

A Comprehensive Guide to Washington, DC • 2009

Review of the XIIth International Myeloma Workshop

*Summaries from the workshop sessions in Washington, DC USA
February 26 – March 1, 2009*



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: Molecular Pathways

Chair:

Brian Van Ness, PhD

University of Minnesota Cancer Center, Minneapolis, Minnesota, USA

The 12th International Myeloma Workshop opening session was “Molecular Pathways” and provided an update from leaders in the field. Dr. Rafael Fonseca from the Mayo Clinic, Scottsdale, discussed chromosomal FISH and its association with pathophysiologic events, prognostic value at baseline disease diagnosis, and its predictive value in therapeutic outcomes. The most significant risk factors identified by FISH remain (4;14) (14;18) and deletion of chromosomes 17 and 13. P53 deletion is also a negative prognostic factor. As other studies have shown, chromosome 1p deletions and 1q gains are also associated with poor outcomes. The Mayo group has further developed the mSMART system of prognostic predictors that include FISH, chromosome 13 del, hyperdiploidy and labeling index in a conglomerate algorithm. However, the utility of this system may not be widely used in community settings, given the technical requirements. Dr. Fonseca compared the value of emerging gene expression profiles versus FISH as prognostic factors and suggested, at present, FISH may be simpler to do and interpret, had more likely insurance coverage, and provided predictions of value in identifying the poor outcome patients. He felt that future publication on myeloma clinical outcomes should report some genetic descriptions of cohorts.

Dr. Avet Loiseau, of Institute of Biologie, Nantes, France, described FISH prognostic factors in agreement with the Mayo descriptions. Additional approaches incorporated genome wide association studies (GWAS) in which 500,000 single nucleotide polymorphisms (SNPs) were screened. Notably, GWAS profiles distinguished hyperdiploid and non hyperdiploid patients. When looking at copy number changes, gains in chr 5 was found to be the most significant predictor of good outcomes, in the hyperdiploid cohorts. Interestingly, the lack of a chr 5 gains paired with a chr 1q gain was a particularly poor prognostic indicator. This led to the suggestion that further work might look to con-

sider potential targets on chr 5. Using a combination of gene expression profiling and chromosomal abnormalities might be among the most predictive combinations. Along with other investigators, Dr. Loiseau noted that the previous association of (4;14) with poor outcomes, was overcome with the use of Velcade. This provided an important discussion point, that prognostic markers, whether expression profiling or chromosomal abnormalities, might show differential effects, depending on therapeutic drugs used. It also suggests that targeted selection of drugs, based on genetic markers might benefit otherwise poor outcome predictors.

Dr. Johannes Drach, from the Medical University of Vienna, examined the mSMART system of Mayo, and noted that while it was useful in the context of standard therapies, it may show altered associations in the context of new therapeutic agents. This echoed the concerns that prognostic predictions become limited by choice of therapy, and that novel agents may require reassessment of prognostic predictors. Again, Dr. Drach noted that Velcade appeared to overcome a number of chromosomal predictors of the past; however, notably, gain of chr1q remained a poor outcome predictor with Velcade. Yet, if combined with Melphalan the chr1q had little difference in overall survival. Dr. Drach further emphasized the key role of the microenvironment and the “secretome” (secreted proteins) among patients, and presented approaches to describe the bone marrow proteomic profile. In comparing the proteomic profiles of myeloma versus MGUS, 5 proteins were identified that were distinct in myeloma expression (not MGUS) – these were, not surprisingly, secreted proteins and proteins associated with adhesion within the microenvironment. This now opens a new opportunity to define disease related and patient specific proteomic profiles that may provide additional prognostic biomarkers of disease progression and response.

Dr. Gareth Morgan, from the Royal Marsden Hospital in London, described studies from the Myeloma IX trial in the MRC system. Using the GWAS 500,000 SNP platform they have identified poor prognosis groups with chr 1p loss, 17p loss, del 13, and 1q gain. They then went on to attempt to map and define minimal regions of the chromosomal predictions, then use this to guide the examination of gene expression changes. From this, a gene FAF1 was identified, as well as CYLD, a negative regulator of the prominent transcription factor, NF-kB. Dr. Morgan felt that there was, at times, a confusion between chromosomal abnormalities associated with the etiology of myeloma and those associated with progression events or therapy associated toxicities (such as neuropathies). Early analyses have begun to identify potential genomics signatures of risk from therapy induced neuropathies. To expand the association studies, his group has been looking at pathways rather than single gene targets, including altered regulation of a family of apoptotic regulators. In addition, Dr. Morgan is proposing that germline (inherited) variations may be combined with tumor specific genetic alterations to best describe or predict outcomes.

Dr. John Shaughnessy, from University of Arkansas Medical Sciences, presented updates on the gene expression signatures that best predict outcomes in both Arkansas trials as well as independent validation trials. The 70 gene profile identifies 51 up-regulated and 19 down regulated genes used to discriminate survival – capturing 25% of the patient variability. Adding other prognostic variables can improve the accuracy to account for up to 50% of the variation. While this sounds like a relatively low number, the limited number of variables provide high level of prediction. The original scoring system was developed on the Arkansas TT2 trial, and when applied to TT3, as well as, a Millenium APEX trial (Velcade vs Dex), the 70 gene model held up as an effective predictor. Dr. Shaughnessy also confirmed that the previous poor prognostic marker 4:14 translocations were lost in Velcade treatment. In a new look at tumor site heterogeneity, gene expression profiles were applied to tumors that were diffuse in the marrow or in focal lesions. DKK expression was notably high in tumors of focal lesions.

This prompted a suggestion that risk density maps could be created that distinguish sites of limited or diffuse tumor versus focal lesions, and that within focal microenvironments tumors exhibit altered gene expression patterns.

Dr. Michael Kuehl, of the National Cancer Institute, described a series of prognostic markers that may distinguish MGUS from myeloma. Hyperdiploids are found in both, as are chr 13 deletions; but progression of MGUS to myeloma is accompanied by secondary translocations and alterations of p18 and Rb proteins. Among the most significant studies he presented was an analysis of 90 myelomas from which earlier serum samples could be examined for evidence of monoclonal spikes indicative of MGUS. Strikingly, 27 of 30 samples examined had monoclonal spikes at least 2 years prior to any diagnosis of myeloma, suggesting MGUS may be a very common, if not consistent, precursor to myeloma. He concluded that de novo myeloma may well be the exception. As mutant ras genes are often found in myeloma, Dr. Kuehl presented an examination of Nras versus Kras mutations, noting that Nras mutations are found in MGUS, but Kras mutation has not been found in MGUS, but is the most common ras mutation in myeloma. This established a paradox, which is confounded by observations of several groups that mutations in Kras appear to be a poor prognostic indicator – significantly greater than Nras mutations. The reason is not clear.

In summary, this session confirmed a number of genetic markers associated with poor prognosis; but it was noted in several presentations that as new therapies emerge, alterations in the prognostic value may shift for some of the genetic aberrations. New genetic biomarkers are continuing to be evaluated, and it is clear that efforts will now include combinations of tumor genetics, microenvironment expression patterns, proteomic profiles, and drug specific targets in better predicting disease progression or response to new therapies. These approaches will reach their full potential once demonstrated as effective in clinical trials that use such markers to stratify patient treatments.

myc targeting cell cycle progression steps through cyclin D provide effective anti-myeloma therapy. Cyclin D1 can be inhibited by a new protein inhibitor called Purpalanol and the authors demonstrated specific cytotoxicity and apoptosis of myeloma cells in vitro using this drug. This effect is inhibited by the bone marrow environment but combination with agents that target cell adhesion mediation drug resistance, such as the IMiDs, may make this an effective antimyeloma agent.

An important paper was delivered by Dr. Russell from the Mayo Clinic concerning oncolytic viral therapy for multiple myeloma. In this process an attenuated measles virus has been shown to be able to infect and kill human myeloma cells via the surface antigen CD46 whilst sparing normal cells. It has also been shown to have potent anti-tumour activity in xenograft models of human myeloma. CD46 is highly expressed in primary myeloma cells and its expression correlates with its susceptibility to the attenuated measles virus.

This process has been translated into clinical trials and Phase 1 studies are under way. The coxsackie virus A21 enters myeloma cells via CD54 and CD55 has also been shown to have oncolytic activity against melanoma and myeloma cell lines.

However; even attenuated viruses remain immunogenic and mechanisms to circumvent antiviral antibodies have been developed by using infected normal autologous carrier cells.

In conclusion this session provided evidence that a number of novel cellular targets and novel means of delivering biological cytotoxicity can be performed and these avenues are very promising for the future.

Session 3: Myeloma – Immune and Antibody Targets

Chair:

Prof. Douglas E. Joshua
University of Sydney, Australia

The Immune and Antibody Targets Session at the XII International Myeloma Workshop concerned basic biology and research into novel targets in myeloma. Dr. Tai from the Harvard Medical School presented a very extensive review on antibody mediated therapy of myeloma. The mechanisms of antibody mediated cell killing include antibody dependant cellular cytotoxicity, complement dependant cytotoxicity and apoptosis and growth arrest initiated by intracellular signalling pathways. There are a number of obstacles to effective antibody therapy including the immunogenicity of xenogenic antibodies, the shedding of the antigen in circulation, the heterogeneity of antigens on plasma cells and the limited number of effector cells at the tumour site.

In addition myeloma is also associated with host immunosuppression. There are a number of surface antigens expressed in myeloma which interfere with complement dependant cytotoxicity and thus may allow tumour escape.

Despite the fact that the anti CD20 monoclonal antibody Rituximab is widely used for the treatment of B-cell malignancies no antibody therapy is approved for use in myeloma and only minimal activity of Rituximab is seen in this disease. A number of potential new antibodies however are in clinical development. These antibodies are directed against myeloma cell surface antigens including CD40, HM-124, IGF-1R, CD56, CS1, CD138, and beta-2 microglobulin. There are also antibodies developed against growth factors such as IL6, DKK1, VEGF. Antibodies against CD40, CD56 and the CS1 antibody Eltuzomab trigger ADCC and inhibit myeloma cell growth both in vitro and in vivo models. A phase 1 multicentre dose escalation study is now open in multiple myeloma. The immunomodulatory drugs including Lenalidomide augment the effect of antibodies. It is of

interest that antibodies directed against DKK1 reverse the inhibitory effect of myeloma cells on osteoblastogenesis.

Future directions of antibody therapy include the engineering of antibody structures to facilitate selective interaction with host immune cells and a better understanding of the immune effects which prevent myeloma patients from mounting a strong response against the tumour.

Yang et al from the MD Anderson Cancer Center presented data on the development of anti-beta 2 microglobulin antibodies which cause apoptosis of myeloma cells in *in-vitro* and in *in-vivo* models. Such antibodies are currently under investigation in humans and are potentially of great value because *beta-2* microglobulin is found on the surface of all myeloma cells in high quantities but is present at much lower amount in normal cells providing for tissue specificity.

Amiot et al from France demonstrated that IL-21 which plays an important role in plasma cell differentiation is a growth factor for myeloma cells. The majority of human myeloma cell lines and primary myeloma cells express the IL-21 and IL-21 receptor. The investigators demonstrated that exposure to IL-21 induced clonogenicity through an autocrine system via IGF-R1. These results support the theory that therapy against IGF could be beneficial in myeloma.

Trudell et al presented important data targeting C-myc expressing myeloma by the addition of cyclin D inhibitor. It is known that cyclin D is dysregulated in almost all myeloma tumours and cyclin D facilitates the activation and transition to S-phase and multiplication. Myc is variously expressed in myeloma but in cells that express

Session 4: Tumor Microenvironment in Multiple Myeloma

Chair:

Irene M. Ghobrial, MD
Dana-Farber Cancer Institute, Boston, MA

Introduction

This is a review of the data presented in the bone marrow microenvironment session at the International Myeloma Workshop in Washington DC in February 2009. The session included presentations from Drs. Dharminder Chauhan, David Roodman, Irene Ghobrial, Angelo Vacca, Karen Vanderkerken and Evangelos Terpos.

Functional Interaction of Plasmacytoid Dendritic Cells with Multiple Myeloma Cells: A Therapeutic Target

The first presentation by Dr. Dharminder Chauhan from Dana-Farber Cancer Institute was on the role of plasmacytoid dendritic cells in Multiple Myeloma (MM). Recent reports demonstrate infiltration of dendritic cells (DCs) at tumor sites, but with unclear significance. Dr. Chauhan and his colleagues examined the pathophysiologic role of plasmacytoid DCs (pDCs) in MM. MM remains incurable despite novel therapies, suggesting the need for further identification of factors mediating tumorigenesis and drug resistance. The study shows increased numbers and more frequent localization of pDCs in MM patients' BM than normal BM. Using both *in vitro* and *in vivo* MM xenograft models, they show that plasmacytoid dendritic cells (pDCs) in the bone marrow (BM) microenvironment both mediate immune deficiency characteristic of MM and promote MM cell growth, survival, and drug resistance. Microarray, cell signaling, cytokine profile, and immunohistochemical analysis delineate the mechanisms mediating these sequelae. Although pDCs are resistant to novel therapies, targeting Toll-like receptors with CpG oligodeoxynucleotides both restored pDC immune function and abrogated pDC-induced MM cell growth. These findings identify an integral role of pDCs in MM pathogenesis and provide the basis for targeting pDC-MM interactions as therapeutic strategy to improve patient outcome. This study therefore

validates targeting pDC-MM interactions as a therapeutic strategy to overcome drug resistance in MM.

p62: A Potential Target for Blocking Microenvironmental Support of Myeloma

Dr. David Roodman from the University of Pittsburgh presented a study on the role of p62 in the bone marrow microenvironment in MM. Adhesive interaction between MM cells and stromal cells increases production of cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, and RANK ligand (RANKL) by the stromal cells, which induces MM cell growth and osteoclast (OCL) formation. Dr. Roodman and colleagues determined whether targeting p62 could affect multiple signaling pathways in MM stromal cells, p62 forms multiprotein complexes, which result in activation of extracellular signal-regulated kinase, p38, and NF- κ B. They determined whether signaling pathways are activated in primary marrow stromal cells from MM patients, their respective roles on MM cell growth and osteoclast formation, and the effects of knockdown or loss of p62 on tumor growth and OCL formation. When primary marrow stromal cells from patients with MM were isolated and cultured for 3 weeks in Dexter-marrow cultures, the stromal cells produced increased levels of IL-6 and VCAM-1 and demonstrated an increased capacity to support the growth of both IL-6-independent and IL-6-dependent human MM cell lines, compared with primary normal marrow stromal cells. These differences appear to be intrinsic to the MM-derived marrow stromal cells. These results indicate that an intrinsic change occurs in the marrow microenvironment of patients with MM that persists even after culture for more than 3 weeks. The basis for this change in the intrinsic properties of the stromal cells is currently unknown, but it may reflect epigenetic changes that occur with chronic exposure of stromal cells to MM cells or cytokines that are upregulated in the mar-

Session 2: Myeloma Signalling Pathways

Chair:

Faith Davies, MD

The Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK

The overwhelming theme of this session was how an increased understanding of the signalling pathways or processes involved in myeloma cell growth, survival and death will lead to the development of newer more effective therapies for patients.

Dr. Hideshima started the session by reminding everyone of the complexity of the situation. Importantly that a number of pathways within the myeloma cell are known to be important for survival, protection against cell death (apoptosis), and cell division (cell cycle), and that there is a degree of cross-over in these pathways. In addition the myeloma cell does not exist in isolation and its interaction and adhesion to the bone marrow stroma (BMS) is important as this releases cytokines (growth factors) critical for myeloma survival.

Recently Dr. Hideshima has been exploring the use of two types of therapeutic compounds within the laboratory – histone deacetylase inhibitors (HDACi) and AKT inhibitors (AKTi).

Histones play an important role in controlling which genes are switched on and active in a cell. When histones are acetylated, the DNA encoding a gene is open and the gene can be expressed and a functional protein made. In contrast when the histones in a gene are deacetylated, the gene is switched off and no protein can be made. In a cancer cell a number of important genes have been switched off, resulting in uncontrollable cell growth. HDAC inhibitors therefore stop the deacetylation of histones and force the cancer cell to switch on genes which were previously switched off. This results in cell death.

There are more than 10 different HDACs and Dr. Hideshima's team have identified a number of them that are of particular importance in myeloma. For instance, HDAC6 plays

a key role in disposing of unwanted proteins. By combining an inhibitor of HDAC6 with bortezomib, a proteasome inhibitor, or 17AAG, a heat shock protein inhibitor, his team have been able to show that the major pathways the myeloma cell uses to recycle proteins are crippled and the myeloma cell dies.

A number of other HDACi are in early phase clinical trials, and Dr. Hideshima presented work looking at the mechanism of action of these, demonstrating that in addition to their effects on histones, they also inhibit important cell growth pathways, as well as, inhibiting the myeloma cells interaction with the bone marrow stroma. For example HDACi are able to inhibit the effects of the cytokine IL-6 or the BMS cells on Jak2/STAT3 signalling pathway.

In the second half of his talk Dr. Hideshima described a further important signalling pathway, the PI3Kinase/AKT pathway. Using an AKTi he was able to demonstrate that cell lines and patient cells underwent cell death due to a decrease in AKT activation (phosphorylation). Importantly he also demonstrated that other members of the pathway particularly PI3K are important in myeloma and that drugs targeting these also result in cell death, and therefore exploring these types of compounds in clinical trials are warranted.

In the second talk of the session Dr. Bergsagel moved on to a slightly different area and described how his team was looking at the genetic changes in plasma cells and the potential impact these have on therapeutic response. He initially reminded everyone of the multi-step process that occurs during myeloma development, particularly the changes that occur as a B cell develops into a plasma cell and how plasma cells from patients with MGUS, newly diagnosed myeloma and relapsed myeloma are different. His team have been performing a comprehensive genetic

analysis on a large series of patients to look at these changes in more detail. He described how a number of genetic changes occur early in the disease process, such as the translocation or swapping of material from chromosome 14 to other chromosomes, or the duplication of whole chromosomes (hyperdiploidy). Other changes occurred during the transition from MGUS to myeloma for example Myc rearrangements, whereas further changes occurred later in the disease process such as deletion of p18, mutation or alteration in p53 and NFκB.

In the latter part of his talk Dr. Bergsagel concentrated on the signalling molecule NFκB. Its role as a survival factor for myeloma has been known for many years (via the cytokines IL6, BAFF and APRIL), however the possibility that mutations occur in NF B has only recently been described. Importantly these changes have potential implications for the way patients respond to treatment, as patients with low expression of TRAF3, one of the members of the NF B pathway, respond poorly to dexamethasone but are highly sensitive to bortezomib. In his concluding statements Dr. Bergsagel proposed a model for the development of myeloma based on the importance of NFκB. In this model the bone marrow stroma activates NFκB signalling in the early stages of MGUS and myeloma, whereas in the more advanced stages, the cell has undergone a genetic change leading to activation of NFκB without the need for the external bone marrow stroma signal.

In the third talk of this session Dr. Stewart described a new strategy that his lab have embarked upon to identify possible new drug targets for myeloma therapy. By using a novel technique called RNA interference or RNAi, they have attempted to identify genes that are important for myeloma cell growth and survival. In this technique a small piece of genetic code, RNA, is inserted into myeloma cells. The inserted RNA recognises the RNA of the myeloma cell, binds to it and interferes with ability of the myeloma RNA to work and thus the expression of its gene, so that the gene is “knocked down.” By systematically knocking down a large series of genes one at a time, it is possible to determine whether a particular gene is important in myeloma cell

survival. Until recently it has been very difficult to use this technique in myeloma cells as it has been technically very hard to insert the SiRNA into a cell, however; Dr. Stewart’s team have developed a method to overcome this problem.

Using a number of different representative myeloma cells and a large library of different RNAi (over 15,000), they have performed a high throughput screen to identify RNAis that killed myeloma cells. As with any experiment they included a series of very robust controls to ensure that positive results were truly positive and didn’t just occur by chance.

In the initial series of experiments, they concentrated on a group of proteins called kinases which have been identified in other cancers as important enzymes controlling cancer cell survival. In addition to their key role in cancer growth, the kinase proteins are also relatively easy to design drugs against and kinase inhibitors have been shown to be effective in a number of different cancer types for example in CML (Imatinib) and in kidney cancer (Sunitinib and Sorafenib). Out of the 1278 known kinases; Dr. Stewart’s team identified that approximately 2% may be appropriate for further investigation, as they were present in myeloma cells, and when knocked down resulted in myeloma cell death. Importantly the knock down of these kinases did not result in the death of normal tissue cell, suggesting their action may be specific for myeloma cells – an important factor when investigating a potential new drug target. Dr. Stewart’s ongoing work is aimed at determining whether synthesising a drug against some of these kinases may be appropriate in myeloma (e.g. GRK6). In other instances drugs are already available against some of the kinase targets (e.g. Aurokinase A and B) and so his team are determining whether these maybe appropriate for clinical use.

In order to provide useful laboratory-based data to support rationale combination studies in the clinic, Dr. Stewart’s team also undertook a further series of experiments. Using the same approach as above they performed experiments to try and identify genes which may increase the amount of cell death induced by the proteasome inhibitor,

bortezomib. In these experiments the RNAi was used in the presence of increasing dose of bortezomib and the amount of cell kill measured. A number of potentiating genes were identified:- for example aurokinase A and CDK5 dramatically increased the amount of cell kill (synergistic) with bortezomib, suggesting taking small molecules which inhibits these genes to the clinic in combination with bortezomib may be an effective clinical strategy.

In the final talk of this session Dr. Shaughnessy presented data on the role of Wnt/ β -Catenin signalling in myeloma. His initial interest in this pathway developed when he identified one of the pathways key molecules, DKK1, to be highly expressed in myeloma patients with bone disease. His team demonstrate that DKK1 plays a central role in bone turnover by activating osteoclasts (cells which destroy bone) resulting in bone pain, fractures and osteolytic bone lesions.

The story however; gets a little more complicated as DKK1 is thought to be a negative regulator or have an inhibitory effect on Wnt signalling. Previous reports in other cancers have shown that Wnt is able to drive cancer progression, and so at first glance the two findings appear contradictory. Dr. Shaughnessy however clarified the situation and presented data concerning the role of Wnt and DKK1 in myeloma suggesting again that, unlike other cancers, the interplay between the effects on the myeloma cell, and the bone marrow stroma cells together are extremely important. This was consolidated in the latter parts of his talk where he presented laboratory data concerning the role of an antibody against DKK1 as a potential therapy for myeloma.

The speakers in the opening session of the Workshop performed a tremendous job and set an incredibly high standard for the rest of the Workshop. They highlighted how the increased knowledge of myeloma signalling and genetic pathways is not just interesting scientifically, but is directly relevant to patient care, as new therapies are being developed based on sound biological rationales. The audience left with an increased knowledge of the intricate and

complicated signalling pathways involved in myeloma cell growth along with real hope and excitement for the future.

than HUVECs. MMECs produced 4 to 40 times more FGF-2 and VEGF, and 3 to 5 times more MMP-2 and MMP-9 than HUVECs. On a cDNA microarray, MMECs displayed up-regulation of angiogenic genes, including VEGF and FGF isoforms, HGF/SF, Tie2/Tek, TGF- β , Gro- α chemokine, fibronectin-1, HIF-1 α , ETS-1, ID3, and osteopontin, compared to HUVECs. MMECs expressed higher amounts of the CXC chemokines IL-8, I-TAC, SDF-1 α , and MCP-1 than HUVECs. Vasculogenesis, i.e., formation of new vessels from hematopoietic stem and precursor cells (HSPCs), contributes to neovessel formation in MM. HSPCs from MM patients at diagnosis were seeded on fibronectin and exposed to VEGF, bFGF, and insulin-like growth factor (IGF): cells were able to differentiate into cells with an MMEC phenotype. Plasma cells and MMECs share symmetric receptor tyrosine kinases (RTKs), such as VEGFR and PDGFRb. The authors observed that a constitutive and autocrine phospho-tyrosine activation of PDGFRb was restricted to plasma cells of MM patients, correlating with higher levels of PDGF-BB compared to plasma cells of MGUS patients or peripheral blood mononuclear cells (PBMCs) isolated from controls. A molecular dissection of VEGF/PDGF-downstream signaling mediators in MM plasma cells and MMECs revealed that c-Src was preferentially activated in response to VEGF in both cells and sustained by a VEGF/VEGFR autocrine signaling in cell cultures. Moreover, the inhibitory effect elicited by silenced c-Src was partially rescued by exposure of siRNA-transfected MMECs to PDGF-BB, which can therefore represent an important paracrine mitogen *in vivo*. Preliminary studies in global protein expression (7) of MMECs and MGECs vs. HUVECs has shown at least 20 proteins differentially expressed in MMECs. Because angiogenesis and lymphangiogenesis actively contribute to cancer progression, future studies to establish the role of these angiogenic proteins in disease may suggest potential new targets for tissue-specific therapies.

Epigenetic regulation of multiple myeloma within its bone marrow microenvironment

Next, Dr. Karin Vanderkerken from Vrije Universiteit Brussel (VUB), Brussels, Belgium presented data on epigenetic reg-

ulation of the microenvironment in MM. As several studies underlined the importance of epigenetic regulation in the context of MM in relation to its local microenvironment, Dr. Vanderkerken and her colleagues assessed the effect of a HDACi (the hydroxamate based histone deacetylase inhibitor JNJ-26481585) on the development of MM disease *in vivo*, either when used as solo treatment or in combination with the proteasome inhibitor bortezomib. They focused on tumor development in the bone marrow, development of angiogenesis and induction of osteolytic bone disease. These studies were performed using the 5TMM models, spontaneously developed syngeneic models that mimic the MM disease closely. The 5T33MM model develops after 4 weeks while the 5T2MM model develops after 12 weeks. The first model was used in a prophylactic setting while the latter one was used in a therapeutic setting, starting treatment from the onset of the MM disease. Both types of treatment with the HDACi resulted in a dramatic decrease of tumor burden in the bone marrow, decrease in bone marrow microvessel density, and decrease of bone disease in the 5T2MM. When used as a combination therapy with bortezomib, they observed a synergistic reduction in number of osteoclasts, trabecular bone volume and an increase in number of osteoblasts, suggesting that low dose of this HDACi can improve the anabolic bone properties of bortezomib (Deleu S, submitted). They furthermore investigated the epigenetic regulation of the tetraspanin CD9. CD9 was found to be expressed in patients with non-active MM disease while patients with active disease showed no expression. This was confirmed in the murine 5T2 and 5T33MM models, showing a decreased expression during disease development. Treatment of the 5TMM cells with the HDACi LBH589 resulted in an increased CD9 expression, while treatment with 5-Aza-2'-Deoxycytidine barely showed an increase. Combination of both inhibitors resulted in a strong synergistic reactivation of CD9 expression. This study indicated that histone modifications and, to a lesser extent, CpG methylation are key epigenetic events involved in CD9 downregulation. In summary, epigenetic phenomena represent an interesting target for treatment in MM and MM stem cells and warrants further studies on targeted

genes and biological sequelae. Additional studies on new and less known epigenetic mechanisms (e.g. acetylation of proteins, miRNA) could furthermore provide new and improved insights in the development and progression of MM.

Novel Anti-Myeloma Agents and Bone Metabolism: Implications in the Management of Myeloma Bone Disease

Finally, Dr. Evangelo Terpos from the University of Athens, Athens, Greece presented his data on novel anti-myeloma agents on bone metabolism. MM is characterized by the presence of osteolytic bone lesions that result in debilitating skeletal complications, such as pathologic fractures, severe bone pain, and hypercalcemia. Over the last decade, novel agents have been used in the management of MM. Immunomodulatory agents (IMiDs), such as thalidomide, lenalidomide, and pomalidomide, and proteasome inhibitors, such as bortezomib, have shown significant anti-myeloma activity in both newly diagnosed and relapsed/refractory MM patients. In addition to their potent efficacy against myeloma cells, these agents modify the interactions between malignant plasma cells and the bone marrow microenvironment, and they alter abnormal bone metabolism in MM. Thalidomide and pomalidomide almost completely abrogated receptor activator of nuclear factor (NF)- κ B ligand (RANKL)-induced osteoclast formation in vitro. Lenalidomide also inhibited osteoclast formation through similar mechanisms, as was the case with the downregulation of PU.1 and cathepsin K gene expression and the reduction of RANKL secretion by bone marrow stromal cells derived from MM patients. In relapsed/refractory MM patients, an intermediate dose of thalidomide (200 mg per day) in combination with dexamethasone produced a significant reduction of serum markers of bone resorption (ie, C-telopeptide of collagen type-I [CTX] and tartrate-resistant acid phosphatase isoform-5b [TRACP-5b]) and also of the sRANKL/osteoprotegerin (OPG) ratio. Bortezomib is a first-in-class proteasome inhibitor with known activity against myeloma. Bortezomib affects osteoclast differentiation and functions in a dose-dependent manner, thus

reducing subsequent bone resorption, while at the same time inducing osteoblast differentiation and increasing the size of osteoblastic colony-forming units. Bortezomib seems to act in both early and late phases of osteoclast differentiation through the inhibition of p38 mitogen-activated protein kinase (MAPK) pathways (early phase), activator protein-1, and NF- κ B signaling (late phase). In relapsed/refractory MM patients, bortezomib was found to stimulate bone formation, producing significant increases of bALP and OC regardless of response to therapy. Furthermore, bortezomib administration in relapsed/refractory patients resulted in a significant reduction of dickkopf-1 (Dkk-1), which is a Wnt-type antagonist that inhibits osteoblast differentiation and function. However, when bortezomib is combined with other anti-myeloma agents, such as melphalan, dexamethasone, and intermittent thalidomide (VMDT regimen), the reduction of Dkk-1, osteoclast stimulators (sRANKL and macrophage inflammatory protein-1), and markers of bone resorption (CTX) was not accompanied by an increase in markers of bone formation (bALP and OC). Recent studies indicate that several other novel agents with anti-myeloma activity also have an impact on bone metabolism in MM. Most of these agents inhibit osteoclast formation. SDX-308 (a novel and potent etodolac structural analogue), AZD6244 (an extracellular signal-regulated kinase1/2-MAPK inhibitor), and KD5170 (an HDAC inhibitor) can inhibit osteoclast formation. Other proteasome inhibitors, such as MG-132 and MG-262, reduce both osteoclast differentiation and activity of mature osteoclasts in vitro, and others, such as epoxomicin, PS-1, and lactacystin, induce osteoblast function and bone formation. In conclusion, novel anti-myeloma agents, such as IMiDs, bortezomib, and more recent ones, alter abnormal bone metabolism in myeloma patients.

Session 5: Phase III Studies – IFM, U.S., Europe, Others

Session Chairs:

Dr. Brian G.M. Durie

Cedars-Sinai Cancer Center, Los Angeles, USA

In this session at the XIIth International Myeloma Workshop, chaired by Dr. Durie and Dr. Heinz Ludwig; results from completed phase III studies were presented, and details of on-going and planned phase III studies were described.

Dr. Philippe Moreau reviewed “Phase III studies that have been completed by the IFM group in multiple myeloma.”

Dr. Moreau presented results which have been previously published or are in press, including IFM 95-01, IFM 99-06, and IFM 01/01, showed superior results with MPT versus MP in patients older than age 65 years. Trial results for younger patients that have been published include IFM 90, IFM 94, IFM 95-02, IFM 99-02, IFM 99-03, IFM 99-04, which showed that for younger patients, ASCT is better than conventional chemotherapy, Mel 200 is the best conditioning regimen, double (tandem) transplants are better than single transplants if the response is less than VGPR, thalidomide consolidation post-ASCT is effective, and ASCT plus mini-allogeneic transplantation is not better than double ASCT.

Discussion. The IFM has made a major contribution to the global myeloma community by conducting a series of trials which provide answers to some of the most pressing clinical questions especially concerning the role of high dose melphalan therapy with stem cell rescue. Further ongoing trials will provide additional important insights.

Dr. Moreau emphasized that regimens with an MP base are especially useful, effective and well tolerated in patients over age 65 years. Dr. Palumbo suggested that low dose dexamethasone either as part of Revlimid/low dose dexamethasone (Rd) or for example the “CTD” regimen can also be valuable (Cytoxan/thalidomide/dexamethasone: MRC trial protocol [see below]). There is an ongoing IFM trial which includes the comparison of Rd vs. MPT.

Dr. Michel Attal presented “Phase III studies that are on-going and future planned studies by the IFM group in multiple myeloma.”

Current or upcoming trials testing new drugs in a high-dose strategy are investigating the following:

- Should a third drug be added to bortezomib plus dexamethasone for induction therapy?
- Lenalidomide as consolidation; low-dose lenalidomide as maintenance vs. placebo
- VRD, stem cell collection, then VRD, then lenalidomide for 1 year vs. Mel 200 ASCT then VRD consolidation, then lenalidomide for 1 year. The group not receiving ASCT can receive ASCT at relapse (IFM2009/DFCI). This is a study at the planning stage.

Dr. Attal indicated that randomized trials are needed to confirm the following:

- Does addition of bortezomib to the high-dose melphalan conditioning regimen for young, newly diagnosed patients increase the response rate?
- What is the role of consolidation with VRD or VTD, induction with VTD or VRD prior to ASCT
- What level of benefit occurs with new drug regimens without ASCT, including MPT, MPR, Rd, TD, VRD
- Are alkylating agents still needed in the era of new drugs?

Discussion. IFM is currently not suggesting the use of allo-SCT because patients with low-risk disease on novel therapy have a median survival of 8 to 9 years. Dr. Barlogie said that this means that 50% of patients are dead in 8 years so he would like to see the probability of 80% survival in 4 years. It was suggested to wait for the results

and conclusions of the IFM2009/DFCI trial in which the novel combinations of VRD vs. Rd are compared with and without ASCT.

Dr. Sagar Lonial presented “Phase III studies that have been completed, ongoing, and planned by the U.S. cooperative groups in multiple myeloma.”

There are four U.S. cooperative groups: ECOG, SWOG, CALGB, and BMT CTN, a relatively new group. Dr. Lonial pointed out that the ECOG structure for clinical trial development was to have a trial for each different phase of disease or treatment, including asymptomatic myeloma, induction therapy, ASCT, non-transplant candidates, and maintenance therapy, so that all practitioners will have a trial to offer all patients at any stage of disease. He noted that two trials each for Waldenström macroglobulinemia and AL have also been proposed.

Completed trials include the following:

- ECOG E4A03 of lenalidomide with either high- (RD) or low-dose (Rd) dexamethasone. Survival curves are now coming together, with a 75% 3-year OS estimate. OS is estimated at 92% at 3 years for patients receiving 4 cycles of induction therapy then high- dose ASCT. For patients who had no ASCT but were treated beyond 4 cycles, 3-year estimated OS was 79%.
- SWOG 0232 compared lenalidomide plus dexamethasone vs. dexamethasone as induction, then maintenance. The trial was stopped early because of the ECOG E4A03 results. Improved responses were seen for lenalidomide plus dexamethasone, and cross-over improved responses. OS was identical for the two arms but the lenalidomide plus dexamethasone arm had a better EFS. Patients with high-risk cytogenetics didn't do as well as those with low-risk disease.

Ongoing or planned trials include the following:

- BMT-CTN 0102: Mel 200 ASCT then randomization to allo-SCT or a second Mel ASCT. The ASCT group will then have observation or thalidomide/dexamethasone

maintenance. Safety and efficacy analyses are planned for 2010.

- CALBG 100104 compares lenalidomide at 10 mg vs. placebo long-term maintenance after one Mel 200 cycle and ASCT.
- ECOG E1A06: MPT vs. MPR phase III trial in newly diagnosed patients who are not transplant candidates.
- SWOG S0777: phase III trial in newly diagnosed patients who are transplant candidates, comparing Rd vs. VRd. Patients with CR, PR, or SD will continue therapy; patients with progressive disease could have ASCT.
- ECOG E1A05: phase III trial of Vd vs. VRd, has been revised to include consolidation therapy.
- BMT CTN: proposed to give all patients Mel 200, then randomize to no consolidation, VRD for 4 cycles, or second Mel and transplantation; all arms receive lenalidomide maintenance, so the trial is asking “what is the role of consolidation?” Approved and expected to enroll summer, 2009.
- ECOG E3A06 and SWOG collaborative phase III trial in patients with high-risk smoldering myeloma: lenalidomide vs. observation. If the disease responds, patients will continue on therapy; if the disease progresses, patients will be removed from the study. Imaging studies will be incorporated.
- ECOG E1A08: phase III trial of post-transplantation maintenance with bortezomib or observation.
- ECOG E2A08: phase II trial of bortezomib, dexamethasone, and pegylated doxorubicin in patients with high-risk relapsed myeloma.
- Carfilzomib plus lenalidomide with low-dose dexamethasone (CRd vs. Rd). The expectation is that this will be a registration trial for Carfilzomib.

- GIMEMA: VTD vs. TD, patients are randomly assigned to induction, then Mel 200 twice. CR increases after ASCT. VTD is associated with a better response at induction and after ASCT, including for patients with poor prognosis. PFS is superior with VTD, but OS is similar for both arms.

Planned trials include the following:

GIMEMA Myeloma Working Party: Best chemotherapy vs. best transplant regimen. Patients less than age 65 years will receive 4 cycles RD, then cyclophosphamide, and have their PBSC harvested. Then they will be randomly assigned to A) 6 cycles MPR, then either lenalidomide or not, and 2 Mel 200 cycles and transplant; or to B) 2 Mel 200 cycles, then lenalidomide or not, and conventional chemotherapy.

Dr. Boccadoro suggested that thalidomide may not be the partner of choice for bortezomib in elderly patients, and other combinations, such as lenalidomide, should be and are being tested.

Discussion. The once-weekly bortezomib dosing was called a step forward, especially for patients with pre-existing peripheral neuropathy. Dr. Boccadoro responded that this was exactly the point of reducing the dose to keep patients on treatment so the discontinuation rate is lower. He said that one of most important factors concerning the new drugs is for patients to stay on treatment. He also noted that a randomized trial would be needed to test VTD before vs. after ASCT, and there are no ongoing trials testing that right now.

Dr. Pieter Sonneveld presented “Phase III studies that have been completed, ongoing, and planned by various Northern European groups in multiple myeloma.”

Dr. Sonneveld pointed out that there are 6 different cooperative groups in the 11 countries in the Northern European area. Trials investigating tandem transplantation, including tandem ASCT vs. ASCT plus allo-SCT, and single vs. double ASCT showed no differences between treatment arms. Dr. Sonneveld concluded from several studies that combination therapy with at least one novel agent was superior to standard conventional chemotherapy, e.g. VAD; there was no effect of a second ASCT; thalidomide

prolongs EFS but not OS. Post-induction response rates are increased further with novel agents, but follow-up is needed for survival data. Ongoing or planned studies will answer questions about new induction regimens, a second allo-SCT vs. second ASCT, maintenance therapy with IMiDs, MPT vs. MPR in newly diagnosed elderly patients who will receive either thalidomide or lenalidomide as maintenance therapy, the efficacy of dose-reduced bortezomib therapy, the effect of novel agents on myeloma with poor-risk cytogenetic abnormalities, and addition of plasma exchange to chemotherapy to increase the rate of renal recovery in newly diagnosed patients with acute renal failure.

Discussion. Differences in trial design and treatment sequencing may account for discrepant results concerning whether thalidomide maintenance improves survival in myeloma with poor risk cytogenetics. Dr. Sonneveld noted that in one study, patients were treated with thalidomide for 2.5 years, but the survival benefit didn't manifest until 5 years later, so whatever was set into effect was not seen until later. He said he will do a meta-analysis of different trials. Dr. Barlogie said he would like to see a long-term follow-up of 7 to 8 or more years later. In response to a question about whether there were sufficient data for weekly bortezomib to make treatment decisions, Dr. Sonneveld responded that the outcome for response, survival, and toxicity were from a phase II trial, so a phase III trial was needed. Dr. Reece said she will have comparative data for 4 cycles before ASCT in a collaborative study with the Mayo Clinic, but this is not a randomized trial. Peripheral neuropathy is lower, but there are no efficacy results yet.

Final Comment. Clearly, a very comprehensive menu of trials was presented and discussed. This hopefully served as an important update for those planning new trials as well as clinicians faced with decisions about the best treatment for individual myeloma patients.

Session 6: Oral Presentations – Clinical – Phase II/III Studies

Session Chair:

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A study of combination of bortezomib, lenalidomide and dexamethasone in 66 newly diagnosed patients of myeloma conducted by Dr. Paul Richardson and others aimed to define maximum tolerated dose of this combination and to assess response rates, CR and PR after 4 - 8 cycles. The protocol was as follows: Bortezomib on days 1, 4, 8, 11, dexamethasone 40 mg/ day on days 1, 2, 4, 5, 8, 9, 11, 12 and lenalidomide continuously from days 1-14. Successive cohorts of 3-6 patients were taken; median age was 58 years and 36 of 66 being males. MPD was reached at dose levels at 4 months with lenalidomide 25 mg, Bortezomib 1.3 mg/m² and dexamethasone 20 mg. Median treatment duration was 9 cycles, and 70 % patients completed 8 cycles with 23 proceeding to ASCT. Toxicities have been manageable, 3-15 % had grade 3-4 haematological toxicity, and DVT was seen in 3 patients. There was no treatment-related mortality. Hyperglycaemia was seen in 6 patients. Best responses were 20 CR (31%), 6 nCR (9%) and 39 PR (60%). Duration of best response was 2.8 months. After a median follow up of 8 months median TTP, PFS and OS have not been reached. Stem cell collection proceeded successfully in 21 of 23 patients. This combination produced high quality durable responses and is well tolerated, with an ORR of 100 %, across all cohorts. Additional analyses are underway for time to events, cytogenetics, proteomics and gene expression profiling and mobilisation strategies.

Another multicenter randomized phase I/II study – “Evolution study” by Dr. Shaji Kumar et al used a combination of Bortezomib, dexamethasone, cyclophosphamide, lenalidomide (VDCR) as frontline therapy in multiple myeloma. The aim of the study was to determine the maximum tolerated dose (MTD) of Cy in combination with VDR. The protocol used was: Bortezomib 1.3 mg/m² on days 1, 4, 8 and 11, dexamethasone 40mg weekly once, lenalidomide 15mg once a day for 14 days and cyclophosphamide on days 1 and 8 on a 21 day cycle for 8 cycles.

This was followed by bortezomib maintenance or ASCT for eligible patients after 4 cycles. Cyclophosphamide dose was increased in a 3+3 dose escalation design, with 3–6 patients per dose level. Total of 25 patients, with median age 61 years were enrolled. There were 13 males and another 13 with ISS stage II or III. On assessment MTD was not reached for cyclophosphamide with only one DLT each at dose level 4 (400mg/m²) and 5 (500mg/m²). Median treatment duration was 6 cycles and overall RR was 96% with 14/25 patients achieving sCR/CR. Most hematological toxicities were grade ½, and most common non-hematological toxicity was peripheral neuropathy (68%). Maximum serum M-protein reduction occurred after 3 cycles. 12/25 underwent stem cell mobilization after 4 cycles with median CD34+ yield of 5.85x10⁶. The study protocol produced high response rates with feasibility of ASCT after 4 cycles. The recommended Phase II dose of Cy was 500 mg/m², the highest dose level tested. The protocol would now be tested in a randomized Phase II setting to determine the combined rate of complete response (CR) plus VGPR for VDC, VDR and VDCR.

An important phase III randomized trial HOVON-65/GMMG-HD4 was conducted by Dr. Pieter Sonneveld and others comparing bortezomib, adriamycin, dexamethasone (PAD) vs conventional VAD as induction treatment prior to High Dose Melphalan (HDM) in patients of multiple myeloma. The study objective was to assess the efficacy (CR+VGPR) of Bortezomib as induction treatment, prior to high-dose therapy, and as maintenance treatment compared to Thalidomide. The protocol consisted of 3 cycles of PAD or VAD followed by stem cell collection using CAD, followed by HDM (200mg/m²) and then bortezomib as maintenance in PAD arm vs. thalidomide maintenance in VAD arm. PAD consisted of: bortezomib 1.3mg/m² on days 1, 4, 8, 11, doxorubicin 9mg/m² IV Push days 1-4, dexamethasone 40mg days 1-4, 9-12, 17-20. Primary end point

was progression-free survival and secondary end point was response rates, overall survival and toxicity analysis. 300 of 825 patients were assessable in this interim analysis, 150 in each arm. Median age was 56.5 years and M:F ratio was 3:2. Patients characteristics were well balanced between the two arms. Overall RR (CR+PR) after 3 cycles were significantly better in PAD (83%) vs. VAD (59%) arm. Again after HDM higher number of patients in PAD arm vs. VAD arm achieved CR/nCR 23% & 9%, respectively. Superiority of PAD was maintained during maintenance phase with 41% of patients achieving CR/nCR in PAD arm vs. 20% in VAD arm. ORR remained significantly better with PAD at all phases of treatment. There was no difference in the stem cell collection and median CD34+ count between the two arms. 88 % of VAD and 87 % of PAD patients received HDM/ASCT. There was no difference in hematological toxicity between the two arms. Only peripheral neuropathy was significantly higher in the PAD arm, but this was manageable with dose modifications. More than 80% patients in PAD arm could complete 3 induction cycles without dose reduction. Patients with high risk cytogenetics such as 13q and t(4;14) showed comparable responses to those with good or intermediate risk cytogenetics with PAD, but fared much worse with VAD. PAD came out as a safe and effective regimen with 42 % of patients achieving at least VGPR/CR after 3 induction cycles and almost 80 % achieving at least VGPR/CR followed by HDM+ASCT. In addition to its feasibility as a pre-transplant induction regimen, PAD showed equal efficacy in high risk cytogenetics.

Dr. Antonio Palumbo and others from the GIMEMA Italian myeloma group conducted a prospective, randomized, Phase III study of Bortezomib, Melphalan, Prednisone and Thalidomide (VMPT) vs. Bortezomib, Melphalan and Prednisone (VMP) in elderly newly diagnosed myeloma patients. The authors hypothesized that VMPT might be superior to VMP as a first line therapy based on the encouraging results of VMPT with ORR in the relapsed patient population reaching that of VMP in the first line setting. The authors also studied the safety of this combination with a weekly infusion of bortezomib. 393 patients (older than 65 years) were randomized to VMP with Bortezomib

1.3 mg/m² IV: days 1,8,15,22; Melphalan 9 mg/m² and prednisone 60 mg/m² days 1-4; Or VMPT which included additional Thalidomide 50mg OD as continuous therapy. This schedule was repeated every 5 weeks for 9 cycles. Patients in the VMPT arm received additional maintenance therapy with bortezomib 1.3 mg/m² on days 1 and 15, and thalidomide 50mg/ day continuously until relapse. Median age was 71-72 years. After a median number of 5 cycles response rates in terms of CR+VGPR were significantly superior with VMPT 55% vs. 45% for VMP (p<0.001). At a median follow-up of 14.5 months TNT and PFS were not different between the two arms. OS at 36 months was 88% for VMPT and 87% for VMP (p=0.75). Toxicity analyses showed VMPT to have more thrombocytopenia, neutropenia, sensory neuropathy, infections, fatigue and thrombosis. Weekly bortezomib was tolerated equally well by all age groups including those >75 years and in comparison to biweekly schedule used in other trials, weekly schedule of bortezomib seemed to have better tolerance and lesser rate of discontinuation in the elderly patients, with perhaps comparable efficacy. The authors concluded that although VMPT improved response rates of VMP, while benefit in PFS and OS would need longer follow-up; and weekly infusion of bortezomib decreases peripheral neuropathy in elderly patients.

The VISTA trial group which compared VMP to MP in non-transplant patients studied the effect of prolongation of therapy on quality of response and of CR on outcome. 668 patients were randomized to receive 9 cycles of either MP or VMP every 6 weeks. The protocol used was: bortezomib 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, 32 for cycle 1-4; and days 1, 8, 22, 29 for cycle 5-9. Melphalan 9 mg/m², days 1-4 for cycles 1-9, and prednisone 60 mg/m² on days 1-4 for cycles 1-9. Primary end point was time to tumor progression (TTP). Additional efficacy end points were - response rate, CR rate, time to response, duration of response (DOR) and time to next therapy (TNT). Median follow-up time was 25.9 months for survival analysis. ORR (IMWG criteria) was 74% and 39% for VMP and MP respectively with 33% CR in VMP group against only 4% in MP. Importantly, 28% (29/102) of CR occurred after cycles 1-4.

Median time to best response and median DOR was 2.3 & 19.9 months respectively for VMP vs. 4.9 & 13.1 months respectively for MP. Long term outcomes were significantly better for VMP vs. MP; TTP, TNT and TFI were 24.0, 28.1, 16.6 months respectively for VMP against 16.6, 19.2 and 8.4 months respectively for MP. 3 year OS was 72% for VMP and 59% for MP with HR of 0.64. CR vs. PR was associated with significantly longer TTP, TNT, and TFI (except OS). And CR+PR vs. <PR was associated with significant benefits for all parameters (including OS). Time to achieve CR whether early (during cycles 1–4) or late (during cycles 5–9), had no impact on clinical benefit and time from CR to subsequent therapy. Although follow-up was short, duration of CR appeared similar in patients receiving <9 vs. all 9 cycles of VMP. This analysis of VISTA demonstrates the prognostic significance of CR on long-term outcomes in the non-transplant setting. There is also an indication that clinical benefit of CR with VMP is similar regardless of time to achieve CR; with late CR being prognostically as important as early CR. As 28% of the patients achieved late CR, this supports the continuation of therapy with VMP to maximal response.

Dr. P. Wijeraman and others presented the final analysis of the HOVON 49 study, a phase III randomized trial comparing MPT with MP as induction therapy in multiple myeloma in elderly patients (>65years). The protocol consisted of minimum 8 cycles of 4 weekly schedules consisting of: Melphalan 0.25mg/kg days 1-5; Prednisone 1mg/kg days 1-5 in MP arm; and additional Thalidomide 200mg OD as continuous therapy in MPT arm. After the end of therapy thalidomide in the dose of 50mg/day was continued as maintenance in the MPT arm. Those who had progressive disease after 3 or 8 cycles were taken off protocol. Primary end point was event free survival. Events included induction failure, death, progression or relapse. Secondary end points were: response rate, progression free survival, overall survival, safety, toxicity and quality of life. 344 patients were enrolled of which 333 were analyzable. Median age

was 72-73 years. 64% of the patients had stage 3A (Durie-Salmon) disease. 57% as against 25% patients went off protocol in MP arm vs. MPT arm respectively. Disease progression was the most common cause in MP arm and toxicity was the most common in the MPT arm. ORR (CR+PR) were significantly better with MPT 62% vs. 47%. There were 29% CR+VGPR in MPT arm as against only 9% in MP arm. EFS at 2 years was 3 times higher in MPT arm 36% vs. 12% ($p<0.001$). OS was 36% for MPT and 25% for MP at 4 years ($p=0.16$). Toxicity analyses showed more grade $\frac{3}{4}$ toxicity with MPT then MP; and these included neurological toxicity, thrombosis and infectious complications. WHO performance status, M protein heavy chain, ISS stage and β_2 microglobulin were significant prognostic factors for EFS and OS. This study showed the significant improvement achieved in terms of event free survival and response rates by adding Thalidomide to Melphalan and Prednisone, although thalidomide also added significantly to the toxicity. The relatively high dose of melphalan used in this study had a negative effect upon normal scheduling of the therapy, as only 35% in MP arm and 38% in MPT arm could receive full dose of the scheduled treatment at the start of 3rd cycle. Impact of cytogenetics on response and survival needs to be further studied.

cells is required in place of M protein provided baseline percentages were > 30%. In addition to the above criteria, if present at baseline > 50% reduction in the size of soft tissue plasmacytomas is also required.

Minor response is defined as a > 25% but < 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50-89%, which still exceeds 200 mg/24h. If present at baseline, the size of soft tissue plasmacytomas of 25-49% reduction is also required. There must be no increase in size or number of lytic bone lesions. The development of compression fractures does not exclude response.

Minor response should be reported separately in clinical trials. It should be separate from the overall response rate.

Stable disease (SD) is defined as not meeting criteria for CR, VGPR, PR, or progressive disease.

Progressive disease (PD) is defined as an increase of 25% from lowest response value in any one or more of the following: (1) Serum M-component absolute increase must be > 0.5 g/dL; (2) Urine M-component increase must be > 200 mg/24h; (3) In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels must be > 10 mg/L; (4) Bone marrow plasma cell percentage must be > 10%; (5) Development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas; (6) Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

Reporting of Efficacy Results

All efficacy results for primary endpoints should be reported only on an intent to treat basis. In the case of secondary endpoints, results based on actual treatment received can also be reported. The reporting of results in subsets of patients restricted to those who completed certain durations of therapy should be avoided. All patients who are registered and met eligibility criteria regardless of whether they actually received therapy or not should be in the denominator for all efficacy calculations. Response

assessments should be performed before next therapy is initiated.

In all clinical trials, patients should be followed every one to two months until PD to enable accurate calculation of time to progression (TTP) and progression-free survival (PFS).

All phase III studies should report overall survival (OS), time to progression (TTP), PFS (progression-free survival), duration of response (DOR) and, if possible, time to next treatment (TNT), 5-year OS rate and 10-year OS rate.

Time to progression (TTP) is defined as the duration from start of treatment to disease progression with deaths due to causes other than progression censored. Progression-free survival (PFS) is defined as the duration from start of treatment to disease progression or death (regardless of cause of death). Both TTP and PFS should be reported

Event-free survival (EFS) depends on how “event” is defined. In many studies, the definition of EFS is the same as PFS. EFS may include additional “events” that are considered to be of importance besides death and progression. This includes serious drug toxicity.

Disease-free survival (DFS) is defined as the duration from the start of CR to the time of relapse from CR. DFS applies only to patients in complete response.

Duration of response (DOR) is the duration from the first observation of PR to the time of disease progression with deaths due to causes other than progression censored. Duration of CR and PR should each be reported

Time to next treatment (TNT) is difficult to accurately compare except in double-blind studies. It is important to report TNT in future phase III trials. TNT is defined from time of registration on trial to next treatment or death due to any cause. The next treatment should start when there is either biological relapse or a significant paraprotein relapse. Biological relapse is defined as requiring one or more of the following indicators of increasing disease and/or end organ dysfunction (CRAB) that are felt related to the underlying plasma cell proliferative disorder: (1) Development of

new soft tissue plasmacytomas or bone lesions on skeletal survey, MRI or other imaging. (2) Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (at least 1 cm) increase as measured serially by the sum of the products of the cross diameters of the measurable lesion. (3) Hypercalcemia (>11.5 mg/dL) [2.65 mmol/L]. (4) Decrease in hemoglobin of > 2 g/dL or to less than 10 g/dL; (5) Rise in serum creatinine by 2 mg/dL or more. (6) Hyperviscosity. In some patients, bone pain may be the initial symptom of relapse in the absence of any the above-listed features.

A significant paraprotein relapse is defined as doubling of the M-component in two consecutive measurements separated by < 2 months; or an increase in the absolute levels of serum M protein by > 1 g/dL or urine M-protein > 500 mg/24h or involved FLC level by > 20 mg/dL plus an abnormal FLC ratio (in two consecutive measurements separated by < 2 months).

Consensus Panel 2

Guidelines for Risk Stratification

This was reported by Drs. Nikhil Munshi, Herve Avet Loiseau, and Kenneth Anderson. The decision to treat is based upon a diagnosis of symptomatic multiple myeloma which includes the CRAB criteria (hypercalcemia, renal insufficiency, anemia, or bone disease). Patients with MGUS or SMM should not be treated. Abnormal findings of fluorescence in situ hybridization (FISH) or conventional cytogenetics is not an indication to begin therapy. There are studies that suggest that bortezomib (Velcade) and, to an extent, lenalidomide (Revlimid) may be able to overcome some of the poor risk features.

Risk stratification is applicable to newly diagnosed patients. There may be change in risk factors at relapse as well. If a patient already has a high-risk feature at diagnosis, it is not necessary to check the same feature at relapse.

Both cytogenetics and FISH should be performed at diagnosis. Specific abnormalities considered as poor risk are cytogenetically detected chromosomal 13 or

13q deletion, t(4;14) and del17p and detection by FISH of t(4;14); t(14;16); or del17p. FISH data should be reported on clonal plasma cells and not all cells. Patients with hyperdiploidy have a better prognosis.

Elevated serum β 2M levels and the International Staging System (ISS) [stage II and III] incorporating β 2M and low serum albumin are considered to predict higher risk disease. Elevated lactate dehydrogenase (LDH) or the presence of extramedullary disease, renal failure, high serum free light chain (FLC) and abnormal kappa/lambda ratio, plasmablastic disease and plasma cell leukemia indicate higher risk.

The Durie-Salmon is less predicative of outcome with use of high-dose therapy and novel agents. It is still considered a means to measure tumor mass and supplements the diagnostic criteria for myeloma.

The number of lytic bone lesions is not of prognostic significance although there are single institution studies indicating that achieving MRI-directed CR has prognostic significance. This observation requires further studies and confirmation. None of the imaging studies are currently recommended for inclusion in risk stratification.

Expression/genomic profile data may be helpful. In one report, a 17-gene subset, and in another, a 15-gene subset divided patients into high risk or low risk patient groups. However, the 15- and 17-gene models do not share common genes

Consensus Panel 3

Guidelines for the Standard Investigative Workup

This was reported by Drs. Meletios Dimopoulos, Robert Kyle, and Sundar Jagannath.

Initial investigation of a patient with suspected multiple myeloma should include a history and physical examination, complete blood count and differential, peripheral blood smear, chemistry screen including calcium and creatinine, serum protein electrophoresis, immunofixation and nephelometric quantification of serum

immunoglobulins, serum free light chain assay, routine urinalysis, 24-hour collection for total protein, electrophoresis and immunofixation, bone marrow aspirate and/or biopsy with cytogenetics (metaphase karyotype and FISH), radiological skeletal bone survey, β 2M and lactate dehydrogenase.

The family history should focus on first-degree relatives with a diagnosis of hematologic malignancies, especially plasma cell dyscrasias. Quantitation of serum immunoglobulins by nephelometry should be performed in addition to measurement of the M spike on electrophoresis. When a patient has only monoclonal light chains, immunofixation for IgD and IgE must be performed; if positive, then quantitation of the immunoglobulins follows. The quantification of serum albumin is important since albumin is a key component of the International Staging System. Immunofixation of an aliquot from a 24-hour urine specimen is required and should be performed even if there is no measurable protein or peak on urine electrophoresis.

The serum free light chain (FLC) assay is recommended in all newly-diagnosed patients with myeloma. It is very important in patients with nonsecretory myeloma (i.e. negative serum and urine immunofixation) and in patients who secrete small amounts of monoclonal protein in the serum and/or urine. Serum free light chain measurement may also be useful for prognosis in patients with solitary plasmacytoma of bone, smoldering multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS). A unilateral bone marrow aspirate and/or biopsy should be done. The diagnosis of myeloma is confirmed when more than 10% clonal plasma cells are detected. Both conventional cytogenetics and FISH should be performed at diagnosis.

The skeletal survey remains the standard method for imaging diagnosis. Magnetic resonance imaging is indicated for evaluation of a painful area of the skeleton and for the investigation of patients with a suspicion of cord depression as well as defining the cause of a newly-collapsed vertebrae. The compression fracture may be due to osteoporosis or myelomatous involvement.

The role of PET-CT is yet to be clearly defined in multiple myeloma.

If the degree of anemia is out of proportion to the myeloma, one must search for evidence of iron deficiency, vitamin B12 or folate deficiency. If hypercalcemia is detected and no bone lesions are seen, primary hyperparathyroidism must be excluded. Primary systemic amyloidosis (AL) must be excluded in the event of unexplained weight loss, low voltage of the electrocardiogram, left ventricular hypertrophy, congestive heart failure, unexplained hepatomegaly, symptoms and signs of sensorimotor peripheral neuropathy, autonomic neuropathy or carpal tunnel syndrome. Congo red staining should be done on a subcutaneous fat aspirate and bone marrow biopsy. One or both are positive in 90% of patients with AL amyloidosis. Biopsy of a suspected organ may be necessary for diagnosis in some instances.

Routine testing for hyperviscosity is not recommended because the viscosity value does not correlate well with clinical manifestations of hyperviscosity. Funduscopic examination is more helpful in defining clinically significant hyperviscosity.

At relapse, most of the workup recommended at diagnosis should be repeated. Cytogenetic and/or FISH analysis should be repeated at relapse if they were normal at diagnosis. If a patient already had an identified high risk feature on cytogenetic or FISH analyses, they need not be repeated at relapse.

Session 8: Hematopoietic Stem Cell Transplantation in Multiple Myeloma

Chair:

Dr. Gösta Gahrton

Karolinska Institute for Medicine, Stockholm, Sweden

Abstract

The main treatment modality for patients under 65 to 70 years of age with multiple myeloma is autologous stem cell transplantation. Important progress has been made during recent years, by supporting the procedure with new drugs. Adding a second transplant, either autologous or allogeneic may improve results.

Report of Presentations

Autologous transplantation

Dr Sergio Giralt presented an overview over recent advances in autografting for multiple myeloma with focus on the importance of the number of stem cells in the graft. Many modalities are used for mobilization, but a combination of cyclophosphamide and G-CSF is the most commonly one used in reports to the CIBMTR during 2004 to 2007. However, many centers use only growth factor. Recently, a new substance – plerixafor (AMD3100) – has proven to be very effective in mobilization of stem cells. By using plerixafor a three fold improvement was obtained in the median time to the target dose, more than 6×10^6 CD34-positive cells/kg. This in turn would make it possible to collect more stem cells in a short time, which is of importance for rapid engraftment and less complications. A comparison was made by transplanting $4-6 \times 10^6$ CD34-positive cells, versus $10-15 \times 10^6$ CD34-positive cells/kg, the higher dose resulting in shorter time to engraftment with peripheral blood stem cells, earlier hospital discharge and better survival. The higher relapse rate with autologous transplantation than with syngeneic twin transplantation previously shown by the European Group for Blood and Marrow Transplantation, was taken as an indication for revisiting the use of purging stem cells for transplantation. However, as pointed out in the discussion, other studies indicate that the poorer results with autologous transplantation may not be infusion of myeloma cells with the graft, but rather lack

of a graft-versus-myeloma effect that has been implicated in twin transplants. Two prospective studies comparing purged and unpurged autologous transplants both did not find evidence of a better outcome with purged transplants. Furthermore a gene marking study supported the view that infused cells in non-purged stem cell products do not cause relapse.

Dr Donna Weber discussed the timing of transplants in the era of novel agents. An interesting survey had been made among European and US centers concerning response goals and preferred transplant modality. Concerning response goals, the majority of centres wanted to obtain complete remission, and to the question if autologous transplantation had a role in the era of novel drugs, 100 percent of the 21 centers responded yes. There was less agreement concerning the induction regimens, but most centers seem to prefer a three-drug combination including bortezomib, thalidomide and dexamethasone, or bortezomib, lenalidomide and dexamethasone. To the question what induction regimen was preferred for patients above 65 years of age, there was a larger spread in responses, although the three-drug regimen was still the most important one overall. A great majority answered that transplantation should be used to consolidate first complete remission, but only 29 percent thought that autologous transplantation should consolidate a second remission. Tandem transplants were preferred by the great majority only for patients with partial remission, indicating that those with complete remission were not candidates for a second transplant. However, concerning maintenance treatment following an autologous transplant, there was a great diversity of answers. There was a slight majority among US centres for those that recommended maintenance therapy until very good partial remission and in patients with high-risk features, while European centres tended to be more liberal in doing it in all patients (43%). The summary was that autologous

row microenvironment in response to MM cells. Studies with siRNA knockdown of p62 demonstrated that p62 in marrow stromal cells play an important role in the activation of PKC ζ , NF- κ B, and p38 MAPK, which were necessary for increased expression of VCAM-1 and IL-6, and that it is an important contributor to the capacity of marrow stromal cells from both MM patients and normals to support the growth of MM cells. In summary, these results demonstrate that p62 plays an important role in the increased NF- κ B and p38 MAPK signaling in marrow stromal cells from patients with MM that results in increased VCAM-1, IL-6, TNF- α , and RANKL production. These data indicate that p62 is an attractive therapeutic target for treating MM and MM bone disease.

Migration and homing in Multiple Myeloma

The next presentation was by Irene Ghobrial at Dana-Farber Cancer Institute. MM is characterized by the presence of multiple lytic lesions in most patients indicating continuous spread of MM cells into and out of the bone marrow (BM). Indeed, studies have demonstrated the presence of a small number of circulating plasma cells in over 70% of patients with MM, indicating that progression of MM occurs through the continuous trafficking of malignant cells to new sites of the BM. Therefore, adhesion of MM cells to the bone marrow niches is not a static process, but an active dynamic process that involves migration of the malignant cells to the specific bone marrow niches, adhesion to the microenvironment, and egress or mobilization of some of these cells into the peripheral circulation to home to other new sites in the bone marrow. Migration of cells through the blood to the bone marrow niches, requires active navigation, a process termed homing. Homing is thought to be a coordinated, multistep process, which involves signaling by stromal derived factor-1 (SDF-1), and its chemokine receptor CXCR4, activation of adhesion receptors such as lymphocyte function-associated antigen 1 (LFA-1), very late antigen (VLA-4/5), cytoskeleton rearrangement, and activation of metalloproteases MMP2/9. Other cytokines that also regulate migration of MM cells include VEGF and IGF-1. Studies of chemokine receptors in multiple myeloma

have demonstrated that MM cell lines express high levels of CXCR3, CXCR4, CCR1 and CCR6. The ligands of these receptors are MIP-1 α , MIP-1 β , SDF-1, CXCL12, and RANTES. Of these, the CXCR4/SDF-1 axis plays a critical role in regulating migration and adhesion of MM cells. Studies to identify expression of chemokine receptors in MM have shown large variations in CXCR4 expression ranging from 10 to 100%. SDF-1 induces migration of MM cells *in vitro* and homing into the bone marrow *in vivo*. CXCR4 knockdown led to significant inhibition of migration to SDF-1 in MM cell lines and primary CD138+ cells. Mobilization or egress of cells out of the bone marrow could be enhanced by disrupting the SDF-1/CXCR4 axis. Inhibitors of CXCR4 such as AMD3100 have been shown to induce mobilization of stem cells AMD3100 (Genzyme, MA) is a bicyclam molecule that reversibly blocks the binding of CXCR4 with SDF-1. Dr. Ghobrial and colleagues showed that the CXCR4 inhibitor AMD3100 induced disruption of the interaction of MM cells with the bone marrow reflected by mobilization of MM cells into the circulation *in vivo*, with kinetics that differed from that of hematopoietic stem cells. AMD3100 enhanced sensitivity to bortezomib *in vitro* by disrupting adhesion of MM cells to stromal cells. The combination of AMD3100 and bortezomib induced significant tumor reduction.

Genes and proteins of myeloma endothelial cells to search specific targets of the tumor vasculature

The next presentation was by Dr. Angelo Vacca from the University of Bari, Bari, Italy. Endothelial cells (ECs) of tumors differ from those of normal vessels. Tumor ECs preferentially overexpress the cell-surface molecules integrin α v β 3 and α v β 5, E-selectin, CD105-endoglin, endosialin and VEGF receptors (VEGFRs) all of which stimulate adhesion and migration. In this presentation, Dr. Vacca and his colleagues sought to determine differences between bone marrow ECs of patients with multiple myeloma (MMECs) from those of patients with MGUS (MGECs) and normal ECs (HUVECs). MMECs expressed 5 to 70 times higher levels of several vascular markers, including Tie2/Tek, VEGFR2, FGFR2, CD105-endoglin, and VE-cadherin

Dr. Donna Reece discussed “Phase III studies that have been completed, ongoing, and planned by the Canadian group in multiple myeloma.”

Dr. Reece observed that in Canada there are about 2000 newly diagnosed patients with myeloma per year, with a disease prevalence of about 6000 patients.

Completed trials include the following:

- MY.07: induction in elderly patients treated with melphalan dexamethasone (Mdex) vs. MP. The trial was stopped because of adverse events. Dexamethasone maintenance resulted in better PFS but not OS.
- MY.11: lenalidomide plus melphalan for newly diagnosed elderly patients (no steroids). G-CSF is not consistently obtainable across Canada. The trial was redesigned as a randomized phase II trial with the ability to alter doses because of continued dose-limiting toxicity (DLT). It was difficult to deliver this therapy so there were no good responses, but 60% PR. Hematologic toxicity occurred especially during the first 3 months, and 40% of patients needed G-CSF. Dr. Reece suggested that prednisone may have an impact on both response and the likelihood of neutropenia.
- MY.10: randomized phase III trial of thalidomide/prednisone vs. observation after ASCT. The trial had slow accrual. OS was the primary outcome. They are waiting for events to complete the final analysis.

Dr. Reece mentioned the desire to study which therapy might be better for patients with t(4;14), since it appears that prognosis is poor after failure of alkylating agents plus prednisone. They have seen fewer patients than expected with this cytogenetic abnormality in a recent assessment.

Discussion. In response to a question as to whether dexamethasone or prednisone was preferable, given that dexamethasone was more toxic to elderly patients, Dr. Reece responded that in Canada they have tended to give prednisone on alternate days, although her bias is for weekly dexamethasone. She says both steroids are similar in toxicity and efficacy, both are well tolerated with appropriate dose/scheduling.

Dr. Mario Boccadoro discussed “Phase III studies that have been completed, ongoing, and planned by Italian and Spanish groups in multiple myeloma.”

Completed or ongoing trials include the following:

- PETHEMA/GEM: Phase III trial of VMP vs. VTP in newly diagnosed elderly patients. Similar response rates, median TTR, time to CR, TTP, and OS were seen in both arms. VTP was associated with cardiac toxicity, VMP with more infections. Peripheral neuropathy was relatively uncommon but higher with VTP.
- GEM05 MENOS65: VBMCP/VBAD + bortezomib vs. TM vs. VTD in younger patients going on to ASCT. TM was inferior to the other 2 combinations after induction and before ASCT. Grade 3 neutropenia was associated with bortezomib, more thromboembolic events with TD, and more peripheral neuropathy with VTD. ASCT increased the CR rate 20% regardless of induction therapy.
- Spanish national multicenter randomized open-label trial in high-risk smoldering myeloma in patients with over 10% bone marrow plasma cells and M-protein over 3 g/L. Patients are randomly assigned to lenalidomide plus dexamethasone or observation. The first safety analysis shows no significant toxicity.
- GIMEMA: VMPT followed by bortezomib plus thalidomide maintenance vs. VMP followed by maintenance; amended to weekly bortezomib to determine if that allows improvement in neurotoxicity. This study includes elderly patients. So far VMPT is associated with a higher response rate of 39 % CR (VMPT) vs. 21% (for VMP). Weekly vs. biweekly bortezomib results in nearly the same CR rates, but peripheral neuropathy is reduced with VMPT. With VMP there is a slight decrease in CR but also reduced peripheral neuropathy. Longer follow-up is needed for PFS and OS assessment.
- Newly diagnosed elderly patients: PAD, induction with MEL 100, consolidation with lenalidomide plus prednisone, and lenalidomide maintenance. This trial is still ongoing, as patients pass through the stages of the regimen the response rates, as one might expect, are increasing.

Session 7: Consensus Panels

Session Chair:

Robert A. Kyle, MD

Mayo Clinic, Rochester, Minnesota, USA

Consensus Panel 1

The International Myeloma Workshop Consensus Panel I was reported by

Drs. S. Vincent Rajkumar, Jesus San Miguel, and JeanLuc Harousseau. It addressed guidelines for the uniform reporting of clinical trials. The Panel addressed lines of therapy, definition of patient populations, response criteria and the reporting of efficacy results.

Lines of Therapy

A line of therapy was defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of either single-agent therapy or combination therapy as well as a sequence of treatments given in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy.

Definition of Patient Populations

Refractory myeloma is defined as failure to achieve minor response while on salvage therapy or progresses while on therapy or progresses within 60 days of last therapy.

There are two categories of refractory myeloma: “relapsed-and-refractory myeloma” and “primary refractory myeloma.”

Relapsed-and-refractory myeloma is defined as a disease that is nonresponsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved a minor response or better.

Primary refractory myeloma is defined as disease that is nonresponsive in patients who have never achieved a minor response with any therapy.

Relapsed myeloma is defined as previously treated myeloma which after a period of being off therapy requires the initiation of salvage therapy. It does not meet criteria for either primary refractory or relapsed-and-refractory myeloma.

Response Criteria

Complete response (CR) is defined as negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas and < 5% plasma cells in the bone marrow. If the only measurable disease is by serum free light chain (FLC) levels, CR requires negative serum and urine immunofixation plus a normal FLC ratio.

Stringent complete response (SCR) is defined as CR plus absence of phenotypically aberrant plasma cells in the bone marrow with > 4 color flow cytometry and a normal FLC ratio.

Molecular complete response (CR) is defined as stringent CR plus negative ASO-PCR (sensitivity 10-5).

Very good partial response (VGPR) must have serum and urine M-component detectable by immunofixation but not electrophoresis or > 90% reduction in serum M-component plus urine M-component < 100 mg/24h. If the only measurable disease is by serum FLC, a 90% decrease in the difference between involved and uninvolved FLC levels is required.

Partial response (PR) requires > 50% reduction of serum M protein and reduction in 24-hour urine M protein by > 90% or to 200 mg/24h. If the serum and urine M protein are unmeasurable, a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria. If serum and urine M protein are unmeasurable and free light chain assay is also unmeasurable, > 50% reduction in bone marrow plasma

transplantation should be used early in myeloma patients and that new agents should be used in combination with autologous transplantation particularly in patients with high risk cytogenetics/FISH. There are still many unanswered questions such as when and how the novel agents should be used, should tandem transplants be used and if so in what patient?. Could maintenance/consolidation treatment substitute second transplant and should transplant be performed at all in patients older than 65 years?

Dr Michele Cavo made a review of single versus double autologous stem cell transplantation, before and after the era of novel agents. He reviewed five prospective trials, including his own Bologna 96. There was an advantage for complete remission in two studies, event-free survival in three studies and overall survival in two studies. An analysis indicated that the studies were very different in design, drug combinations and drug dosages. The summary was that tandem transplantation is probably of benefit for patients who have not obtained a complete remission following the first transplant. However, with new drugs included either in induction regimens or following the first autologous transplantation, this conclusion may be changed. Prospective, randomized studies were therefore warranted.

Dr Bart Barlogie reported results of the several “total therapy” studies designed by the Little Rock Group. Over the years, three total therapies have been reported and total therapy 4 and 5 are ongoing. Total therapy 1 is an intensive therapy including several drugs up front at diagnosis followed by tandem autologous transplants. In total therapy 2 consolidation with thalidomide including regimens were introduced and in total therapy 3 bortezomib was in addition included up front to shorten the time to transplantation. The intensification and the use of new drugs have continuously improved results. Total therapy 3 was particularly important to improve survival compared to total therapy 2 in low-risk myeloma, where a 90-percent five-year overall survival was obtained. There was only minor improvement in high-risk myelomas. Dr. Barlogie emphasized the importance of PET scanning to evaluate focal lesions that were important for the prognosis. Gene array models were pre-

sented, indicating that subgroups with very good prognosis could be delineated, and the distinction between good prognosis and poor prognosis groups was apparent. New total therapies (4 and 5) may improve results further, but with the current results with total therapy 3, it seems difficult to improve survival, at least in low-risk patients. Longer follow-up is needed for total therapy 4 and 5 before judging the benefit. Dr. Barlogie claimed that adding novel agents to the tandem autologous transplant procedure now has a projected 65-percent ten-year survival. The research is now focused on high-risk disease.

Dr Thierry Facon discussed the importance of post-transplant maintenance therapy. Three phase III studies indicated that maintenance with thalidomide after autologous transplantation was beneficial for response following a 3-12 month post-randomization treatment period. Several studies are ongoing, randomizing between thalidomide, bortezomid or lenalidomide for maintenance treatment. However, although data suggest that consolidation is effective, there is a lack of yet analyzable randomized studies. Although most studies suggest that there should be a benefit, there is at least one study, i.e. MRC Myeloma 9 that has shown no improvement in overall survival with thalidomide maintenance treatment. Further studies have to be done to clarify whether maintenance treatment is superior, and if so, what kind of maintenance that should be used. Also, the length of maintenance treatment has yet to be determined.

Dr Henk Lokhorst reported on the upfront inclusion of thalidomide instead of vincristine in the combination with doxorubicine and dexamethasone (TAD versus VAD) before autologous transplantation in the HOVON 50 study. The study comprised 556 patients and 82% eventually received the autologous transplant. Complete remission rate was higher in the TAD group which translated in better event-free and progression free survival, but with no significant improvement in overall survival.

Dr Mario Boccadora presented a study comparing the classical melphalan 200mg/m² (Mel200) for conditioning before autologous transplantation to a reduced dosage, 100 mg/m² (Mel100) in an attempt to reduce toxicity.

Although there was some reduction in mucositis and gastro-intestinal toxicities with Mel100 the CR rate tended to be lower and the progression free survival was poorer with the lower dosage. There was no significant difference in overall survival.

Dr Massimo Offidani reported a study in elderly patients (> 65 years) comparing two regimens one including thalidomide (+ doxorubicine and dexamethasone) ThaDD (n=66) given in 6 courses without subsequent transplantation and one using the same thalidomide regimen, but with only 4 courses given followed by autologous transplantation (ThaDD + HDT)(n=26). Although the CR rate was higher in the ThaDD+HDT group there was no significant difference in PFS or OS. The conclusion that patients over 65 years of age may not benefit from autologous transplantation must be taken with caution considering the small size of the material.

Allogeneic transplantation

Dr William Bensinger reported on the results of allogeneic transplantation at the Fred Hutchinson Center in Seattle USA. From 1977 to 2008, 278 patients, most of them with high risk prognostic factors, have received an allogeneic transplant. Many of them have received the transplant in an advanced stage of disease. Myeloablative conditioning has been used in somewhat more than half of the patients, while non-myeloablative reduced-intensity (RIC) conditioning treatment has been used in 120 patients. The complete remission rate was 42 percent in non-myeloablative transplants, and the treatment-related mortality was less than 20 percent, an impressive reduction compared to the high transplant-related mortality amounting to more than 50 percent with myeloablative treatment. As previously shown by the EBMT, the relapse rate was higher with non myeloablative treatment than with myeloablative, and the incidence of acute graft-versus-host disease less with non-myeloablative, while chronic graft-versus-host disease was more frequent. Of particular interest was that the 10-year survival was around 40 percent in this rather poor prognosis group of patients. More than 20 percent of the patients were progression-free between seven and nine years in the group of tandem auto/ RICtransplants.

Dr Philippe Moreau presented an update of the previously reported IFM 99-03 study comparing tandem autologous transplantation (n=166) to tandem auto/RIC allogeneic transplantation (n=46) based on the availability of an HLA identical sibling donor ("genetic randomization"). The conditioning regimen was very different from the original Seattle regimen using TBI 2 Gy. The IFM 99-03 consisted of busulphan 2 mg/kg/d for 2 days + fludarabine 25 mg/kg/d for 5 days + ATG, Imtix, Genzyme 2.5 mg/kg/d for 5 days, days -5 to -1. The update showed essentially the same results as previously published by IFM, i.e. no significant difference in survival or event free survival, but a tendency for poorer results for the auto/allo group. It was discussed if the poorer results as compared to other results (see below) were due to the inclusion of ATG in the regimen that may reduce the graft versus myeloma effect.

Dr Gösta Gahrton presented the EBMT study designed to compare tandem autologous/ non-myeloablative allogeneic transplantation to autologous transplantation - either single or tandem. Based on genetic randomization 100 tandem auto/RICallotransplants were compared to 250 autotransplants on an intention to treat basis. The transplant-related mortality at 24 months was 12% in the allo group versus 5 % the auto group. The progression-free survival and overall at 72 months were significantly superior in the tandem auto-allo group compared to the auto group (36 % versus 15 % and 65 % versus 50 % respectively). In the discussion concerning the role of allogeneic transplantation there was diversity of opinions, but there seemed to be an agreement that further prospective clinical trials using RIC conditioning for allotransplants were warranted and that combination with new drugs should be performed. It was pointed out that there are now five prospective studies, three published ones (one presented above) and two presented only at meetings, comparing autologous/ RIC allo transplantation to autologous transplantation – single or tandem. Three have shown superior outcome or a tendency for superior outcome with the auto-allo approach, one has so far shown no difference, and one has shown a tendency for inferior outcome with the auto RIC-allo approach.

Session 9: Phase II-III Clinical Trial Session

Session Chair:

Prof. Mario Boccardo, MD

Divisione di Ematologia dell'Università di Torino, Torino, Italy

Several trials have shown the superiority of high-dose therapy (HDT) versus conventional therapy in myeloma patients; in terms of both response rates and survival, but relapse still occurs. Different strategies have been tested in order to improve transplant outcomes. In this session, six phase II-III clinical trials regarding HDT followed by stem cell transplant in newly diagnosed myeloma patients were presented. Three studies evaluated the impact of introducing novel drugs (thalidomide and bortezomib) in the transplant setting. Prof. Lokhorst presented the final analysis of the phase III trial Hovon-50; this trial was designed to evaluate the effect of thalidomide during induction treatment and as maintenance in patients with Multiple Myeloma (MM) who were transplant candidates. 556 patients were randomly assigned to receive 3 induction cycles with Vincristine, Doxorubicin, Dexamethasone (VAD) in arm A or, Thalidomide 200 orally, days 1-28 + AD (TAD) in arm B. After stem cell mobilization, patients were to receive 1 or 2 courses of high dose melphalan 200mg/m² (MEL200) followed by maintenance with alpha- Interferon (Arm A) or Thalidomide 50 mg daily (Arm B). Thalidomide significantly improved overall response rate (ORR), as well as, quality of the response before and after HDT: ORR was 87% and 79% ($p < .01$), at least Very Good Partial Remission (VGPR) 65 % and 54% ($p < .01$), Complete remission (CR) 30% and 21 % ($p = .03$), respectively in favour of the Thalidomide arm. Thalidomide also significantly improved Event Free Survival (EFS) (from median 22 months to 33 months; $p < .001$) and PFS (from median 25 to 33 months; $p < .001$). Overall survival (OS), however, in both arms was comparable, 62 months in Arm A and 59 months in Arm B ($p = .96$). Thalidomide combined with intensive therapy improved response, EFS, PFS; however this did not translate into better OS. In the trial conducted at Emory University by Dr. Kaufman and colleagues, escalating doses of bortezomib (B) were combined with MEL200, in order

to, determine the optimal dose and schedule of this combination. 41 patients were randomized to receive either B 24 hours before MEL200 (Arm A) or B 24 hours after MEL200 (Arm B). Doses for B were escalated from 1.0 mg/m² up to 1.6mg/m². Enrolled patients underwent bone marrow aspirate before B and before stem cell infusion, in order to, assess plasma cell apoptosis. The planned dose of B at 1.6mg/m² was reached. Neutrophil and platelet engraftment were no different between the two arms. The VGPR rate was 51% at 100 days post transplant, with 94% achieving PR or better. Fold increase in apoptosis was higher in Arm B when compared to Arm A. The combination of B with MEL200 as conditioning for HDT was safe with promising VGPR rate. Administration of B following MEL200 may be superior to B before MEL 200. Dr. Offidani and colleagues addressed the issue of the role of HDT after induction with new drugs in elderly MM patients. The outcome of patients treated with ThaDD (thalidomide, dexamethasone, and doxorubicin) alone was compared with that of patients receiving ThaDD plus HDT. 62 patients non eligible for HDT received 6 courses of ThaDD and 26 eligible for HDT received 4 courses of ThaDD followed by either MEL200 or MEL100 with stem cell support. Consolidation with HDT increased the response rates with VGPR rising from 61% to 81% and CR from 46% to 57%. However TTP, PFS and OS were similar between the 2 groups, suggesting that the outcome of elderly patients eligible for transplantation treated with Thalidomide combinations does not seem to be improved by intensification with HDT. The GIMEMA group compared in a randomized, phase III trial, the efficacy and toxicity of MEL200 and of intermediate-dose melphalan (100 mg/m², MEL100). All patients received 2 induction cycles with VAD and after stem cell harvest; all patients received a double transplant approach conditioned with either MEL200 or MEL100. 298 patients were randomly assigned either to MEL200 or to MEL100.

The VGPR rate was higher in MEL200 group (37% versus 21%, $p=0.003$), but CR was 15% in the MEL200 group and 8% in the MEL100 group ($p=0.07$). MEL200 was associated with a superior EFS (44.5% vs 18.3%; $p=0.02$), while the 5-years overall survival (OS) was comparable (59.2% vs 44.7%; $p=0.22$). The incidence of grade 3-4 hematologic toxicities was comparable in the two arms, while grade 3-4 non-hematologic adverse events were higher in the MEL200 group. The role of allogeneic transplantation was evaluated in the two studies presented by Dr. Moreau and Prof. Gahrton respectively. Dr. Moreau presented the long-term follow-up results of IFM99-03 and IFM99-04 trials: MEL200 plus autologous transplant (ASCT) was compared to reduced-intensity conditioning regimen (RIC) allograft (fludarabine, antithymocyte globulin and low dose busulfan) in younger patients with high-risk (b2microglobulin > 3 and chromosome 13 deletion by FISH analysis at diagnosis) de novo MM. In both protocols, induction regimen consisted of VAD (4 courses) followed by MEL200. When a HLA-sibling donor was available, ASCT was followed by RIC allograft (IFM99-03). When no donor was available, patients were randomised to receive a second ASCT with MEL200 +/- anti-IL6 monoclonal antibody (IFM99-04). 65 patients had an available HLA-identical sibling donor and were included in the IFM99-03 trial, and 219 were included in the IFM 99-04 trial. With a median follow-up of 56 months, the EFS did not significantly differ from tandem ASCT to single autograft followed by allo-RIC (median 22 vs 19 months, $p = 0.58$). There was a trend for a superior OS in the double ASCT trial (median 48 vs 34 months, $p=0.07$). These long-term results indicate that, in a subgroup of high-risk patients with de novo MM, a tandem autologous transplant procedure is at least equivalent or even superior to a combination of autologous followed by RIC allogeneic stem cell transplantation. In the trial presented by Prof. Gahrton auto-ASCT followed by RIC-allo was compared to auto-ASCT alone. Patients with an HLA-identical sibling were allocated to the auto/RIC-allo arm and patients without a matched sibling donor to the auto-alone arm. Conditioning for auto was MEL200 and for RIC-allo was fludarabine plus TBI. The CR rate was comparable in the 2 arms (43% in the auto/RIC-allo arm and 40% in the

auto-alone arm; $p=.49$). At 3 years after transplantation, there was no significant difference between the treatment arms with respect to OS, PFS or relapse rate. However; in patients with deletion 13 the CR rate and the relapse rate were superior using the auto/RIC-allo combination.

Session 10: Oral Presentation – Clinical Care

Session Chair:

Heinz Ludwig, MD

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The French group of JP Fermand¹ reported a trial employing thalidomide/dexamethasone for induction and for maintenance therapy in patients older than 66 years. The title was somewhat misleading, since patients were randomized to either melphalan-cytosine-dexamethasone or to the same regimen plus thalidomide for 3 months. After 3 months, patients of both groups received melphalan-cytosine-prednisone until achievement of a plateau phase. Thereafter patients were amenable for randomization for either thalidomide/dexamethasone maintenance therapy or control. 164 patients with a mean age of 73 years had been enrolled. After the induction phase a VGPR or better was observed in 32% of patients treated with the thalidomide containing regimen compared to 9% in the other group ($p < 0.0001$). After a median of 5 cycles of melphalan-cytosine-dexamethasone, rates of VGPR remained stable (31% in patients induced with thalidomide containing and 9% induced without thalidomide containing regimen). Maintenance therapy with thalidomide/dexamethasone resulted in significantly longer event-free survival compared to the control arm (median 44 vs. 12 months, $p = 0.021$), but no significant difference was noted regarding overall survival. Overall survival at 3 years was 73% in patients started on the thalidomide containing regimen and 72% in the other group ($p = 0.66$). Estimated 3 year survival rate after start of maintenance therapy was 64% in patients randomized to maintenance therapy and 74% in those without further treatment ($p = 0.52$). The treatment was relatively well tolerated. Thromboembolic complications were seen in 22% and 13% ($p < 0.22$) and peripheral neuropathy in 20% and 4% ($p = 0.003$) of patients induced with or without thalidomide in addition to melphalan-cytosine-dexamethasone ($p < 0.22$).

In conclusion, a short induction with a thalidomide containing regimen yielded higher rates of VGPR compared to chemotherapy without thalidomide, but did not impact on

overall survival. Likewise, maintenance therapy with thalidomide/dexamethasone significantly improved event-free survival, but had no effect on overall survival.

The Australian study group represented by Andrew Spencer² presented their data with thalidomide consolidation therapy after conventional induction therapy following high dose melphalan conditioning and ASCT in patients < 65 years of age. 129 patients were randomized to indefinite prednisolone and 114 to the same maintenance therapy plus 12 months of thalidomide consolidation/maintenance treatment. Thalidomide-prednisolone resulted in a significantly higher rate of CR and VGPR after 4, 8 and 12 months of therapy (65% vs. 44%, $p < 0.01$, 63% vs. 40%, $p < 0.01$, 63% vs. 40%, $p < 0.01$, respectively), and in a significantly higher progression-free survival rate at 3 years (42%) compared to prednisolone (23%, $P < 0.001$). Overall survival rate was also significantly higher with thalidomide-prednisolone consolidation therapy (86% vs. 75%, $p = 0.004$). The improvement in PFS and OS was independent of the quality of the response after ASCT (CR+VGPR vs. PR). There was no difference in survival between both groups 12 months after disease progression which is in contrast to the observation of some other groups that observed significantly shortened survival in patients relapsing after previous exposure to Thalidomide. Patients in the thalidomide-prednisolone arm experienced more neurological toxicities (all grades: 52%, grade 3+4: 10%), but frequencies of other side effects, particularly of thromboembolic complications were similar in both arms. Of note 88% of patients remained on therapy until month 12.

Meletios Dimopoulos³ presented results of lenalidomide/dexamethasone (LD) in previously treated patients with preexisting neuropathy (grade ≥ 2) or of the same combination plus bortezomib (BRD) in patients without neuropathy (grade < 2) in relation to cytogenetics, renal

function and other parameters. 85% of patients had been pretreated with thalidomide and 63% had been considered to be resistant thalidomide. Bortezomib had already been employed in 83% of patients, 54% of which had been considered resistant to bortezomib. 46% of patients had high risk cytogenetic features as determined by FISH, and a non-hyperdiploid karyotype was detected in 21%. A significant myeloma response was noted in 49% of patients with no significant difference between the BRD and the RD regimen (ORR: 48% vs. 50%). Of note, responses were seen in 29% of thalidomide and in 42% of bortezomib resistant patients. The outcome to therapy in cytogenetic risk groups was: del17q: 14%, t (4; 14): 33%, ampl 1q21: 36%, non-hyperdiploid karyotype: 9%. A thromboembolic event was seen in one patient only. In summary, both regimens were found to be active in patients with previous resistance to Thalidomide and Bortezomib. In addition to response data, the authors addressed the impact of both regimens on markers of bone turnover also. Treatment with both therapies resulted in a significant decrease in serum levels of RANKL and in the ratio of RANKL/Osteoprotegerin. This effect should result in a significant decrease in bone resorption. The result was more pronounced with BRD compared to RD ($p < 0.02$). Levels of Dkk-1, an indirect inhibitor of osteoblast activity were reduced with BRD, but increased during therapy with RD. These findings are consistent with increased bone formation with the BRD regimen which was supported by a concomitant increase in markers of bone formation like bALP and osteocalcin.

Results of maintenance treatment with either Thalidomide (Thal) plus Interferon (IFN) or with interferon alone after induction therapy with Thal-Dexamethasone or MP in elderly patients with MM were presented by Heinz Ludwig⁴ on behalf of the Central European Myeloma Study Group. 289 patients (median age: 72 years) had been enrolled into the induction part of the trial. Of the 135 patients who completed the planned 9 cycles of therapy with either stable disease or better, 128 had been randomized to either Thal-IFN or to IFN only. Median follow up after the second randomization was 35.7 months. Patients remained for a median of 10.2 months on Thal-Dex and for 7.7 months on IFN maintenance treatment. Thal-IFN therapy resulted in a

significantly longer PFS compared to IFN only (22 months, vs. 12.6 months, log rank test, $p = 0.024$) but overall survival was similar between both arms (55 months, vs. 56.8 months, $p < 0.95$). PFS and OS by pretreatment showed a significantly shorter PFS in patients started on MP and randomized to IFN maintenance compared to the three other groups (PFS, 7.6 months, Thal-Dex \Rightarrow Thal-IFN, 24 months, MP \Rightarrow -IFN, 16.6 months, MP \Rightarrow -Thal-IFN, 27.6 months, log-rank test, $p = 0.061$) but OS by induction therapy was similar in all groups.

Cytogenetic data were available in 55 patients which were categorized according to their cytogenetic risk profile in a group with high risk (t (4; 14), t (14; 20) Del 17p and abnormalities of 1q21) and a cohort with standard risk (all others). PFS tended to be longer in patients without unfavorable FISH findings compared to the standard risk group but differences were not significant (median: 29.8 vs. 15.4 months, log-rank test 0.088), The median of OS has not been reached in those with standard risk and was 47.6 months in those with cytogenetic high risk features (log rank test: 0.23)

Hematologic toxicity was similar between both groups, but patients on Thal-IFN maintenance experienced significantly more grade 1-3 neuropathy, grade 1-2 constipation and grade 1-3 skin toxicity. Grade 1-2 fatigue and dyspnea was slightly, but not significantly more frequent in patients on Thal-IFN maintenance therapy. Other non hematological toxicities were similarly distributed in both therapy arms.

James Berenson⁵ presented an interesting randomized trial comparing kyphoplasty with conventional care in patients with ≤ 3 painful compression fractures and a pain score of ≥ 4 (VAS, visual analogue score). Patients with solitary plasmocytoma at the fraction site were excluded. The primary endpoint was the one month change in the 25 point Roland-Morris Disability questionnaire, an instrument validated for assessing back-specific physical functioning. 36% of the 134 patients enrolled presented with multiple myeloma, while the majority of the other patients had been diagnosed with breast-, lung-, prostate- or other cancers. The proportion of patients with 2 or 3 vertebral compres-

sion fractures was well balanced between both groups. Baseline Roland-Morris and pain scores were evenly distributed between both groups also.

Kyphoplasty resulted in a significant improvement in the Roland-Morris score (-8.3 points, 95% CI, -6.2, -10.5) while no difference was seen in conventionally treated patients (-0.1 points, 95% CI, 0.9,-1.0; $p < 0.0001$). At one month, kyphoplasty patients had improved back pain (-4.1 points, 95% CI, -3.2,-4.9) while in the non-surgically treated patients no change was noted (-0.5 points, 95% CI, 0.04,-1.0, $p < 0.0001$).

Kyphoplasty was well tolerated with only one SAE (myocardial infarction) which was attributed to anesthesia and which resolved with further therapy. In conclusion, kyphoplasty was found to be significantly superior to conventional therapy both in terms of pain reduction as well as in terms of improvement of the back-specific physical functioning. The report did not specify the conventional measures taken in the control group. From the commentator's European perspective, local radiotherapy (20-40 cGy) to the affected vertebral bodies, which is highly effective and well tolerated, would significantly have improved pain and functioning in the control group. The concern regarding bone marrow toxicity, when given to small areas is not substantiated by scientific data.

The Irish group represented by Curly T. Morris⁶ showed a comparison of results obtained with their PAD (Bortezomib-Adriamycin-Dexamethasone) regimen with VAD or VAD-like regimens in patients with relapsed/refractory myeloma. Three cohorts of patients were compared: 1. patients treated with VAD after relapsing from autologous transplantation, 2. similar patients, but without previous transplantation, 3. patients refractory to VAD. Patients in group 1 and 2 were allowed to have received one further line of therapy following VAD but patients in group 3 had to proceed directly to PAD. Of the first group 8 patients achieved CR after PAD compared to 3 post VAD ($p = 0.013$). The depth of response was higher in the former group with a reduction in the paraprotein concentration by a median of 88% compared to 60% post VAD ($p < 0.003$). At the time of reporting, only few patients had been enrolled into the second group and treatment results with VAD or VAD like regimen appeared to be similar to those obtained with PAD. Of the 18 patients recruited to group 3, 75% showed superior response with PAD compared to the previous VAD or VAD like regimen. In conclusion, this study underlines the high activity of PAD in patients previously exposed to VAD or VAD-like regimen even in those who proved to be resistant to VAD. The regimen was well tolerated and is a valuable treatment choice after VAD therapy.

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Session 11: Pro and Con Session

Chair:

Raymond L. Comenzo

Tufts University Medical Center, Boston, Massachusetts

On Sunday morning March 1, 2009 the XIIth International Myeloma workshop moved to the International Ballroom of the Hilton Hotel in Washington DC after 3 full days at the Marriott Wardman Park just across the Taft Bridge on Connecticut Avenue. The second session on that Sunday Morning was the Pro and Con Session during which a series of important issues in myeloma therapy were debated by experts in the field.

The menu of novel agents to treat multiple myeloma has grown significantly over the past decade and these agents have had a major impact on patient outcomes and overall survival. Nevertheless, it is not clear whether the agents should be used at the same time together or in sequence, one after another. The first Pro and Con session concerned that issue.

Dr. Morie Gertz from Mayo clinic argued in favor of simultaneous use of novel agents in initial therapy. Dr. Gertz pointed out the important results of recent trials in which the novel agents thalidomide or bortezomib were added to the traditional agents melphalan and prednisone. The combinations with the novel agents were clearly superior with respect to event-free survival and frequently superior with respect to overall survival for patients with multiple myeloma who were not stem cell transplant candidates. In addition, adding the novel agent bortezomib to initial therapy resulted in a higher rate of complete and very good partial responses, based on a recently completed IFM study in patients eligible for stem cell transplant. This is particularly important because the need for a second transplant is markedly reduced as the result of having a previous bortezomib containing combination regimen. Dr. Gertz also emphasized that the time to next therapy in patients treated with combinations of novel and traditional agents was also usually delayed; that is, that relapse occurs later in the course of disease.

Dr. Joan Blade from Barcelona took the opposite position and argued in favor of the sequential use of novel agents in initial therapy. In elderly patients who are not stem cell transplant candidates the multi-drug initial therapy regimens have been shown to have significant toxicity and clearly raise the question as to whether or not longer survival can be achieved with a gentler approach rotating novel and traditional agents. He reminded the audience that for many years the combination of melphalan and prednisone was as good as or better than any combination of other chemotherapeutic agents. It was also noted that the opportunity exists for tailored sequential therapy based upon the clinical features of an individual patient and how they fit with the toxicities of novel agents. He suggested, for example, that elderly patients with aggressive disease might be candidates for melphalan, prednisone and bortezomib; however patients at risk for renal failure might be candidates for bortezomib and dexamethasone. He also suggested that the use of immunomodulatory agents long-term after initial therapy might enable patients to manage multiple myeloma as a chronic disease. The availability of novel agents in his view translated into increased choices for the management of patients with sequential therapy.

In the rebuttal Dr. Gertz noted that Dr. Bladé would win the debate if this were 1969. He also noted that the projections regarding improvements in survival that Dr. Bladé had commented upon were being reviewed at this time. Dr. Bladé responded by noting that patients whose clinical features of disease excluded them from the current clinical trials, (e.g. features such as renal failure with a creatinine exceeding 2.0mg/dL), are exactly the category of patients that require tailored therapy. Therefore, he argued, in the elderly, sequential therapy made sense because we cannot cure their disease and a tailored approach was most reasonable; while in younger patients one could imagine that those with less aggressive disease could be given

sequential therapy as well, including a stem cell transplant. Those with more aggressive disease would require a different approach.

In the discussion period, the question was asked whether the data supported the continued combination of agents in induction therapy. Dr. Gertz noted that in the Total Therapy II trial from Arkansas there was no demonstrated overall improvement in survival for those who received thalidomide unless they had prior cytogenetic abnormalities. Another questioner noted that in cell line experiments there was no evidence that sequential therapy was inferior to combination therapy. A third commented saying that the discussants “both are right and that we should not look at multiple myeloma as one disease.” He said, “In low risk groups sequential therapy is likely an appropriate approach while in high risk groups combined therapy is needed”.

As luck would have it, the next controversial area followed logically from that comment. Should myeloma therapy be based on risk groupings? Should patients be stratified in some way prior to receiving therapy? Dr. Angela Dispenzieri from Mayo clinic spoke in favor of risk stratification. She noted that we already stratify based on risk. For example, age is a stratification factor for the use of autologous stem cell transplant. Performance status and renal function also result in stratification of patients and we already use tumor characteristics to determine who should or shouldn't be treated: distinguishing, for example, monoclonal gammopathy of undetermined significance from smoldering myeloma and symptomatic myeloma. We define symptomatic myeloma as a monoclonal gammopathy with end-organ damage and know some of the risk factors that have been identified are prognostic in retrospective analyses. We also note that prospective studies have been difficult to conduct for defined risk groups.

IFM 99-02 was a prospective attempt to use high and low risk factors to stratify patients, and no difference in overall survival was identified between patients who received autologous followed by allogeneic transplant

and those who received tandem autologous transplant. Dr. Dispenzieri noted that there was increasing awareness of risk in the community as the use of cytogenetics and FISH has increased in recent years; that in the modern era it is becoming increasingly important to define risk groups for patients and their physicians; and that data were not yet available with novel agents to answer the question of whether continuous chemotherapy or a stem cell transplant was a better road to take. In addition, there is no prospective data using novel agents to help determine the roll of single or tandem autologous stem cell transplant. She commented on the impact of novel agents in some of the trials that have already been conducted with a particular emphasis on the available data on thalidomide and high-risk cytogenetics such as t(4;14) or del 17p. In the IFM evaluation of the role of cytogenetics and FISH those patients with the t(4;14) and del 17p had a median survival of only 12 months even with stem cell transplant. In IFM 99-02, the thalidomide maintenance trial, there was no benefit to thalidomide in patients with del 13 whereas in the Arkansas Total Therapy II trial there was a benefit to patients with cytogenetic abnormalities who received thalidomide.

In contrast, in MRC Myeloma IX, patients with del 17p who received thalidomide had distinctly inferior progression free and overall survival. Dr Dispenzieri also noted that the claims regarding the efficacy of bortezomib in patients with high-risk cytogenetics and FISH were all post-hoc subgroup analyses based on the APEX and VISTA trials. Recent data from IFM and from Total Therapy III indicate that bortezomib might indeed benefit patients with t(4;14) and del 17p but the conclusion remains unconfirmed prospectively at this time. In addition, emerging data suggests that lenalidomide may work in the same fashion; however, we are not looking prospectively at risk stratified groups on clinical trials and therefore such claims will be difficult to adjudicate.

Speaking against risk stratification as a basis for determining therapy, Dr. Jesus San Miguel argued that we have not yet reached the era of individualization of therapy. With respect to cytogenetic abnormalities he noted that

MGUS patients displayed similar abnormalities to multiple myeloma patients, raising the question as to why those same cytogenetic abnormalities can cause different prognoses in myeloma. He argued that it was premature to use genetic risk stratification to mandate specific therapies. He went on to note that there are many unsolved questions involving novel agents and low-risk cytogenetics and whether the density or duration of therapy mattered more. He noted that only 2 of the 5 studies of the combination melphalan, prednisone and thalidomide showed an overall survival benefit and that these may have been related to the resistant relapses that could have occurred with thalidomide. He went on to state that all of the prior treatment paradigms used before the era of novel agents needed to be re-evaluated and that simply accepting treatment plans based on prognostic factors from a prior era would be a significant clinical error. A review of the thalidomide maintenance data indicated that only standard risk patients seem to benefit from thalidomide maintenance. He also noted that the question as to whether or not patients achieving a complete response after initial therapy might benefit from stem cell transplant remains an open one, although the initial information indicates that a more profound response and a decreased amount of minimal residual disease can result in enhanced responses with stem cell transplant. He went on to note that the goals of treatment differed depending on patient age. Thus, the goal in younger patients should be cure while in those aged 65 to 80 long term overall survival with adequate quality of life would be appropriate goals. In patients over the age of 80; quality of life might be the most important goal. Therefore, clinical trials would need to continue to be comprehensive up front in order to improve treatment efficacy.

In rebuttal, Dr. Dispenzieri countered that although it appeared that bortezomib modified high risk disease, prospectively defining risks in clinical studies and in the community remains an important goal. We do not know every aspect of the prognostic risk factors in the era of novel agents. Most of what we know has resulted from post-hoc analyses. An alternate approach would be to do risk-based studies that are powered to answer questions of interest.

She emphasized that it is important for us to realize what we know and do not know as we move forward in attempts to improve outcomes for myeloma patients. Dr. San Miguel responded that the gap in overall survival of myeloma patients in large trials based on age remain significant. He felt that among younger patients it was important to push for a cure and then look to decrease toxicity; while in older patients who live a median of 4 years at best from diagnosis we should continue treating patients comprehensively tracking both efficacy and toxicity. In the discussion period, a prominent investigator lectured those present when he stated: "I think we need to put the patients in clinical trials to have a comprehensive biological analysis of their disease and to use appropriate analyses of outcome to identify cohorts who may benefit from future specialized therapy." This physician noted that the use of risk stratification or of all novel agents up front for young patients was perhaps reasonable but we have not reached a plateau yet and therefore it is perhaps premature to take that road. He agreed with Dr. San Miguel regarding the critical role of age and co-morbidities yet also noted that we need to employ risk-based approaches in elderly patients who are not on clinical trials.

The third and final pro and con session focused on the role of allogeneic stem cell transplant in multiple myeloma. Historically, conventional myeloablative bone marrow transplant resulted in treatment-related deaths in 40% of myeloma patients and long-term survival and possible cure in a minority. The modern era has seen the emergence of non-myeloablative reduced intensity allogeneic transplant for multiple myeloma patients often after an initial autologous transplant. Arguing in favor of the use of allotransplant was Dr. Jayesh Mehta from Chicago. He emphasized the graft-versus-myeloma effect that has been noted by transplanters and reported that the side effects of allogeneic transplant needed to be balanced against this outcome. He stated that allotransplants had been somewhat misused in several different ways. In some instances, simply because the patient had an HLA-identical related donor, allogeneic transplant was pursued – "because it's there." Alternately, in the hands of other investigators,

allogeneic transplant has been used as a last resort and patients who are candidates for palliative care receive allo-transplant with significant complications as a result. He concluded that the proper road to take was to use allogeneic transplant judiciously in the context of well designed clinical trials and that combining allogeneic transplant with maintenance with novel agents was a very reasonable road to take. He emphasized the importance of continuing to study allogeneic transplant in a systematic way in the current era.

Arguing against allogeneic transplant was Dr. Jean Paul Fermand from the French Myeloma Transplant group. He viewed allotransplant as perhaps having a role in myeloma but noted that there was no evidence of a plateau in survival in any of the prior studies that have been performed. The reason for this was likely the size of the tumor mass and our inability to effectively control the disease. Patients in complete remission still have perhaps 10⁹ or 10¹¹ residual tumor cells and the immunologic impact of allotransplant may not be able to overcome this large a number of target cells. The graft-versus-myeloma effects has limitations in part “due to the weak and variable expression of target antigens.” He noted that myeloma had an intermediate sensitivity to donor lymphocyte infusions in graft-versus-tumor effects. The treatment-related risks, however, in allotransplant have been very high for myeloma patients and the fact that the graft-versus-disease effect is usually associated with graft-versus-host disease made allotransplant nearly unacceptable to his mind. “Because efficacy implies toxicity we are faced with giving a high risk therapy to a low risk patient.” He argued that multiple myeloma was not a good indication for allogeneic transplant even with autologous followed by non-myeloablative reduced intensity allogeneic transplant as the approach. He also noted that the donor versus no donor design of several notable trials was inherently flawed because it did not allow for appropriate randomization. In addition, recent data on molecular remissions post-allotransplant indicated that there was no plateau in overall survival.

In rebuttal, Dr. Mehta responded that Dr. Fermand had in fact supported his view with respect to the need for judicious use of allotransplant! He emphasized that there is a place for this treatment option in the setting of clinical trials. Dr. Fermand responded that there were basically four issues: (1) myeloma is not an ideal disease because of the toxicity associated with efficacy; (2) the toxic risk is too high for a low risk patient; (3) there was no benefit of reduced intensity conditioning after an initial autologous transplant in contrast to a second autologous transplant; and (4) that the pursuit of cure in a few patients was associated with too high a cost in mortality, morbidity and quality of life for the majority of patients.

A prominent investigator in the audience defended the use of allogeneic transplants in the setting of clinical trials but also stressed that it was an experimental procedure and should be done in clinical trials. Dr. Fermand agreed that when we have an improved form of allotransplant we should pursue it based on clinical trial data. Dr. Mehta argued that high risk patients with high risk disease would likely be candidates for such a high risk approach. Dr. Gosta Gharton then rose and spoke in a clear voice. He said the data had been misread and that numerous studies showed a benefit to allotransplant with the reduced intensity approach. He noted that treatment-related mortality at 2 years with the auto-mini allo approach was 12% versus a 5% treatment-related mortality with tandem auto transplant, and that progression free and overall survival in three studies comparing allo- and auto-transplant was better in the allotransplant arm. He also noted that improvements with novel agents and with novel cellular therapies, and new ways to decrease graft-versus-host disease, would make allogeneic transplant a much more viable option in the near future.

Dr. Mehta noted that the use of biology for randomization remains problematic and therefore the application of allotransplant and improved versions of it should be confined to patients with high risk disease. Dr. Fermand commented that if you needed a lot of patients to

demonstrate a benefit then the benefit is likely minimal and that the important question of quality of life could be lost. He disagreed with Dr Gharion and suggested that the data were not strikingly in favor of allotransplant. Several questioners from the floor noted that the use of novel agents in the setting of allotransplant could have unexpected consequences including the occurrence of solid tumors. It was the sense of the meeting that well controlled clinical trials continue to be required to advance this field.

Overall the Pro and Con session was well received by all those in attendance and was a forum for vigorous discussion of important issues for myeloma patients and their physicians. Future sessions of this type in coming IMW meetings are eagerly awaited.



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