxorubicin (days 1 and 4) was introduced after a planned safety analysis.

Dr. Ludwig then presented results of a randomized trial comparing thalidomide-dexamethasone (TD) with MP. This trial enrolled 274 elderly patients (median age 72 years), and consists of a second part with patients being randomized after induction to thalidomide-interferon or interferon maintenance only. Response rate was significantly higher (65% vs. 53%) and time to response significantly shorter in the TD group (6 weeks vs. 16 weeks). TD resulted in higher toxicity particularly in patients >72 years of age, and resulted in more early deaths within the first six months after start of therapy (21 vs. 9 early deaths). This translated into a tendency for shorter survival in the older patients treated with TD compared with

those on MP (median 56.5 months vs. 25.4 months). In patients ≤ 72 years of age, there was no difference in survival (median: 57.9 vs. 50 months). TD resulted in survival similar to MP in patients with gain of 1q21, but was inferior to MP in patients without this risk factor. Median survival after the start of maintenance was 41 months in patients with interferon maintenance, while median survival had not been reached yet in those on maintenance treatment with thalidomide and interferon combined. Patients on TD experienced more thalidomide-related toxicity, such as neuropathy, constipation, and psychologic disturbances, and had a higher cumulative rate of thromboembolic complications (16% vs. 6%), while grade 3 and 4 leukopenia was more frequent in patients treated with MP.

Dr. Kenneth Anderson (Dana Farber Cancer Institute, Boston, Massachusetts, United States), speaking on behalf of principal investigator Darminder Chauhan, discussed novel proteasome inhibitors as therapy for MM. Although Dr. Anderson thinks that the mechanism of action of proteasome inhibition in multiple myeloma is unclear, it is known that it overcomes intrinsic drug resistance conferred by the NF- κ B signaling pathway, and also affects interactions with adhesion molecules, cytokine response, and angiogenesis. More effective future therapeutic strategies to treat myeloma may include targeting the aggresome, an area of protein accumulation in the cell, in combination with proteasome inhibition, given the synergistic activity seen in solid tumors and leukemias. In addition to bortezomib, the first-in-class proteasome inhibitor, two other proteasome inhibitors are in development. One, PRI71, is an irreversible inhibitor of the chymotryptic proteasome activity, like bortezomib, but has qualitative and quantitative differences in activity. Phase 2 clinical trials are planned. NPI-0052 (Salinisporamide A) inhibits both NF- κ B activity and the chymotryptic and tryptic proteasome activity, and acts on the caspase 8 pathway, whereas bortezomib acts on the caspase 9 pathway. It is not clear which of these activities correlates with clinical activity. In preclinical studies, NPI-0052 was synergistic with lenalidomide in both steroid resistant and sensitive myeloma cells. NPI-0052 is also synergistic in vitro and in animal models with bortezomib. Other ways

to block the proteasome pathway include at the level of ubiquitin ligases or the immunoproteasome, by attacking activity of the proteasomes specific to hematologic cancers that are not expressed in non-hematologic or normal hematologic cells. Combining agents that target protein catabolism via both the proteasome and the aggresome will be important not just for the treatment of myeloma, but for other types of cancer as well.

Dr. Constantine Mitsiades (Dana Farber Cancer Institute, Boston, Massachusetts, United States) discussed the therapeutic implications of inhibition of heat shock proteins (Hsp's). Hsp's are ubiquitous chaperone molecules that are relatively restricted to client proteins and are implicated in the pathophysiology of malignant cells. Dr. Mitsiades noted that malignant cells may be able to overcome therapies that target only one specific step in a pathway in malignant cells. Hsp client proteins in myeloma include Akt (protein kinase B), insulin-like growth factor (IGF)-1, and IKK (I kappa B kinase). Proteasome inhibition may up-regulate several Hsp's in myeloma, providing a rationale for the use of Hsp inhibitors. Geldanamycin is the prototypical small molecule inhibitor of Hsp90. In preclinical studies it has been shown to overcome resistance to bortezomib, TRAIL (tumor necrosis factor-alpha-related apoptosis-inducing ligand), and immunomodulatory drugs (e.g., thalidomide or lenalidomide), and may enhance the response to bortezomib. Although the acetylation status influences Hsp90 function, HDAC (histone deacetylase) and Hsp90 inhibitors are not interchangeable. Barriers that need to be overcome in the clinical use of Hsp inhibitors include formulation, dosage, and schedule. Dr. Mitsiades pointed out that as better vehicles are developed, it may be possible to deliver higher (more therapeutic) doses and to individualize treatment by targeting the agent to tumor tissue, e.g., by using a lipophilic agent to target bone marrow. Although oral formulations offer ease of use and flexibility, intravenous deliv-

ery may be preferable in the setting of co-morbidities that affect bioavailability, when bypassing the liver is required, and when close monitoring of the patient is desirable.

Dr. A. Keith Stewart (Mayo Clinic, Scottsdale, Arizona, United States) discussed targeting kinases and IgH translocations in MM. The translocation t(4;14), which occurs in 15% of patients with myeloma, dysregulates 2 oncogenes, MMSET and FGFR3. Dr. Stewart called the presence of t(4;14) in myeloma the genetic equivalent of the accelerated phase in chronic myelogenous leukemia (CML). Because t(4;14) is seen in both MGUS and myelomas with a prolonged course, it is necessary but not sufficient for a poor prognosis. Poor outcome is seen with many therapies; although bortezomib may abrogate this, the follow-up time is short, and Dr. Stewart thinks that bortezomib is unlikely to remove the adverse prognostic features of t(4;14). Targeting receptor tyrosine kinases beyond FGFR3 is important, because kinases are dysregulated in myelomas of other genotypes. Tyrosine kinase inhibitor TKI-256, formerly CHIR-258, now in a phase I trial, has only recently been escalated to a pharmacologically active dose range. Other approaches to developing targets include using RNAi (inhibiting genes one at a time with synthetic oligonucleotides) to create a genetic map of vulnerability, to understand the mechanism of action of drugs, to define small molecule targets, and to determine drug sensitivities for rational drug combinations. Myeloma cells are hard to transfect, which is an obstacle to this approach. The first step is to look at myeloma cell lines and patient cells to see if targets identified in cell lines are clinically relevant. RNAi screening identified 26 relevant kinases. Of these, myeloma-specific kinases that when inhibited result in cell killing include Aurora kinase A and PKN1. Dr. Stewart predicts that combining small molecule kinase inhibitors with bortezomib should be a successful strategy. Genome-wide screening for sensitizers to bortezomib and lenalidomide are ongoing.

Session 5: Frontline Treatment of Myeloma

Chairs:

Jesus F. San Miguel

Universidad de Salamanca, Spain

Konstantinos Tsatalas

Democritous University of Thrace, Alexandroupolis, Greece

Dr. Phillip Griep (Mayo Clinic, Rochester, Minnesota, United States) discussed the establishment of the International Staging System (ISS) for myeloma. The system classifies myeloma into three stages based on serum beta-2-microglobulin and albumin levels. The stages correlate with risk and survival. Serum albumin may be measured by protein electrophoresis (PEL) or by chemical tests. M-spikes, especially over 25 g/L, appear to increase albumin levels measured by PEL, whereas chemical tests (e.g., bromocresol green or bromocresol purple) measure albumin and other proteins such as gamma globulin, but are not affected by an M-spike; results can be adjusted to compensate. Other methods for albumin measurement include immunonephelometry, the gold standard for measurement in cerebral spinal fluid, and capillary zone electrophoresis (CZE), which may be used more in the future. However, overall, differences in measurement and therefore staging had no impact on survival curves in a study of a large group of patients. The use of PEL may avoid having to do an additional test. Either PEL or chemical methods of determining serum albumin levels may be used for staging, and publications of trial results should specify which method was used. Dr. Bart Barlogie (Arkansas, United States) commented that clinicians should be consistent with the type of test used for individual patients and within a clinical trial.

Dr. Michele Cavo (Bologna University School of Medicine, Italy) presented results of clinical trials of thalidomide with dexamethasone or in doxorubicin-based regimens as primary treatment before autologous stem cell transplantation (ASCT). These newer regimens have shown a significant increase in response rates when compared with conventional regimens in use in the 1990s. Although the rate of deep vein thrombosis (DVT) is high with thalidomide- or doxorubicin-based regimens, the overall risk of

mortality is 5% or less. Limited thalidomide exposure in these up-front regimens has resulted in a low rate of grade 3 or 4 neurotoxicity. An open issue is whether regimens including thalidomide result in a better overall outcome. Although there is an increase in the complete response (CR) or very good partial response (VGPR) rates as well as in event-free survival (EFS), overall survival (OS) may not be increased. Data currently are limited and conflicting. Dr. Cavo suggested, however, that OS may not be the best marker of post-ASCT outcome. He also suggested the need for randomized trials comparing regimens containing thalidomide and melphalan with bortezomib or lenalidomide plus dexamethasone-based regimens. The ongoing phase 3 trial (GEMENA Bologna 2006), comparing bortezomib plus thalidomide and dexamethasone to thalidomide plus dexamethasone as induction therapy prior to double ASCT has enrolled 250 patients. Preliminary results should be available at the American Society of Hematology meeting in December, 2007.

Dr. Sundar Jagannath (St. Vincent's Comprehensive Cancer Center, New York, United States) believes that OS is the ultimate gold standard for evaluating treatment of multiple myeloma, and that attempts to increase the CR rate after induction (pre-transplant) will improve the CR rate post-transplant, ultimately increasing OS. In phase 2 trials, bortezomib as frontline therapy in various drug combinations has resulted in high CR rates both before and after high-dose chemotherapy, and appears to overcome high-risk cytogenetics including del(13), Rb deletion, and t(4;14). The use of bortezomib with pegylated liposomal doxorubicin (Doxil) allows a steroid-sparing regimen that Dr. Jagannath noted has a response rate almost as high as the combination of bortezomib plus doxorubicin plus dexamethasone. He said that the use of thalidomide as

a short induction platform was not as good as that seen with bortezomib. Induction therapy with novel agents has increased the post-transplantation CR rate and reduced the need for second transplants, but increases in progression-free survival (PFS) and OS need to be demonstrated. Nevertheless, there is a role for integration of bortezomib into high dose therapy as an induction regimen.

Dr. S. Vincent Rajkumar (Mayo Clinic, Rochester, Minnesota, United States) described the ideal frontline regimen as having an oral route of administration, a manageable adverse event profile, and an excellent ability to allow stem cell harvest and transplant. This would ideally result in a 100% response rate (RR), 100% survival at 4 months (allowing stem cell harvesting, although the patient may choose to stay on therapy rather than have an ASCT), as well as 100% survival at 1 year, with an excellent long-term (5-year) survival. SCT has resulted in modestly improved survival compared with conventional chemotherapy. Dr. Rajkumar suggested early transplant might result in better quality of life, although there is no phase 3 trial demonstrating that frontline transplant is better than transplant at relapse. In addition, the early death rate is about 10% for ASCT. Although the OS for patients receiving lenalidomide plus low-dose dexamethasone is significantly higher than for those receiving lenalidomide plus high-dose dexamethasone in the ECOG E4A03 trial, no response rate data were available at the time of the meeting. Response data are expected in the near future. The Mayo Clinic suggests lenalidomide plus low-dose dexamethasone as standard treatment for patients not on a clinical trial. In the relapse setting, Dr. Rajkumar suggested using three agents, e.g., bortezomib, lenalidomide, and low-dose dexamethasone, rather than “punishing” patients with high-dose dexamethasone added to lenalidomide or bortezomib.

Dr. Thierry Facon (Hôpital C. Hunez, Lille, France) presented frontline treatment for patients who are not eligible for stem cell transplantation (SCT). Although myeloma is a disease primarily of older patients, the elderly remain a less-well studied population, particularly those over the age of 75 years. The addition of thalidomide to melphalan

plus prednisone for elderly patients who are not SCT candidates is more popular in Europe, whereas thalidomide plus dexamethasone is used more in the United States. However, high-dose dexamethasone can be more toxic in elderly patients, and Dr. Facon feels that melphalan plus prednisone is the best choice for them. The addition of thalidomide to melphalan plus prednisone in patients over 75 years in the IFM 01-01 trial has shown an increase in PFS and OS at the interim analysis at 24 months of follow-up. The addition of lenalidomide to melphalan plus prednisone to treat a small number of patients (n=54) with a median age of 71 years has shown an increased response rate (RR), EFS, and OS when compared with historic controls treated with thalidomide and melphalan plus prednisone, and provides the rationale for the phase 3 MM-015 study. The addition of bortezomib to melphalan plus prednisone has also increased time to progression, PFS, and OS, and is the basis of the phase 3 VISTA study. Dr. Facon noted that the addition of either bortezomib, lenalidomide, or thalidomide to melphalan plus prednisone resulted in similar OS, RR, and EFS. The types of adverse events associated with lenalidomide (DVT, neutropenia), bortezomib (neuropathy), and thalidomide (DVT and neuropathy), should be taken into consideration. The IFM 2007-01 study will compare thalidomide plus melphalan plus prednisone with lenalidomide plus low-dose dexamethasone (with and without lenalidomide maintenance, which was added after the initial trial planning) in newly diagnosed patients over the age of 65 years with no upper age limit. Dr. Facon noted that most maintenance trials were post-SCT in younger patients. The primary objective, PFS, was questioned by Dr. Bergsagel, who suggested that OS should be looked at. Dr. Facon responded that it is difficult to decide what the best primary objective is, and that it might not be OS.

Dr. Mohammed A. Hussein (Lee Moffitt Cancer Center, Tampa, Florida, United States) discussed the management of toxicities from novel agents, including the IMiDs thalidomide and lenalidomide, and the proteasome inhibitor bortezomib. Toxicities associated with novel agents include thromboembolic events (TE) or hypercoagulable states, neurologic toxicities, hematologic toxicities, and skin reac-

tions. TE are associated with the use of thalidomide and lenalidomide, but are also associated with untreated amyloid and MGUS as well as with multiple myeloma. Studies suggest that the use of bortezomib might eliminate the risk of TE. Further study is needed to compare low-dose aspirin with low molecular weight heparin as prophylaxis against TE. Neurologic and hematologic toxicities associated with bortezomib or the IMiDs may require dose reduction and/or less frequent doses. Skin reactions may be non-symptomatic, requiring monitoring and allowing continuation of myeloma therapy, or symptomatic, requiring discontinuation of myeloma therapy and treatment of the symptoms. Dr. Hussein commented that the patient must be viewed as a whole, and can't be ignored while only the disease is targeted. He agreed with a comment from Dr. Berenson that peripheral neuropathy associated with bortezomib was manageable and reversible, and that new agents, e.g., Lyrica, alpha lipoic acid, and Cymbalta, could be used to treat the symptoms of neuropathy. However, these need further study.

Forty years ago, when the first publication described prognostic factors in myeloma, performance status, hemoglobin, calcium levels, and blood urea nitrogen were identified as being associated with survival. The list of potential prognostic factors has increased, but Dr. Joan Bladé (Hospital Clinic, Barcelona, Spain) believes that these factors will lose their impact as novel agents overcome poor risk factors. It should also be possible to develop new therapies that will target specific molecular pathways that confer poor outcome. Gene expression profiling (GEP) and array comparative genomic hybridization (aCGH) have allowed patients to be divided into subclasses with different prognoses. Dr. Bladé noted that one of the best prognostic factors is an individual's response to chemotherapy, and that stabilization of disease with conventional chemotherapy represents lower-risk disease. He pointed out that MGUS is already a clone that may be stable for years, so it is an important model for disease progression once it escapes the regulatory mechanisms that maintain this stable state.

Session 6: Debate I

Moderator:

Dr. Raymond Alexanian

MD Anderson Cancer Center, Houston, Texas, USA

Dr. Jean-Luc Harousseau (CHU Hôtel-Dieu, Nantes, France) and Dr. Mario Boccadoro (Ospedale San Giovanni Battista, Torino, Italy) debated whether achievement of complete response (CR) should be a major objective of the treatment of multiple myeloma. The debaters presented their arguments, and a discussion followed. Dr. Alexanian, the moderator, emphasized that there were no winners and losers in the debate, which was meant to clarify a controversial subject.

Should CR achievement be a major treatment objective?

YES. Dr. Harousseau

Dr. Harousseau reviewed data from three situations to support his argument that CR should be a major treatment objective. One situation includes trials of high-dose therapy followed by double autologous stem cell transplant (ASCT), in which all patients are randomized, where CR and very good partial response (VGPR) are associated with longer event-free survival (EFS) and overall survival (OS). The second situation is represented by trials of conventional chemotherapy with and without novel agents, e.g., melphalan-prednisone (MP) vs. MP-thalidomide (MPT), in which increased CR rates translate to greater OS. Third, in relapsed/refractory myeloma, Dr. Harousseau stated that the objective should still be to induce CR, because in this setting CR is also associated with longer OS based on data from trials of lenalidomide or bortezomib plus dexamethasone vs. dexamethasone alone. Dr. Harousseau concluded that CR/VGPR is associated with longer progression-free survival (PFS) and OS in all of these clinical situations, although he agreed with Dr. Alexanian that some patients who are not in CR do live longer.

Dr. Harousseau brought up several questions that remain to be answered. These include: Which definition of CR

is clinically relevant, e.g., that of the European group for Blood and Marrow Transplantation (EBMT) or that of the International Myeloma Working Group (IMWG)? What is the best measure of CR, e.g., molecular, flow cytometry, MRI, or immunofixation (IF)? Should VGPR should be included in analysis, as it is in studies in which CR rates are low? Is maintenance after CR useful? Dr. Harousseau believes it is not. And, finally, is it better to have CR before or after SCT? Dr. Boccadoro asked if the quality of CR after treatment with dexamethasone was the same as CR after ASCT. Dr. Harousseau felt that molecular remission was better than IF-negative CR, but because molecular techniques are not available everywhere, a new definition of CR might be based on free light chain. Dr. Alexanian wondered if the magnitude of CR was as important as patient quality of life.

Should CR achievement be a major treatment objective?

NO. Or “YES, BUT...” Dr. Boccadoro

Dr. Boccadoro maintained that there was no direct relationship between CR and survival, using data from other trials, although he acknowledged that in any tumor, in any setting, increasing the CR rate is the first step toward a cure. He suggested three reasons that CR should not be a treatment objective, although he suggested changing his point from “no” to “yes, but.” First, CR might be a cosmetic effect of the therapy, and that EFS in his opinion is a better measure of disease stabilization. Second, in patients with high serum free light chain levels, which is a marker of an aggressive myeloma subtype with poor prognosis, rapid response to treatment might be defined as CR, but EFS and OS are poor. Third, CR may be associated with increased survival in patients whose disease was benign anyway; this may be clarified in the future using gene expression profiling.

Dr. Harousseau commented that studies from the 1990s where CR rates were very low cannot be compared with more recent studies where CR rates are very high. Both he and Dr. Boccardo commented that whether CR after novel therapies was equivalent to CR after chemotherapy or high-dose therapy remained to be determined. Dr. Harousseau pointed out that OS depends in part on the efficacy of salvage therapy after relapse.

Dr. Alexanian noted in a review of trial data that CR was not necessarily a prerequisite for 10-year survival, but that patients with CR did have a better chance of surviving 15 to 20 years. There are several pathways to CR, he said, and if CR lasts over two years, patients will tend to have a long survival.

Session 7A: Oral Presentations I

Session Chair:

Dr. Linda M. Pilarski

University of Alberta and Cross Cancer Institute, Edmonton, Alberta, Canada

Overview: This series of oral presentations focused on identification of preclinical models and new drug targets. It included an exciting new model for amyloidosis, screening to identify kinases as new targets in myeloma and sensitizers for bortezomib, inhibitors of DNA methylation in myeloma, therapies targeted to cell cycle proteins, inhibition of cell adhesion-mediated drug resistance, and the use of free light chain and flow cytometry to monitor response to treatment.

Dr. Bonnie K. Arendt (Mayo Clinic, Rochester, Minnesota, United States) presented her work on a new preclinical model for primary amyloidosis, showing the establishment of amyloid-forming human cell lines. Advances in the understanding of primary amyloidosis have been hampered by the lack of a model system within which to study this aggressive disease, making this work highly significant for promoting understanding of primary amyloidosis. Two cell lines were established from the same patient. The cells were extensively characterized for phenotypic, molecular, and genetic characteristics. Importantly, the cells express the same light chain as the malignant cells from which they were derived and have an identical VDJ gene rearrangement and fibril formation as the ex-vivo cancer, thereby confirming the validity of the cell lines as representative of the disease. Light chain purified from the two cell lines contained a beta structure expected for immunoglobulins. Long, straight unbranching fibrils consistent with the size and shape of amyloid fibrils were observed. To further study the ability of the cell lines to generate amyloidosis, a NOD SCID xenograft preclinical model was established. Xenografted mice developed organ involvement with extensive amyloid deposits. Molecular analysis confirmed that the infiltrating cells had the same VDJ amyloid signature as the original cancer, confirming their involvement in the disease process in these xenografted mice. The development of this powerful preclinical model

for primary amyloidosis is a significant breakthrough for studying the disease.

Dr. Rodger Tiedemann (Mayo Clinic, Scottsdale, Arizona, United States) presented the results of his inhibitory RNA (RNAi) screening for new kinase targets in KMS11 and JJN3 myeloma cell lines, and embryonic kidney and lung carcinoma cell lines. The screening strategy involved treating cells with RNAi gene silencing of kinome (signaling kinases expressed by cells) to identify those kinases that are essential for cell growth (a lethal screen). The transfection strategy achieved 90% transfection efficiencies with siRNAs, using low concentrations of siRNAs to minimize off-target effects on the cell lines. Death of the RNAi-treated cells indicated that the targeted kinases are essential for cell survival. The screen also included a search for kinases that sensitize to the proteasome inhibitor bortezomib. About 5% of kinome siRNA caused <4 standard deviations in cell line viability. Myeloma-lethal and bortezomib-sensitizing kinase targets were selected by multiple independent siRNAs, with at least two validated siRNAs and two scrambled sequence siRNAs. Most of the targeted kinases were essential for survival of the myeloma cell lines, leading to lethal outcomes. Some targeted kinases were lethal for all cell lines tested, however, most appeared to specifically target myeloma. Based on microarray screening, a comparison of healthy, normal plasma cells expressed sets of kinase genes that were different from those expressed by primary myeloma plasma cells from patients. Overall, the lethal RNAi screen identified 44 vulnerable kinases and 22 kinases that sensitized to bortezomib. Dr. Tiedemann also showed that survival kinases are not universally vulnerable. This work is expected to lead to a series of small molecule inhibitors that synergize with bortezomib and may also exert independent cytotoxicity.

5-azacytidine (5AC) is an inhibitor of DNA methylation and is clinically useful in some diseases. Dr. Tanyel Kiziltepe (Dana Farber Cancer Institute, Boston, Massachusetts, United States) reported her work characterizing the cytotoxic mechanism for this drug that results in myeloma cell damage and apoptosis. Cytotoxicity was detected by colorimetric assays for mitochondrial function, flow cytometry, immunocytochemistry, and western blotting, looking at phosphorylation that signals double strand break responses in myeloma cells. 5AC was found to be cytotoxic to MM cell lines and primary MM cells, but not healthy plasma cells or bone marrow cells. It was cytotoxicity against both conventional therapy-sensitive and -resistant cell lines. Inhibitor analysis showed that 5AC induced double strand breaks mediated by the ATR gene but not by the ATM gene. In contrast, doxorubicin induces double strand breaks mediated by ATM inhibitors. As predicted by these patterns, synergistic cytotoxicity was detected with 5AC plus doxorubicin against both doxorubicin-sensitive and -resistant cell lines. 5AC-induced apoptosis was found to include both caspase-dependent and -independent pathways, as well as involving Mcl cleavage, BAX, Puma and Noxa upregulation. 5AC overcame survival advantages conferred by the cytokines IL-6 or IGF-1. Importantly, 5AC inhibits adhesion of MM cell lines to bone marrow stromal cells. It appears that 5AC induces double strand breaks and apoptosis even within the bone marrow microenvironment, thereby overcoming the protective effect of the stromal environment on myeloma cells.

Dr. Chen-Kiang (Weill-Cornell Medical College, New York, United States) presented work showing that cell cycle control is deregulated in myeloma pathogenesis, indicating the need to target the cell cycle with new therapies. G1 cell cycle control is a key regulatory component for the mammalian cell cycle, and hence is a predicted target for novel therapies. In this context, CDK4/6 activity provides an excellent potential target within the cell cycle. P18 is required for cell cycle termination during plasma cell differentiation in G0 to G1 transitions as part of cell cycle reentry. CDK4/6-specific phosphorylation of the Rb protein is a functional assay for the progression through early G1

that correlates with myeloma progression. Thus, inhibition of CDK4/6 will eliminate Rb phosphorylation. PD0332991 is a small molecule inhibitor of CDK4/6 that is administered orally, and is reversible, water soluble, and cell permeable. It inhibits Rb phosphorylation of primary myeloma cells in the presence of bone marrow stromal cells. It also inhibits myeloma growth in vivo, as measured using the 5T33 murine myeloma model. PD0332991 is synergistic in combination with bortezomib. A brief treatment with PD0332991 followed by bortezomib inhibits tumor growth in a rapidly disseminated NOD/SCID xenograft model of human myeloma, with no overt toxicity. The combination therapy is superior to either drug alone. Dr. Chen-Kiang suggests that this represents the first cell cycle based therapy in myeloma.

Dr. Lori Hazlehurst (Moffitt Cancer Center, Tampa, Florida, United States) presented her work on cell adhesion-mediated drug resistance arising from interactions between myeloma cells and their bone marrow microenvironment. Interactions between myeloma cells and extracellular matrix molecules provide de novo resistance, proposed to protect against chemotherapy mediated cell killing. Integrins sequester signaling proteins into clusters. An inhibitory peptide called HYD1 was used to inhibit beta-1 integrin-mediated cell adhesion as a means to increase the efficacy of standard chemotherapy. HYD1 is a D amino acid peptide that inhibits adhesion of alpha 4 and alpha 5 beta 1 integrins to fibronectin, as compared with a scrambled peptide that does not block adhesion of the 8226 cell line to a bone marrow stromal cell line. Dr. Hazlehurst found that the cell death induced by HYD1 was independent of caspase and had characteristics of autophagy, a form of cell death that involves bulk degradation of proteins and organelles. The cell membrane expands, sequesters cytosolic material, and the organelles fuse with the lysosome to degrade their contents. Autophagolysosomes are detected in HYD1-treated cells. In suspension cultures or in cultures of myeloma cell lines on stromal layers, HYD1 has activity as a single agent as well as in combination with melphalan, with which it synergizes to enhance melphalan-induced cell killing. In a SCID-Hu model involving growth of myeloma cells in

a fetal bone implanted in an immunodeficient mouse, a combination therapy of HYD1 and melphalan stops tumor growth more effectively than either drug alone as measured by levels of free light chain. HYD1 was effective when injected intraperitoneally, suggesting it has good bioavailability. The inhibition of tumor growth by HYD1 indicates that in vivo, myeloma cell lines are dependent upon beta-1 integrin-mediated survival signals for their clonal expansion. These preclinical studies suggest that beta-1 integrin represents novel target for drug targeting, and that HYD1 may be a new therapeutic agent to enhance the efficacy of standard chemotherapy in myeloma patients.

Dr. Roger Owen (Leeds, United Kingdom) presented an analysis from the intensive pathway of the MRC Myeloma IX trial. In this trial, younger patients, typically <70 years of age, were randomized to one of two induction schedules, CVAD and CTD, followed by high dose melphalan (HDM) with stem cell support. Patients were then randomized to maintenance with thalidomide or to no further therapy. This trial closed in May 2007, having recruited 1114 patients. The aim of the study was to evaluate the applicability of the serum free light chain (SFLC) assay and bone marrow flow cytometry to assess response to therapy, as compared with conventional assessment with serum and/or urine paraprotein estimation. Both SFLC and flow cytometry assays were performed in central laboratories, which allowed for an independent assessment of response. The SFLC assay was informative in >95% of patients, including virtually all those with light chain disease and >60% of

patients with non-secretory disease. A normal SFLC assay at the end of induction appeared to predict a conventional complete response (CR) at day 100 following HDM. It was also noted that 21% of patients had an abnormal assay following HDM, but it remains to be seen whether this identifies a population of patients with a greater risk of early progression. Flow cytometry was also highly informative as >95% of patients had an aberrant plasma cell phenotype based on the expression of CD19, CD56, and CD45. This assay used had a reproducible sensitivity of 0.01% and compares favorably with molecular methods of assaying minimal residual disease. Most patients had disease detectable by flow cytometry at the end of induction but approximately 50% of patients became negative for minimal residual disease following HDM. 30% of patients in conventional CR had detectable minimal residual disease at day 100 post HDM. Earlier studies by the same group have previously demonstrated that detectable minimal residual disease at day 100 predicts early progression, but long term follow-up is awaited in this cohort. It was also noted that a proportion of patients with no detectable disease by flow cytometry had a persisting paraprotein. The majority of these patients had an IgG paraprotein which had not yet resolved due to the longer half-life of IgG. Dr. Owen concluded that the SFLC assay and flow cytometry were highly applicable techniques that could be provided centrally in the context of a large multicenter trial. They appear to provide a more rapid assessment of response in patients treated with high dose intensive therapy than measuring paraprotein levels, and may ultimately prove to have significant prognostic value.

Session 7B: Oral presentations II

Session Chair:

Dr. Jan Westin

Sahlgrenska University Hospital, Gothenberg, Sweden

Overview: In this session, six presentations addressed questions of relevance for different phases in the therapy of newly diagnosed multiple myeloma, from the choice of up-front therapy, to high-dose melphalan (HDM) treatment, followed by autologous stem cell transplant (ASCT), the effect of an added allogeneic stem cell transplantation, the value of attaining a complete remission (CR), and the additional effect of maintenance therapy.

As induction therapy for patients planning to undergo HDM treatment and ASCT, the combination of vincristine-Adriamycin-dexamethasone (VAD) has now been abandoned by most groups because of its toxicity and inconvenience. The search is ongoing for a better and less toxic regimen. From the Spanish PETHEMA group Dr Laura Rosiñol (Barcelona, Spain) presented data from a phase II study (n = 40) of the use of bortezomib and dexamethasone, given in alternating cycles, as induction therapy. The overall response rate was high (82 %), and in the majority of cases very rapid. No further responses were seen after cycle 5 and 6. Also, patients with cytogenetic findings generally considered to have a negative impact responded well. The toxicity was rather mild and no serious neuropathy was seen. In all patients stem cells could be adequately collected. The authors conclude that the combination of bortezomib and dexamethasone is an effective up-front therapy, and that the study supports the use of a short course with this regimen (to a maximum of four cycles) for newly diagnosed patients.

Standard treatment for younger patients (below the age of 65 to 70 years) is now considered to be one or two cycles of HDM, followed by ASCT. Patients in good general condition and with a HLA-compatible donor can also benefit from an added allogeneic transplantation, which has now been studied and discussed for some time, but no definite answer has been obtained. In this session, results from two

studies of this issue were presented, one resulting in a positive answer, and one in a negative answer.

First, Dr. Philippe Moreau (France) gave an update from the French IFM group regarding their protocols 99-03 and 99-04, comparing autologous transplantation followed by reduced intensity allogeneic transplantation to double ASCT. A total of 284 patients with newly diagnosed myeloma, all below the age of 66 years and with high-risk disease, were included. All were initially treated with VAD and one cycle of high-dose melphalan and ASCT. When a HLA-compatible sibling was available (n = 65), ASCT was followed by an allogeneic transplantation (protocol 99-03). The remaining 219 patients were randomized between a second cycle of HDM (with an M dose of 220 mg/m²) or HDM 220 mg/m² combined with anti-IL-6 monoclonal antibody (protocol 99-04). No difference in survival was found between the two arms in the latter part of the study. When comparing the 65 patients from study 99-03 with the pooled patients from the 99-04 study, the patient characteristics were fairly identical. No difference in event-free survival (EFS) could be observed, but the overall survival (OS) was significantly better in patients treated with double ASCT compared with the allogeneic group. For patients who completed the assigned treatment, the median OS was 66 months in the double ASCT group, compared with 35 months in the allogeneic group (P = .01).

Then, Dr. Benedetto Bruno (Torino, Italy) presented an update of an Italian study of 162 newly diagnosed patients with a HLA-typed sibling, randomized between ASCT + reduced intensity (low dose TBI 2 Gy) allogeneic transplantation (n = 80) and double ASCT (n = 82). All risk categories were included. Fifty-eight patients in the allogeneic arm and 46 in the double ASCT arm completed the assigned treatment. When analyzed according to intention-to-treat, as well as looking specifically at those patients who com-

pleted the assigned treatment, both EFS and OS differed significantly between the two arms, in favor of patients given ASCT + allogeneic transplantation. However, in a multivariate analysis, after adjusting for age, sex, disease stage, beta-2-microglobulin, and a number of other factors, the presence of a HLA-identical sibling was significantly correlated with a better EFS and OS.

The studies are not identical in design and patient material, and well illustrates the difficulty in studies of this problem. However, in spite of the seemingly diverging results, both presenters still considered reduced-intensity allogeneic transplantation as a possible option for newly diagnosed young myeloma patients with a HLA-identical sibling. The transplant-related mortality was in both studies rather low (11% in the French study and 7% in the Italian study). Work can still be done in order to improve the pre-transplant cytoreduction, the conditioning regimen, and prevention of graft vs. host disease (GVHD). Allogeneic transplantation represents for the moment the only potentially curative treatment for multiple myeloma, and data presented by Dr. Bruno indicated that molecular remissions can be maintained for long periods of time.

In a phase II study from four centers within the Nordic region (two in Stockholm and one each from Turku and Copenhagen), Drs. Bo Björkstrand and Hans E. Johnsen treated 101 patients younger than 60 years with double ASCT. The findings in this group were compared with the final results of a previously published Nordic Myeloma Study Group (NMSG) trial of single ASCT to patients below age 60 years (n = 348). The response rate was found to be higher after double ASCT [CR + very good partial response (VGPR) 60% vs. 40% in the single ASCT study], and the EFS was significantly better. However, the estimated overall 5-year survival was identical, 50% in both studies. In a multivariate analysis the type of transplant regimen was not significant. Furthermore, in a 1:1 case-control analysis between the two studies, neither EFS nor OS differed significantly between the studies. The authors concluded that in this retrospective study, double ASCT did not improve the final outcome.

In the next presentation Dr. Andrew Spencer reported on behalf of the Australian Leukemia and Lymphoma Group results from a randomized phase III study of combined thalidomide-prednisolone maintenance therapy vs. prednisolone alone after single ASCT. A total of 243 patients were randomized. Both arms received zoledronate monthly. The target dose of thalidomide was 200 mg for a maximum of 12 months. After 8 months only half of the patients were on the full dose and 20% had stopped taking the drug; after 12 months 64% of patients were still on thalidomide. The toxic side effects were as expected, but generally mild. The group receiving both thalidomide and prednisolone had increased responses during the 12 month maintenance phase compared with those receiving prednisolone alone ($P < .001$). The improvement was more marked in patients who did not have CR/VGPR at the start of maintenance treatment. Both PFS and OS were significantly better in the thalidomide-prednisolone arm compared with those patients given prednisolone alone. The positive findings of thalidomide maintenance after ASCT in this study support previous data from the French IFM group. However, the effect does seem to be more “additive” than true “maintenance,” and mainly observable in patients with suboptimal response to ASCT.

Finally, Dr. Joaquin Martinez-Lopez, representing the Spanish PETHEMA group, looked at the prognostic impact of the post-transplantation response status. From a total of 1088 patients, 740 were assessed for response after ASCT. They were all initially treated with a multidrug cytostatic regimen, followed by one or two ASCT. The response was defined as CR, when immunofixation (IF) was negative, and as e/nCR if immunoelectrophoresis was negative but IF positive. CR occurred in 40%, e/nCR in 17% and partial remission (PR) in a further 32% of patients. After a median follow-up of 50 months, both EFS (the main end-point of the study) and OS were significantly better in patients with CR than in patients with e/nCR. Multivariate analysis confirmed the independent prognostic impact of response status post-transplantation. The authors suggest that response status after ASCT may be used as a surrogate marker for predicting disease outcome.

Session 8: Pathophysiology/New Treatment Development

Chairs:

Dr. William S. Dalton

Moffitt Cancer Center, Tampa, USA

Dr. Sosana Delimbasi

Department of Hematology, Evangelismos Hospital, Athens, Greece

William S. Dalton, (Lee Moffitt Cancer Center, Tampa, Florida, United States) discussed drug resistance in myeloma. Myeloma cell lines have been used for testing drug resistance, however one major problem is that myeloma cells in patients grow in the bone marrow microenvironment, not in isolation as cell lines do in culture. One of Dr. Dalton's working hypotheses is that the bone marrow microenvironment and creates a sanctuary for tumor cells and protects them against insults, including radiation, drugs, and biologics. The aim of therapy should be not only to reduce the tumor burden and eliminate residual disease, but also to prevent the bone marrow microenvironment from helping drug resistance to develop. The interaction of myeloma cells with the bone marrow microenvironment can be divided into two categories: 1) physical contact involving cell adhesion molecules and their ligands, and 2) soluble factors, e.g., IL-6. One approach to study these interactions is to isolate factors and ligands, determine how they are affected by various therapeutics, then add them back into the system to assess their effect. Gene expression profiling (GEP) and other techniques can also be used to identify important factors in drug resistance. Once factors are identified, strategies to block them can be developed. One approach has been to use the decapeptide HYD1 to block cell adhesion-mediated drug resistance mediated by beta-1-integrin activity.

Targeting myeloma cell growth factors in multiple myeloma was discussed by Dr. Bernard Klein (Montpellier, France). Factors that promote the growth of myeloma cells are logical therapeutic targets. These include B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL), a member of the TNF family of cytokines that promotes B cell survival; epidermal growth factor (EGF) family members; IL-6; and insulin-like growth factor (IGF)-1. Atacicept

(formerly called TACI-Ig) is a soluble receptor that binds to APRIL. It is in phase 1 clinical trials in patients with myeloma, resulting in decreased immunoglobulin (Ig levels), decreased numbers of plasma cells, and stable disease in some patients without treatment-related adverse events, and no effect on T cells or other non-B cells.

Dr. Noopur Raje (Dana-Farber Cancer Institute, Boston, Massachusetts, United States) presented her work on Akt as a therapeutic target in multiple myeloma. The complex Akt signaling cascade, which is important in myeloma and other cancers, is central to many pathways coupled to cell surface receptors having down stream effects on the cell cycle, survival, protein synthesis, and cell growth. IL-6, which induces signaling in myeloma cells via phospho-STAT 3 and MAP kinase, also induces phospho-Akt in a dose and time dependent manner. Akt activity can be blocked by compounds including LY295002, a specific PI3 kinase inhibitor, which overcomes the protective effects of IL-6. Activated or overexpressed Akt is related to drug resistance, e.g., to Apo2L/TRAIL, doxorubicin, and bortezomib. There are several compounds that inhibit Akt or PI3 kinase in development or early trials in myeloma, including Enzastaurin, an oral protein kinase (PK) C inhibitor, Perifosine (KRX-0401), a synthetic phospholipids that inhibits phosphorylation of Akt and downstream target proteins, mTOR (mammalian target of rapamycin) family inhibitors, e.g., RAD-1 and CCI 779, and SGN40, a humanized monoclonal antibody to CD40 that inhibits Akt phosphorylation. Additional trials of these compounds, including in combination with novel agents such as lenalidomide or bortezomib, are planned or ongoing.

Dr. Freida K. Stevenson (Southampton, United Kingdom) speculated that one day vaccination against myeloma might

go hand-in-hand with drug therapy. Vaccination strategies are designed to engage the immune system to suppress the growth of myeloma cells by generation of specific anti-myeloma antibodies and/or cytotoxic T cells. Advantages of vaccination include the ability to induce remission and recover immune function. It is also possible to vaccinate donors of allogeneic stem cells for transplantation and transfer immunity. In addition, unlike some solid tumors, myeloma cells are accessible to both antibodies and immune T cells. Disadvantages to vaccination are the long time it takes both to develop vaccines and to mount an immune response once the vaccines are developed. Myeloma is immunosuppressive, which may affect the ability to respond to a vaccine. Few patients with myeloma have a matched allogeneic donor, making vaccination of donor stem cells available only to those few individuals. Patients with myeloma are able to respond to tetanus toxoid after autologous stem cell transplantation (SCT), so it is possible to restore immune function. Strategies are being developed in other cancers, e.g., lymphoma and prostate cancer, and may be employed for myeloma vaccines. DNA vaccines rely on CpG repeats not frequent in the mammalian genome but present in bacteria to activate innate immunity, antigen molecules to elicit CD4 and CD8 cells, and microbial sequences to activate helper T cells and break tolerance. Identification of the most appropriate target antigens in myeloma will be crucial; two possibilities include cancer testis antigen and NY-ESO 1 antigen.

Dr. Nikhil C. Munshi (Dana-Farber Cancer Institute, Boston, Massachusetts, United States) discussed additional vaccination strategies, including the creation of fusion cells from myeloma cells or proteins and dendritic cells. One drawback is being able to obtain sufficient patient myeloma cells to make the vaccine, and although in a small study CD4 or

CD8 T cells expressing interferon gamma were induced, this response decreased over time. Another approach is to use a peptide-based vaccine to induce cytotoxic T lymphocytes targeted to cell surface proteins expressed on myeloma cells. Targets may be selected from overexpressed genes identified by DNA microarray analysis. Immunomodulatory drugs such as lenalidomide may be useful in increasing the immune response to vaccines.

Dr. Gareth Morgan (Royal Marsden, London, United Kingdom) discussed the pharmacogenetics of myeloma. Two types of genetic variation can be considered in myeloma: tumor-specific variation such as translocations and inherited variations including single nucleotide polymorphisms (SNPs). The aim of pharmacogenetic studies in myeloma is to identify those changes that are prognostic factors and use them to design better therapies. Dr. Morgan pointed out that although some genetic changes are considered to be poor prognostic factors, e.g., $t(4;14)$, it is also known that some patients with myeloma or MGUS who have these factors survive well for long periods of time. However, the presence of several poor prognostic factors together may confer an even worse prognosis, e.g., deletion of 16q in the presence of $t(4;14)$ or deletion 17p. The Bank on a Cure[®] chip contains 3400 SNPs in about 700 genes that are likely to be very important in defining host and tumor behavior. These include host factors likely related to a susceptibility or resistance to developing thromboembolic events (TE), possibly via variations in clotting pathways, inflammatory responses, and drug metabolism via the cytochrome P450 pathway. Risk stratification based on SNP profiling may be useful in identifying those patients most likely to need intervention to prevent TE and in selecting the type of intervention, e.g., aspirin vs. low molecular weight heparin or other anticoagulant.

Session 9: Stem Cell Transplantation in Multiple Myeloma

Chair:

Dr. Gösta Gahrton

Karolinska Institute for Medicine, Stockholm, Sweden

Introduction

High-dose treatment followed by either autologous hematopoietic stem cell (ASCT) support or allogeneic bone marrow transplantation (BMT) for multiple myeloma was introduced in the 1980s. ASCT saves the patient after the myeloablative conditioning and BMT in addition has a graft versus myeloma (GVM) effect. ASCT has so far been the most common treatment modality for patients younger than 60 to 70 years of age, while BMT has been used in a limited number of patients due to significant transplant related mortality (TRM) and graft versus host disease (GVHD). However, recent improvement in supportive care and the use of reduced intensity non-myeloablative conditioning (RIC) before BMT has increased the interest in using this treatment modality. This session summarized present knowledge with both types of treatment, ASCT and BMT.

Dr. Michel Attal (Toulouse, France) presented the Intergroupe Francophone du Myelome (IFM) experience in optimization of SCT. The IFM has pioneered prospective studies comparing ASCT and chemotherapy as well as improvements in the conditioning and post ASCT treatment. The first randomised study, IFM90, on 200 patients, published in 1996 demonstrated the superiority of ASCT. Median overall survival (OS) and event-free survival (EFS) were 57 and 44 months, respectively, for patients who underwent ASCT, compared with 44 and 18 months for those who received chemotherapy. The differences were most strongly pronounced in patients under the age of 60 years. In long-term follow-up these differences were sustained: the 7-year EFS after ASCT was 20%. These results were later confirmed in two randomized and two case-control studies. However, in three other randomized studies, there was only improvement in EFS but not in OS, or no benefit in outcome. Attempts to improve results of ASCT include the use of new drugs, i.e., thalidomide,

bortezomib, or lenalidomide in the induction treatment, in the conditioning regimen, and/or as maintenance after ASCT. The IFM investigated the use of dexamethasone + bortezomib (DEX-VEL) as compared with VAD (vincristine + doxorubicin + dexamethasone (IFM 2005 01) for induction before ASCT in 480 patients. In an interim analysis of response rate in 167 patients, DEX-VEL was superior [partial response (PR) versus very good partial response (VGPR) was 82% and 43% versus 67% and 26% respectively]. However, the impact on progression free survival (PFS) and OS has not yet been analyzed. Other induction combinations are being tried in ongoing studies, but conclusive results are not yet available.

New drugs have also been used in the conditioning regimen. In a pilot study of 25 patients that did not respond with near complete remission (nCR) after induction treatment, bortezomib was combined with melphalan (melphalan 200 mg/m² day - 2 + bortezomib 1 mg/m² days -6, -3, +1, +4) for conditioning. After 3 months, CR was 31% and CR + nCR 77%. The toxicity was moderate. Another attempt to improve conditioning has used a combination of arsenic trioxide and ascorbic acid added to conventional dose melphalan (200 mg/m²). In a pilot study of 17 patients with relapsed disease the response rate was 87%.

Maintenance treatment with chemotherapy after ASCT has previously failed to show a benefit. IFM has used maintenance treatment after ASCT in a three-armed prospective randomized study of 597 patients (IFM 99 02). Patients received either a) no maintenance, b) pamidronate or c) pamidronate + thalidomide. The 4-year post-diagnosis probability of survival was 77%, 74%, and 87% respectively. However a survival benefit in the thalidomide arm was only seen in patients that were not in CR after ASCT. Trials using lenalidomide are ongoing.

Thus there seems to be reason to expect improved results in the near future of ASCT using new approaches with new drugs, either in the pre-treatment induction phase, in the conditioning or as maintenance. Thalidomide or other drugs, combined with dexamethasone, should probably be used during induction, but for conditioning melphalan 200 mg/m² is still the gold standard. Maintenance with thalidomide might be considered in patients not in CR following ASCT. The first attempts to use ASCT in tandem were followed by prospective randomized studies comparing single and double ASCT. In two studies there was no benefit in either EFS or OS of second transplant. In one study EFS but not OS was significantly improved by double transplantation, while two studies, including the French IFM94-study comprising 399 patients, demonstrated a benefit both in OS and EFS. However, in a subgroup analysis of this study, the benefit of the second transplant was only seen in patients who did not reach VGPR or CR after the first ASCT.

Dr. Hartmut Goldschmidt (Heidelberg, Germany) presented results of the German prospective randomized study of 358 patients comparing single (n=178) and double (n=197) ASCT. The patient characteristics were similar to those in other prospective studies. Induction was with vincristine + idarubicin + dexamethasone (VID) or VAD (first randomization) and conditioning before each transplant was melphalan 200 mg/m². The median time from the first to the second transplant was 141 days. Thus the timing of the second transplant was similar to that in other studies and within the window previously shown to be most efficient (less than 6 to 12 months) in a retrospective study by the EBMT of 7,452 patients. There was no significant difference between the two treatments, neither in CR rate, nor in PFS or OS. Therefore, there is no agreement as to the benefit or not of a second transplant. It seems clear that patients in CR after a first ASCT do not benefit from a second one, but it is still unclear if other subgroups may benefit.

If elderly myeloma patients are defined as those that are more than 60 years of age, this patient group comprises about 85% of myeloma patients. About 65% are older than 65 years and 37% are older than 75 years. Until now it

was not clear if elderly patients benefit from autologous transplantation as compared to standard chemotherapy. In the IFM90 study no clear benefit of autologous transplantation versus chemotherapy was seen in patients older than 65 year, while Dr. Antonio Palumbo (Torino, Italy), et al., demonstrated superior survival with Mel 100 (melphalan 100 mg/m² for conditioning followed by ASCT) compared with standard melphalan + prednisone (MP). A benefit of transplantation versus standard chemotherapy in patients both below 60 and between 60 and 65 years of age was demonstrated in a retrospective, population-based study in 657 patients, performed by the Nordic Myeloma Study Group.

Recent results of combinations with thalidomide, lenalidomide and/or bortezomib with dexamethasone and/or melphalan without transplantation have challenged the view of a benefit of transplantation in elderly patients. Facon et al. compared melphalan + prednisone + thalidomide (MPT) without transplantation to Mel 100 and MP in a prospective study of 441 patients 65 to 75 years of age. MPT was superior to both Mel 100 and MP concerning response (PR 81% versus 73% versus 40%), PFS (median 30 months versus <24 months) and OS (median 50 months versus <36 months). Combinations with lenalidomide and bortezomib may give even better results. In a comparison between MPR (melphalan + prednisone + lenalidomide) and MPT upfront in patients 56 to 75 years of age the CR+VGPR rate was increased to 48% versus 37% with the lenalidomide combination and EFS and OS were significantly improved compared to historical controls. Upfront MPV (melphalan + prednisone + bortezomib) as compared with MPT in patients 65 to 85 years also had a significantly improved CR+nCR rate (43% versus 37%). Follow-up times are still relatively short for upfront new drug treatment with or without transplantation. However further studies will clarify if reduced high dose conditioning (Mel 100) followed by autologous transplantation still has a place in patients older than 60 to 65 years when using new drug combinations upfront.

Dr. Herman Einsele (Würzburg, Germany) reviewed studies looking at prognostic factors for outcome following

autologous transplantation. In an analysis of 4,322 patients reported to the EBMT myeloma registry transplanted from 1986 through 2000, favourable pretransplant prognostic factors were low age, response to chemotherapy before transplantation, only one line of primary induction treatment, Durie & Salmon stage I or II, and a low beta-2-microglobulin value at diagnosis. In other studies, additional factors like a high CRP- or LDH-levels as well as low serum albumin levels have been associated with a poorer outcome. In more recent years, karyotypic abnormalities have emerged as the most important prognostic factors. Poor outcome is seen in patients with del(13), t(4;14), and t(14;16). Gene expression profiling has recently shown that overexpression of CKS1B located to 1q21 is associated with poor prognosis. Several studies have demonstrated the following among peritransplant prognostic factors: melphalan 200 mg/m² is associated with better survival than TBI + melphalan; peripheral blood stem cells that are used as source for the transplant are superior to bone marrow; and reaching CR at any time is associated with a better prognosis. Attempts to circumvent the poor prognostic impact of del(13) or t(4;14) have been mainly unsuccessful; however in some smaller studies it has been claimed that that patients with del(13) or t(4;14) have responded nearly as well as those lacking the aberrations if bortezomib or lenalidomide have been included in the upfront treatment.

Dr. Sergio Giralt (MD Anderson Cancer Center, Texas, United States) discussed going beyond high dose melphalan as a conditioning regimen and Dr. Henk Lokhorst (Utrecht, The Netherlands) discussed allogeneic transplantation. Allogeneic transplantation in multiple myeloma has been performed since the early 1980s. It has the potential to cure patients with many hematological disorders, including multiple myeloma. A high proportion of patients obtain not only a hematological complete remission but also a molecular remission. The myeloablative conditioning treatment usually consists of total body irradiation (TBI) in a dose of about 10 Gy, fractionated or non-fractionated and combined with high-dose cyclophosphamide. However, although great improvements have been made in later years, myeloablation in myeloma is hampered by a signifi-

cant transplant-related mortality. Therefore, attempts have been made to reduce the conditioning dose (RIC). Several clinical trials have shown that engraftment can be obtained and the idea is that a graft-versus-myeloma (GVM) effect should be enough to eradicate most of the myeloma cells, sparing the normal cells and thus diminishing transplant-related mortality. It is also assumed that the GVM can be enhanced by adding donor lymphocytes later on to prevent or to treat threatening relapse.

Results of allogeneic myeloablative transplantation has improved significantly since 1994 as compared to transplants earlier as shown in a previous EBMT registry study. However transplant related mortality is still high and therefore attempts to reduce the intensity in the conditioning regimen (RIC) have been made. In a recent registry study in the EBMT it could not be proven that RIC transplants were superior to standard myeloablative conditioning. TRM was reduced significantly, but the relapse rate was increased. However the study was hampered by comparing many different regimens, many of them including ATG or Campath in the conditioning regimen. Campath was associated with very poor outcome, due to both increased TRM and increased relapse rate.

Recently Dr. Bruno et al. reported impressive results of RIC conditioning in myeloma compared to autologous transplantation. 245 consecutive patients 65 years of age or younger with stage II or III myeloma treated at five Italian centers were included in the comparison based on genetic randomization. All patients received a first autologous transplantation. Patients that had an human leukocyte antigen (HLA) identical sibling donor were offered a RIC (TBI 200 cGy) transplant as second transplant, while those who did not have a sibling donor received a second autologous transplant. Out of 162 patients that underwent HLA typing 80 had an identical sibling and of these 58 completed the auto-allograft program. OS was superior both in the patient group that had an HLA identical sibling (n=80) and in the patient group that received the RIC transplant (n=58) as compared to the group that did not have an HLA identical sibling (n=82) or that received the double autologous transplant (n=46) respectively. The comparable EFS was

significantly superior only in the group with an identical sibling, but there was a tendency for superiority also in the group that actually received the transplant ($P=.07$). An update with longer follow up at the Kos meeting further strengthened the validity of the results.

Preliminary results by the Hovon group (Hovon50 and 54) showed similar results. In the Hovon50 study all patients 18 to 65 year of age with stage II or III myeloma received an autologous graft after an induction period. 556 patients were included. 93 patients had an HLA identical sibling donor and 87 of them had received the RIC (TBI 200 cGy) allotransplant at follow up and were eligible for evaluation. Patients that were included in Hovon54 had a 3-year OS of 82%, which was not statistically different from the rest of the HOVON 50 patients but was superior to OS in a patient group previously treated with myeloablative conditioning (Hovon24).

Recently the EBMT presented similar preliminary results of a comparison between auto/RIC-allo and single auto or auto/auto. Out of 356 patients that had received a first autologous transplant 108 with an HLA identical sibling received a RIC (TBI 200 cGy + fludarabine) transplant. Preliminary results showed no significant difference in OS or PFS at a median follow up time of 23 and 27 months in the auto and auto/allo group respectively. However a tendency (not significant) for crossing over of the OS curves to the advantage of auto/allo group was seen around 48 month from transplant.

Dr. Nikolas Kroger (Hamburg-Eppendorf, Germany) discussed donor lymphocyte infusions (DLI) and other post-transplant strategies. Donor lymphocyte infusions have the potential to induce remission in patients relapsing after allogeneic transplantation. Response is seen in 30% to 50% of patients and is associated with acute and chronic GVHD. If acute GVHD is induced, as many as 80% of patients may respond, but only 33% if there is no acute GVHD. In a recent study, 52% of the patients responded: 35 PR and 17 CR and EFS and OS were significantly superior in those patients that had CR. Similar results are seen after standard myeloablative and RIC transplants

Attempts have been made to use donor lymphocyte infusion as preventive treatment or to improve remission status after transplantation. In a study of 23 patients that had responded with PR ($n=20$) or VGPR ($n=3$), 15 entered CR after the infusion. Again those who entered CR had a better EFS than those who did not. DLI may be even more efficient if combined with new drugs like thalidomide, lenalidomide, and/or bortezomib. In a pilot study of 18 patients DLI + thalidomide gave a 67% response rate and still only 11% of the patients had acute GVHD of which none was severe. Thus there may be reason to hope that combining DLI with new drugs could improve GVM without inducing more GVHD

Summary and conclusions

Autologous hematopoietic stem cell transplantation is still the main treatment option in patients with multiple myeloma under 60 to 65 years of age. New drugs, i.e., thalidomide, lenalidomide, and bortezomib, may improve results when used during the induction period or as maintenance treatment. In elderly patients (more than 60 to 65 years), it is less clear if transplantation should be used. In patients above 70 years there is no evidence for a benefit of transplantation. There are conflicting views on whether a second autologous transplant improves outcome. If used it should only be performed in those patients who do not have CR after the first transplant.

Allogeneic transplantation has an option to cure a fraction of myeloma patients, The relapse rate is lower than with autologous transplantation irrespective of standard myeloablative or reduced intensity(RIC) conditioning. However transplant related mortality is higher than with autologous transplantation, particularly if standard myeloablative conditioning is used. RIC allogeneic transplantation has a lower transplant related mortality than myeloablative transplantation but the relapse rate is higher. Due to the high transplant related mortality with myeloablative conditioning RIC transplantation is favored. Ongoing studies comparing RIC transplantation to autologous transplantation in patients under 60 to 70 years indicate favorable outcome with RIC, but longer follow-up of ongoing studies is needed for firm conclusions.

Session 10: Other Plasma Cell Dyscrasias

Session Chair:

Robert A. Kyle, MD

Mayo Clinic, Rochester, Minnesota, USA

Introduction

The “Other Plasma Cell Dyscrasias” session included presentations on monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) by Dr. Robert Kyle from the Mayo Clinic. It was followed by a presentation by Dr. Raymond Alexanian of M.D. Anderson (Houston, Texas, United States) on solitary plasmacytoma of bone and of extramedullary plasmacytoma. Diagnosis and prognosis of AL amyloidosis was presented by Dr. Giampaolo Merlini (University of Pavia, Italy). The response, assessment and treatment of AL amyloidosis was provided by Dr. Morie A. Gertz of the Mayo Clinic. The role of high-dose therapy and AL amyloidosis was given by Dr. Raymond L. Comenzo from Memorial Sloan-Kettering (New York, United States). Light-chain deposition disease was covered by Dr. Nelson Leung from the Mayo Clinic Division of Nephrology. Dr. Angela Dispenzieri of Mayo Clinic summarized the newer aspects of POEMS syndrome (osteosclerotic myeloma). Neuropathy associated with paraproteins was the subject of a detailed presentation by Dr. Eduardo Nobile-Orazio (University of Milan, Italy).

Monoclonal gammopathy of undetermined significance (MGUS) is defined as having a serum monoclonal (M) protein <30 g/L, <10% plasma cells in the bone marrow, and no end organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions). MGUS is found in 3% of persons >50 years of age and 5% of those >70 years. The risk of progression to multiple myeloma (MM), Waldenström’s macroglobulinemia (WM), primary amyloidosis (AL), and related disorders is 1% per year. Size of the monoclonal protein, type of M protein (IgM or IgA have an increased risk), and the free light chain ratio (FLC) are major risk factors for progression. Patients with risk factors consisting of an abnormal serum FLC, non-IgG MGUS, and an elevated serum M-protein value >15 g/L have a risk of progression of 58% at 20 years, compared with 37% with 2 risk factors

present, 21% with 1 risk factor present, and 5% when none of the risk factors are present.

Smoldering multiple myeloma is an asymptomatic proliferative disorder of plasma cells and characterized as having a serum IgG or IgM monoclonal protein of 30 g/L or higher and/or 10% or more plasma cells in the bone marrow, but no evidence of end organ damage. In a cohort of 276 patients with SMM, active MM or AL developed in 162 persons during follow-up. The probability of progression to active MM or AL was 51% at 5 years, 66% at 10 years, and 73% at 15 years; the median time to progression was 4.8 years. The overall risk of progression was 10% per year for the first 5 years, approximately 3% per year for the next 5 years; and 1% per year for the last 10 years. On multivariate analysis, the serum M-protein level and the number of plasma cells in the bone marrow emerged as significant independent risk factors for progression. The median time to progression was 2 years in Group 1 (plasma cells >10% and serum M protein >30 g/L), 8 years in Group 2 (plasma cells >10% and serum M protein < 30 g/L), and 19 years in Group 3 (bone marrow plasma cells <10% and a serum M protein of >30 g/L) ($P<.001$). The type of serum heavy chain added significantly to the multivariate model containing the 3 prognostic risk groups.

Dr. Alexanian stated that approximately 2% of patients with multiple myeloma and bone destruction have a solitary lytic lesion. He emphasized the need for magnetic resonance imaging (MRI) of the thoracic and lumbar spine in addition to a metastatic bone survey. A monoclonal protein is found in the serum in approximately 75% of patients; the level was usually <10 g/L. Monoclonal light chains (Bence Jones protein) may be found, but the amount is modest. Levels of uninvolved serum immunoglobulins are usually normal. Treatment consists of high doses of radiotherapy to the solitary lesion. He recommended a dose of 45 Gy in

25 fractions over 5 weeks. The overall survival in 4 reported series ranged from 9 to 11 years.

Solitary extramedullary plasmacytoma is characterized by clonal plasma cells outside the bone marrow and no evidence of multiple myeloma. Approximately 85% of cases involve the head and neck. Dr. Alexanian recommended that radiotherapy in a dose of 35 to 45 Gy plus prophylactic irradiation of regional lymph nodes when the oral cavity, pharynx, larynx or parotids are involved. Disease-free survival after 10 years is approximately 60%. One-fourth of patients developed multiple myeloma.

Dr. Merlini discussed the diagnosis and prognosis of AL amyloidosis. AL amyloidosis is a plasma cell disorder characterized by the deposition of monoclonal light chains in many organs. It results in tissue damage and ultimately organ failure. He emphasized the need for early diagnosis because severe amyloid organ involvement precludes the use of effective therapy. Any patient with nephrotic range proteinuria, unexplained right-sided heart failure, progressive peripheral neuropathy, unexplained hepatomegaly, orthostatic hypotension, or unexplained weight loss should be screened for amyloidosis. The diagnosis depends upon the demonstration of deposits with apple-green birefringence after Congo red staining or electron microscopic demonstration of non-branching fibrils 10 nm in diameter. Fine-needle aspiration of abdominal fat is a rapid, inexpensive, and sensitive approach. Another option is biopsy of the minor labial salivary gland. Renal and hepatic biopsies are useful, but there is a small risk of bleeding. The type of amyloid deposition must be determined. This can be accomplished by immunohistochemistry, immunoelectron microscopy, or by biochemical methods. For the diagnosis of AL amyloidosis, one should document the presence of a monoclonal plasma cell proliferation. Thus, a bone marrow examination must be performed in all patients with suspicion of AL. Immunofixation of the serum and urine is essential and is positive in 97% of patients. Use of the serum free light chain assay (FLC) complements immunofixation and is very useful for monitoring response to therapy. Median survival of AL amyloidosis ranges from 2

years to 3.9 years. Most patients with AL amyloidosis die of cardiac complications. Elevated serum cardiac troponins are related to poor prognosis.

Response as well as therapy of AL was discussed by Dr. Gertz. He mentioned that radio-labeled amyloid P component with iodine-123 or iodine-131 will detect deposits of amyloid in the spleen, liver, and kidneys in 87%, 60%, and 25% of patients, respectively. He emphasized that the SAP scan does not distinguish AL from other forms of amyloidosis. Response to treatment has a profound effect on survival. Hematologic responders have better survival than non-responders, and response occurs in up to two-thirds of patients. Complete hematologic response occurs in one-third of patients. He described a study from the National Amyloidosis Center in the United Kingdom in which free light chain concentrations were measured in 262 patients. The 5-year survival in patients who had a 50% reduction in FLC was 88%, whereas it was only 39% in those who did not achieve a 50% reduction in FLC. In another study of high-dose melphalan and autologous stem cell transplantation, Santhorawala reported a complete response in 41%. In this study, the likelihood of clinical improvement was greater and survival was longer if the FLC concentration decreased by >90%.

The Italian Amyloidosis Treatment Group reported the use of melphalan 0.22 mg/kg and dexamethasone 40 mg daily, both for 4 days every 28 days. The response rate was 67% and organ responses occurred in 48%. There were only two treatment-related deaths in the first 100 days. The median survival was 5.1 years. Thalidomide plus dexamethasone as well as lenalidomide combined with dexamethasone have both shown activity in AL amyloidosis with hematologic responses in the range of 60% and organ responses of approximately 30%.

The role of high-dose therapy in AL amyloidosis was presented by Dr. Comenzo. He pointed out that only one-third of newly-diagnosed untreated patients with AL amyloidosis have sufficient organ reserves to tolerate high-dose melphalan with a stem-cell transplant (SCT). Two-thirds of

patients experience at least a partial hematologic response, but only half of the responders achieve a complete hematologic response. In the remaining one-third of patients, this treatment fails; the patients do not respond and have a poor prognosis. Stem-cell transplant in AL amyloidosis resulted in 20% to 40% treatment-related mortality, but currently has fallen to less than 5% if patients are carefully selected. In a multicenter, randomized, prospective phase III trial, SCT was compared with oral melphalan and dexamethasone. Comparison of response rates and survival between those alive at least 3 months post-SCT and those who completed at least 3 months of oral melphalan and dexamethasone showed no difference. For both groups, the hematologic response rates were 65%. The median survival was 48 months for SCT and 58 months for melphalan and dexamethasone. On the other hand, a case-cohort analysis has shown a survival advantage in good performance status patients treated with SCT. Dr. Comenzo emphasized that patients with systemic AL amyloidosis should be treated whenever possible on clinical trials in order to advance our understanding and management of the disease.

Dr. Leung defined light chain deposition disease (LCDD) as a plasma cell disorder characterized by deposits of monoclonal light chains or, less frequently, light and heavy chains or heavy chain only. The incidence of LCDD is unknown. Almost all patients with LCDD present with renal manifestations such as renal insufficiency, proteinuria, or hypertension. The heart and liver may also be involved with light chain deposits. Approximately 75% of patients with LCDD consist of monoclonal kappa light chain deposits. Treatment consists of corticosteroids and cytotoxic agents similar to those used in the treatment of multiple myeloma. High-dose melphalan with stem cell rescue has also been beneficial. In a report of 6 patients with LCDD, complete hematologic responses were achieved in 86% following SCT and were alive at a median follow-up of 12 months. It appears that high-dose melphalan followed by autologous stem cell transplant may be the treatment of choice for LCDD.

Dr. Dispenzieri defined POEMS syndrome (osteosclerotic myeloma) as the presence of peripheral neuropathy (P), a monoclonal plasma cell disorder (M), and paraneoplastic features including organomegaly (O), endocrinopathy (E), skin changes (S), papilledema, edema, pleural effusion, ascites, or thrombocytosis. Actually, all patients with POEMS have at least one osteosclerotic bone lesion, an elevation of plasma levels of vascular endothelial growth factor (VGEF), or coexistent Castleman's disease. Not all features of the disease are required to make a diagnosis. Although the plasma cell clone is linked to the peripheral neuropathy and other clinical features, the mechanism is not yet understood. It is essential for all patients with an unexplained sensorimotor peripheral neuropathy to have a metastatic bone survey in an effort to detect osteosclerotic lesions. Tumorcidal radiation to the osteosclerotic lesions (if localized) is an effective mode of therapy. If the osteosclerotic lesions are widespread, high-dose melphalan followed by autologous stem cell transplantation is useful.

Dr. Nobile-Orazio discussed the paraproteinemia-related neuropathies. He pointed out that symptomatic neuropathy may be found in at least 8% of patients with monoclonal gammopathy; thus, it is one of the leading causes of neuropathy in older patients. The presence of symptomatic neuropathy is higher in IgM than IgG or IgA MGUS. Patients with IgM MGUS have a chronic progressive, symmetric, and predominantly distal neuropathy. The monoclonal protein frequently reacts with MAG (myelin-associated glycoprotein), chondroitin sulphate C, sulfatide, and a number of gangliosides. Almost 50% of patients with neuropathy associated with an IgM paraprotein have monoclonal proteins reactive with MAG. The neuropathy is characterized by a distal and symmetric sensory neuropathy with ataxia and postural tremor of the upper limbs. Motor impairment is less prominent and often appears later. The course is slowly progressive. Electrophysiologic and morphologic studies are consistent with a demyelinating neuropathy. Therapy is not satisfactory and consists mainly of plasma exchange and cytotoxic agents. Occasionally, patients respond to corticosteroids, intravenous immunoglobulin, or alpha interferon. Rituximab has shown benefit. Approximately

one-third of patients with a peripheral neuropathy and IgM have no antibodies reactive with any of the nerve antigens. The pathogenesis of the neuropathy in these patients is unclear.

Neuropathy may be associated with IgG and IgA monoclonal gammopathies. The relationship between IgG monoclonal proteins and neuropathy is not clear. Neuropathy associated with multiple myeloma is clinically heterogeneous, reflecting the presence of different pathogenic mechanisms. In approximately one-half of the patients, the neuropathy is due to the deposition of light chain amyloid

(LC amyloidosis). Autonomic impairment including postural hypotension is often seen in this setting. Chronic demyelinating neuropathy may be a feature of IgG MGUS. These patients are indistinguishable from those with chronic inflammatory demyelinating polyradiculopathy (CIDP).

IgA MGUS may be associated with sensorimotor peripheral neuropathy. This condition is not well-defined. The clinical and electrophysiologic features are quite heterogeneous, making it impossible to identify a prevailing type of presentation. There is little evidence that IgA monoclonal proteins have a primary pathogenic role in the neuropathy.

Session 11: Oral Presentations III

Chair:

S. Vincent Rajkumar, MD

Mayo Clinic, Rochester, Minnesota, USA

Many interesting and important new findings were presented in the “Oral Presentation III” session. The abstracts in this session primarily dealt with advances in our understanding of myeloma tumor biology, but also had relevance to improving therapy and outcome for the disease. In particular, the last abstract of the session by Hulin et al. may affect the standard of care for patients with myeloma who are over 75 years of age.

Dr. Jonathan Keats (Mayo Clinic Arizona, United States) opened the session with his presentation titled “High-Resolution Mapping of Common Gains and Losses in Myeloma.” Dr. Keats and colleagues have been working to find specific genetic factors that lead to the development and progression of myeloma. In this study, they used a sophisticated new technique called array comparative genomic hybridization (aCGH) that is very good at picking out small genetic abnormalities that are otherwise hidden. They found numerous new genetic alterations, with each sample having a range of 2 to 58 abnormalities. The presence of more than 20 abnormalities was associated with more aggressive disease. Further work on the new abnormalities identified in this study will help better understand how myeloma originates and what factors contribute to its progression.

The work done by Keats and colleagues relied on microarray technology which is increasingly used in the study of cancer to study thousands of genes at one time. Mr. Vincent Sieben (University of Alberta, Edmonton, Canada) presented a new technology called “microchips” in a talk titled “Microchips for Optimized FISH Screening in Myeloma.” Interphase fluorescence in situ hybridization (FISH) is a very good method to find genetic abnormalities in myeloma cells. But it is complex, and more automated methods are needed. Mr. Sieben presented a new automated “lab-on-a-chip” device that may alter the way FISH is

done in the future. He showed that the new technology is 10 times less expensive and has a 10-fold higher throughput than conventional FISH testing.

Dr. Olivier Decaux on behalf of the French IFM group presented a very interesting talk titled “Molecular Prognosis in Multiple Myeloma: The IFM Experience.” Currently we use a few risk factors based on simple laboratory and genetic tests to predict survival in myeloma. Survival of patients with myeloma varies widely, and if we can predict outcome, we will be able to tailor therapy according to a patient's need. To develop a more accurate model to predict survival, Dr. Decaux and colleagues studied 250 myeloma patients by gene-expression profiling (GEP), a microarray-based technique which allows us to study tens of thousands of genes, using one small sample of the patient's myeloma cells. They identified 15 genes that were highly predictive of survival. This finding coupled with similar efforts underway at other institutions will help us develop a risk-based method of treating myeloma in the near future. In fact, the next abstract in this session “Gene Expression Profiles as Prognostic Factors for High-Dose Therapy and Bortezomib in Patients with Multiple Myeloma,” by Dr. Annemiek Broyl (Erasmus Medical Center, Rotterdam, Germany) demonstrated the potential utility of gene expression based risk-factors in myeloma therapy. Recent studies that indicate that myeloma may not be a single disease, but rather a collection of 6 or more genetically distinct sub-types, were confirmed.

Next, Dr. Douglas W. McMillin (Dana Farber Cancer Institute, Boston, Massachusetts, United States) presented another dazzling new technology in his talk “Compartment-Specific Bioluminescence Imaging (CS-BLI): A High-Throughput Approach to Identify Novel Anti-Myeloma Therapies that Overcome the Protection of Stromal Cells.” This technology overcomes limitations of conventional assays that are

not amenable to studying myeloma cells in their microenvironment. To do this one needs to be able to co-culture myeloma cells with bone marrow supporting cells called stromal cells. The study showed that this is possible by using a novel compartment-specific bioluminescence imaging (CS-BLI) assay. This technique will be very useful in testing new drugs and identifying active drugs in a more reliable way.

In terms of new drugs, Dr. Steffen Klippel (Dana Farber Cancer Institute) presented interesting new data on a small molecule called PRLX in a talk titled "In Vitro and In Vivo Anti-Myeloma Activity of PRLX, an Orally-Bioavailable Agent Against Mutant Ras-Transformed Cells." Ras is an important gene that is involved in cancer, and mutations of ras occur in 40-60% of multiple myeloma and are felt to be culprits in myeloma progression in many patients. The new drug blocks the ras pathway, and appeared active against 34 of 46 human myeloma cell lines tested, including myeloma cells resistant to conventional chemotherapy, lenalidomide, and bortezomib. It is a promising novel drug that will likely be tested in the clinic soon.

Towards the end of the session, Dr. Suzanne Lentzsch (University of Pittsburgh Cancer Institute, Pittsburgh, United States), presented a study looking at why patients receiving lenalidomide sometimes develop blood clots. The talk was

titled "Cathepsin G Is Upregulated in Patients Treated with IMiDS." Her group found that a protein called cathepsin G that can activate blood platelets may be involved. They found that drugs like lenalidomide may increase the levels of cathepsin G and contribute to platelet activation and subsequently blood clots. This study has value and will aid in us in developing strategies to better prevent blood clots by understanding better the mechanisms involved.

The final abstract of the session was presented by Dr. Cyrille Hulin on behalf of the French IFM group. This was a major study that will affect how elderly myeloma patients (>75 years of age) are treated. The talk titled "Melphalan-Prednisone-Thalidomide (MPT) Is also Superior to Melphalan-Prednisone (MP) in Patients 75 Years of Age or Older with Untreated Multiple Myeloma (MM). Preliminary Results of the Randomized, Double-Blind, Placebo Controlled IFM 01-01 Trial," comes in the wake of two similar trials that were presented last year showing the same results. What was unique about this trial was that it specifically targeted patients over the age of 75 years who have not been well-studied in previous studies. The study enrolled over 200 patients, and showed that response rates and survival were superior with the three drug MPT combination compared with the older regimen of MP. Final analysis of this study will determine whether clinical practice changes in this population.

Session 12: Debate II

Moderator:

Jean-Luc Harousseau
CHU Hôtel-Dieu, Nantes, France

Dr. Jean-Luc Harousseau moderated a debate between Dr. Jean-Paul Fermand (Hôpital Saint-Louis, France) and Dr. Bart Barlogie (Arkansas, United States) on the subject of whether autologous transplant should be part of the primary treatment in multiple myeloma. Dr. Harousseau commented that it was a strange paradox that high dose therapy with transplant, which has been the standard of care for over ten years for younger patients, should still be a matter of debate. He posed the following questions: Is autologous stem cell transplant (ASCT) useful? Is there a role for further dose intensification with double vs. single ASCT? Which patients will benefit from ASCT? Is there a place for ASCT in the era of novel therapies?

Should autologous transplant be part of the primary treatment in MM?

NO. Dr. J.P. Fermand

Dr. Fermand amended his response to the overall question from “no” to “maybe.” He noted that ASCT can contribute to overall survival (OS), and there have been at least three randomized trials showing a long-term survival benefit of ASCT over conventional chemotherapy. However, there are also at least three trials showing no benefit in OS. He attributes this to differences in study design, and pointed out that when the duration of standard dose therapy is at least one year, ASCT in comparison no longer shows an advantage. He suggested that very large numbers of patients are needed to demonstrate a clear advantage of high dose therapy and ASCT, and that the advantage may be in progression free survival (PFS) not OS.

Dr. Fermand also stated that it is critical to assess patient quality of life. With novel therapies used in induction regimens, there may not be a survival advantage after high dose therapy, although the response rate before high dose therapy may be higher than that seen with induction using

conventional chemotherapy. He questions the “more is better” strategy, his description of Dr. Barlogie’s Total Therapy (TT) regimens, and believes that new strategies can be developed for long term disease control by combining conventional agents with novel therapies. Dr. Fermand recommended determining the sequence in which novel and older therapies should be administered, defining treatment regimens for both standard and high dose therapies, and examining the use of targeted therapies in a new generation of randomized studies.

Should autologous transplant be part of the primary treatment in MM?

YES. Dr. B. Barlogie, USA

Dr. Barlogie reviewed the results of trials of TT1, TT2, and TT3, noting that the eight-year median survival for patients receiving TT2 was unprecedented. TT3 requires a shorter induction period, so 70% of patients make it to the second consolidation after the second ASCT. Dr. Barlogie also pointed out that by using MRI it is possible to detect focal lesions that are sites of eventual relapse. In at least some patients, plasma cells from these focal lesions are distinct from random bone marrow by gene expression profiling (GEP). Detection of complete response (CR) by MRI lags behind evidence of clinical CR in these lesions, which can contain hyposecretory myeloma stem cells. GEP has been used to identify a high-risk subpopulation of patients treated with TT3 whose OS is lower than the non-high-risk subpopulation. However, TT3 results in superior event free survival (EFS) in both high- and lower-risk populations compared with TT2. Dr. Barlogie believes that cure should be the goal of treatment, and that treatment strategy must reduce the burden of tumor cells to ensure a durable CR. One of his concerns is to maintain the bone marrow in good condition during initial treatment to allow optimal ASCT.

Dr. Harousseau posed several questions. One concerned whether continuation of conventional chemotherapy for over one year would increase the CR rate. Dr. Fermand believes that CR rate is not the issue, but that longer therapy merely delays relapse. Dr. Barlogie commented that this would only affect the myeloma cells that were chemotherapy sensitive. In response to questions about patient quality of life with TT, Dr. Barlogie mentioned that his funding didn't support quality of life studies, but that patients he treated were committed to their therapy, and that 80% of them remained on this therapy. Dr. Fermand pointed out that the risk, cost, and constraints of TT must be associated with reduced quality of life, particularly in patients with a short life expectancy. Furthermore, he stated that TT using all available therapies is at the expense of less effective salvage at relapse, suggesting that treatment tools

should be used more rationally. Dr. Barlogie mentioned that therapies have to be adjusted to a patient's comorbidities, including age and renal failure.

Dr. Harousseau concluded that both Drs. Fermand and Barlogie seem to agree that novel agents can improve therapeutic approaches whether using ASCT or not. In the ensuing discussion, Dr. Wang pointed out that it would be difficult in many geographic locations to use detection of focal lesions by MRI as a marker for long term survival. Both debaters also agreed that there were more important things to do to improve the treatment of myeloma than to study whether purging stem cell grafts in conjunction with novel therapies would improve the response following SCT.

Session 13: Current and future perspectives in multiple myeloma

Chairs:

Dr. Meletios A. Dimopoulos

Alexandra Hospital, Athens, Greece

Dr. Mario Boccardo

Ospedale San Giovanni Battista, Torino, Italy

Dr. Brian G. M. Durie (Cedars-Sinai Cancer Center, Los Angeles, United States) discussed the importance of new and evolving response criteria. Response criteria are important for evaluating therapy in myeloma, particularly as new agents continue to become available, and the goals in myeloma treatment evolve from trying to cure the disease to maximizing the duration of survival. It is difficult to use long term survival, not only because of the length of time needed for follow-up, but also because of the confounding issue of post-protocol treatment. Shorter term survival is an important early indicator of initial response and early relapse. Important markers for response include survival, adverse events contributing to death, and progressive disease. Dr. Durie reviewed several important studies showing improved response rates associated with the introduction of novel therapies. New response categories to consider include biochemical relapse and clinical relapse, based on CRAB criteria (development of bone disease, anemia, renal dysfunction, and hypercalcemia) as indicators for moving on to the next therapy; sequential therapy may be important in the absence of cure. However, cure and disease control may have similar endpoints, e.g., at least four years disease-free or at least 10 years without relapse. New endpoint strategies are needed, including the incorporation of new molecular tests, to compare the results from different trials.

Accepted risk factors that are readily available, quantitative, cheap, and useful include age, performance status, beta-2-microglobulin, albumin, lactate dehydrogenase, C-reactive protein, and free light chains. Imaging techniques such as MRI and CT/PET, while accepted as identifying focal disease and relapse, are not readily available or cheap, and therefore not as useful. Risk factors that are less accepted for use in determining treatment or that are less available,

less likely to be reimbursed, or more technically challenging include cytogenetics, FISH, GEP, SNP (single nucleotide polymorphism DNA analysis), and proteomics. However, it is probably too early to institute risk-adapted treatment for patients with myeloma.

Dr. Jesus F. San Miguel (University of Salamanca, Spain) summarized how treatment of myeloma could be individualized in the era of multiple novel agents. Like lymphoma, myeloma is probably not a single entity. Dr. San Miguel doesn't believe that low risk myeloma exists, and prefers categorizing it as standard or high risk. He approaches treatment by first stratifying patients by age and whether or not they are transplant candidates. He also believes there is a role for maintenance therapy. He proposes bortezomib-Adriamycin-dexamethasone or lenalidomide plus dexamethasone for induction and MEL200 for transplant candidates with standard risk, followed by thalidomide or lenalidomide with or without prednisone or dexamethasone for maintenance, acknowledging that studies are needed. For early relapse (within a year), non-cross-resistant agents followed by reduced intensity conditioning (RIC) allogeneic stem cell transplantation (SCT) may be considered. Relapse within one to three years (intermediate) post-SCT can be treated sequentially with novel agents, and with RIC allogeneic SCT in patients less than 55 years of age. For later relapse (after three years), Dr. San Miguel recommends re-induction and a second autologous SCT (ASCT).

For high risk transplant candidates, induction with alternative non-cross-reactive therapies and ASCT or RIC allogeneic SCT OR alternating targeted therapies with standard therapy (induction with a novel agent plus ASCT) is recommended; or these patients can be enrolled in clinical trials.

For patients with primary refractory disease, myeloablative therapy supported by ASCT can be an option. For non-responding disease, patients with stable disease do as well as those with chemotherapy-sensitive myeloma. However, progressive disease is associated with poor outcome. so non-cross-reactive therapy with RIC allogeneic SCT is recommended. In the presence of renal insufficiency, VAD requires no dose adjustment, and bortezomib is effective.

For elderly patients who are not transplant candidates, six cycles of a melphalan-prednisone combination [MP plus either thalidomide (T), lenalidomide (R), or bortezomib (V)] are good options. Dr. San Miguel suggested MP-V for patients with a risk of thromboembolic events or with poor adherence to oral therapy, MP-R for patients with antecedent peripheral neuropathy, MP with either oral IMiD for those far from a hospital, and MP-T as the lowest cost regimen of these combinations. He believes that lenalidomide with low dose dexamethasone may also be an option for elderly patients, even the very elderly (those over 75 years of age), although reducing the dose of the IMiDs or dexamethasone may be appropriate. There are no data for maintenance therapy in the elderly. For newly diagnosed elderly patients in relapse, the condition of the patient must be considered in deciding among active therapy, clinical trials, or less active therapy (e.g., oral cyclophosphamide plus low-dose prednisone).

Dr. Pieter Sonneveld (Rotterdam, The Netherlands) presented an overview of the present and future of the European Myeloma Network (EMN). The EMN was established in 2003 to coordinate both laboratory research and clinical trial groups for multiple myeloma and related diseases. The goals of the EMN are to disseminate the expertise of a joint program that includes establishment of a European-based laboratory and clinical network of excellence to support translational research, technology and training already existing; to coordinate clinical research, especially clinical trials, including those for orphan diseases related to myeloma; and to establish an online system for communication, documentation, education, information, and registration. The EMN, which includes 130 mem-

bers, is open to new members, particularly those from new European Union member states and from Eastern Europe. The three linked scientific working areas focus on disease mechanisms, on prognostic factors and disease monitoring, and on therapeutics. Clinical and preclinical work include seven areas: clinical trials and new drugs, allogeneic SCT and immunotherapy, pathogenesis and biology, quality control and standardization, orphan plasma cell diseases, educational programs for both the public and health-care professionals, and the establishment of consensus guidelines on clinical practice related to myeloma, particularly for countries where these do not now exist. For example, a goal of EMN is to gain access to newer drugs, and to introduce them to patients earlier than is the current practice. In 2008, grants will be available to study allogeneic SCT and immunotherapy.

EMN has MSCNET, a large cooperative grant to support the search for the myeloma stem cell using flow cytometry, starting with characterization of subsets of pre-myeloma and myeloma cells. EMNBIO is another proposal to develop standards and norms for biologic samples for EMN member use. A third proposal, EMNOMICS will develop a genomic platform for detecting prognostic biomarkers in myeloma. Other efforts of EMN include workshops for developing common standards for laboratory techniques and related quality control, including FISH, multiparametric flow cytometry, and gene expression profiling. EMN is focusing on diseases that are so rare that organizing a clinical trial in any individual member country would be difficult. Independent trials include a phase II trial for untreated patients with Waldenström's macroglobulinemia, proposed trials for POEMS syndrome and amyloidosis, and meta-analysis of four trials comparing MP vs. MP-T.

Finally, the multiple myeloma conference concluded with a discussion of future perspectives in the management of myeloma by Dr. Kenneth C. Anderson (Dana-Farber Cancer Institute, Boston, Massachusetts, United States). He noted that the novel agents thalidomide, lenalidomide, and bortezomib, which were initially tested in the relapsed/refractory myeloma setting, have moved into the

induction/first-line therapy setting, and are also being used in the transplant and maintenance settings. Progress in the treatment of myeloma that is continuing includes identification of novel targets in the myeloma tumor cell and supporting bone marrow stroma, further identification of prognostic and risk factors based on biology, and development of combination regimens that will have increased anti-myeloma activity with reduced risks of development of drug resistance and toxicity. Dr. Anderson reviewed the use of genomic technologies to identify over-amplified gene products in myeloma to test as targets for new therapeutics, e.g., monoclonal antibodies, or vaccines. An antibody to CS-1, expressed on the surface of myeloma and plasma cells, is already in early clinical trials. Many targets have already been identified, such as peptides predicted to have high binding affinity in the presence of HLA-A2, including sequences from insulin-like growth factor-1, syndecan-1, and cyclin D1, which are expressed on the cell surface, and therefore are potential vaccine targets. Other new targets may be identified by sequencing mutations in the components of signaling pathways necessary for the survival of myeloma cells. The use of array CGH will be useful for identifying other potential therapeutic targets.

Dr. Anderson emphasized the importance of the bone marrow microenvironment and its interaction with myeloma cells. Therapeutics targeting changes in the bone marrow microenvironment during the binding of myeloma cells, e.g., bortezomib, have contributed to the progress in treatment over the last five years. Dr. Anderson pointed to new, improved *in vitro* and *in vivo* models of myeloma that better reflect this interaction, allowing study of pathogenesis as well as testing of new therapies. Plasmacytoid dendritic cells can be grown in culture, supporting the growth of myeloma cells, may allow identification of the myeloma stem cell, and may be useful for testing therapies. Cytokines may be targeted in the future as part of

combination regimens. An antibody to vascular endothelial growth factor (VEGF) receptor is in early trials. In addition to targets on the cell surface and cytokines, a third class of targets may be intracellular molecules essential for survival pathways in myeloma cells or in the cells of the microenvironment, e.g., osteoclasts, that are required for tumor growth. Dr. Anderson reviewed other therapeutics in development and early clinical trials; these include a cyclin inhibitor and new proteasome inhibitors. He noted that the immunoproteasome may become an important target, because it is expressed only in hematologic malignancies, and not in normal cells. He suggested that the aggresome will become an important target as well, and that targeting both the proteasome and aggresome together should be highly synergistic.

Dr. Anderson concluded with a discussion of rationally-based combination therapies for myeloma. These include combinations of one or more novel agents, each with a different mechanism of action, e.g., bortezomib plus Doxil or lenalidomide or Hsp90 inhibitor; or lenalidomide plus an mTOR inhibitor or one of the new proteasome inhibitors. He noted that bortezomib plus Doxil was recently approved, and predicted that bortezomib plus the Hsp90 inhibitor tanespimycin may be the next combination approved, as a phase III registration trial is underway. He also mentioned HDAC (histone deacetylase) inhibitors as a potential combination therapeutics in myeloma. The combination of lenalidomide with other immune therapies may also be effective. High throughput screening technologies may aid in identification of effective drug combinations, and should be useful in determining the effect on both myeloma and stroma cells as new culture methods are developed. Dr. Anderson observed that much progress in the treatment of myeloma has been due to the cooperation among academia, industry, and regulatory agencies.



International Myeloma Foundation

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

TheIMF@myeloma.org

www.myeloma.org

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