XII INTERNATIONAL MYELOMA WORKSHOP

Excerpts from text by Lynne Lederman, PhD

Introduction

The XII International Myeloma Workshop (IMW) was held from February 26 to March 1, 2009 in Washington, DC. Approximately 1000 attendees exchanged ideas during the meeting sessions, symposia, poster sessions, and working breakfast and lunch sessions, and at two dinner events. This meeting was originally scheduled to be held in India, but was moved to the US subsequent to the tragic events in Mumbai. Meeting organizers Drs. Nikhil Munshi, Vincent Rajkumar, Sundar Jagannath, and Vinod Raina, along with colleagues Drs. Mammen Chandy and Atul Sharma, hope to have the opportunity to organize the workshop in India at a future date.

Overview

Topics presented included myeloma molecular and signaling pathways, myeloma immune and antibody targets, the bone marrow microenvironment, clinical trial results, pathogenesis, risk stratification and prognostics, new therapeutic agents, and transplantation in myeloma. Oral clinical presentations covered clinical trials, new agents, and clinical care; basic biology sessions covered novel and potential therapeutic targets. The Consensus Panel presentations discussed Guidelines for the Uniform Reporting of Clinical Trials in Myeloma, Guidelines for Risk Stratification in Myeloma, and Guidelines for Standard Investigative Work-up in Myeloma. There was a presentation on Statistical Issues in the Design and Analysis of Clinical Trials in Myeloma, along with several sponsored symposia and poster sessions. The final day of the conference included pro and con discussions, presentation of Phase II studies and plenary abstracts, and a future perspectives session. This write-up summarizes some of the key issues discussed during the IMW meeting. Please visit the IMF website www.myeloma.org to read the full report.

Molecular Pathways

The opening session included Dr. Rafael Fonseca's discussion of chromosomal fluorescent *in situ* hybridization (FISH) and its association with pathophysiologic events, prognostic value at baseline disease diagnosis, and its predictive value in therapeutic outcomes. He compared the value of emerging gene expression profiles versus FISH as prognostic factors. This session confirmed a number of genetic markers associated with poor prognosis; but it was noted that, as new therapies emerge, alterations in the prognostic value may shift. These approaches will reach their full potential once demonstrated as effective in clinical trials.

Phase III Studies

The US/DFCI approach -- novel agents as part of new combinations -- focus on relapsed myeloma

Dr. Ken Anderson presented on behalf of Dr. Paul Richardson. He commented that bortezomib, lenalidomide, thalidomide, and pegylated doxorubicin shouldn't be called "new" any more. He noted that since the introduction of these agents, median survival of patients with myeloma has been prolonged from 3 to 7 years. Using these agents in combination should increase efficacy, avoid resistance, and result in a more favorable side effect profile.

Early combination studies -- new combinations for multiple myeloma

Dr. Antonio Palumbo observed that in the Phase III trial of bortezomib plus pegylated doxorubicin, the addition of the second agent increased efficacy. Three-drug combinations that have been tested show increased response rates. However, it is unclear which is the best three-drug combination. Fourdrug combinations are also promising. Randomized studies are needed.

Anti-angiogenic agents

Dr. Shaji Kumar reviewed the role of angiogenesis. He cited two paradigms of drugs which are known to have anti-angiogenic properties. Dr. Kumar concluded that bone marrow endothelial cells in myeloma were a valid target, although it was likely that this strategy may not work alone, so a combination approach with myeloma cell-targeted therapy plus EC targeted might work best.

Transplant

Dr. Sergio Giralt presented "New mobilization and conditioning strategies (Autografting for myeloma in 2009)." He said that the use of novel agents for induction does affect outcome, and that researchers were starting to address issues about the quality and amount of cells that are being collected.

Dr. Giralt suggested a refocus on improving the stem cell product, determining the minimum number of cells to collect, looking at the effect of infused cell numbers on reduction of the still-considerable symptom burden, and improving immune reconstitution, noting that lymphocyte recovery is associated with better outcome.

Dr. Donna Weber discussed "Timing of transplant in the era of new drugs." Before novel agents, transplants offered the advantage of better survival. Dr. Weber observed that it will take powerful studies to determine if transplantation is still needed with currently available therapies. She thinks that some form of maintenance consolidation after transplant seems warranted. Other questions to be answered include the length of induction and the best combinations of agents.

Dr. Michele Cavo discussed "Single or double autologous stem cell transplantation (ASCT) before and after the era of novel agents." He reviewed the history of ASCT for myeloma from the recognition that there was a dose response to melphalan, to the observation of increased CR rate and OS with a single ASCT vs. conventional chemotherapy, to the investigation in Phase III trials of double or tandem ASCT as a way to further improve outcome.

Dr. Bart Barlogie presented "Total therapy (TT) for multiple myeloma." He reviewed the past 20 years of TT which he characterized as an "evolution from palliation to cure." He maintains that there is a role for tandemtransplants in myeloma.

Dr. William Bensinger discussed "Allogeneic donor transplants for multiple myeloma in Seattle." He presented the results of allo-ASCT in 278 patients treated from 1977 to 2008. Dr. Bensinger suggested that posttransplant maintenance therapy with one of the novel agents and more targeted conditioning regimens might improve outcomes.

Dr. Thierry Facon presented "Post-transplant maintenance." He said that the advent of novel agents and their use in combination therapies have contributed to achieving optimal regimens for post-transplant consolidation and maintenance therapies. Dr. Facon reviewed trial results for maintenance therapy with thalidomide. Bortezomib and lenalidomide are also being tested for consolidation/maintenance as single agents and in combinations. He addressed Phase III trials to assess the role of consolidation and maintenance post-transplant, which may answer some of the outstanding questions concerning post-transplant consolidation and maintenance.

Pro and Con Sessions

Simultaneous versus Sequential use of Novel Agents

Dr. Morie Gertz argued for simultaneous use of novel agents in induction therapy and Dr. Joan Blade argued for sequential use. The concept of conventional therapy is changing, and there are no data showing that sequential treatment is inferior to combination therapy. It was also noted that different populations of patients may require different approaches.

Risk Stratification

Dr. Angela Dispenzieri favors basing therapy on risk stratification, which is based on patient characteristics, including age, performance status, renal function, and co-morbidities; and on tumor characteristics. Dr. Jesus San Miguel is against basing therapy on risk stratification, but says treatment can be individualized. In the ensuing discussion, Dr. Rajkumar stated that this was not the time for risk stratification, and urged putting patients in trials, doing a biologic analysis up front, carefully analyzing response, then tailoring treatment to specific patients. He suggested offering a high risk treatment approach to patients who wouldn't benefit as much as those with standard risk disease.

Allogeneic Transplantation

Dr. Jayesh Mehta favors using allogeneic transplantation while Dr. Jean-Paul Fermand is against it. The transplant-associated mortality for allo-SCT is 12% vs. 5% for ASCT at 2 years. Improvement should focus on methodology, including new drugs, reducing

GvHD, and keeping GvM. Dr. Mehta said allo-SCT should be based on prognostic factors and be used to treat patients with very high risk disease and poor prognosis.

Consensus Panels

Guidelines for the Uniform Reporting of Clinical Trials in Myeloma

Dr. Vincent Rajkumar discussed issues concerning response criteria. The IMWG Uniform Response Criteria are recommended for use in future clinical trials. PET (positron emission tomography) and MRI (magnetic resonance imaging) will not be incorporated formally into the response criteria for assessing the depth of response but additional single center clinical studies are encouraged. The time at which each response assessment was conducted should be reported, and should be made before initiation of subsequent therapies. Time to best response should be reported, otherwise studies can't be compared.

Dr. Jesus San Miguel discussed additional definitions, including the distinction between relapsed-refractory and primary refractory disease. It was suggested to add a qualifier describing which type of therapy or drug(s) to which the disease was refractory or non-responsive. Efficacy results for Phase III trials should include OS (overall survival), TTP, PFS (progression-free survival), DOR (duration of response), and, if possible, TNT (time to next therapy, defined as time from registration on a trial to the next treatment or death due to any cause, whichever comes first), 5-year OS and 10-year OS.

Guidelines for Risk Stratification in Myeloma

Dr. Nikhil Munshi said that the main purpose of risk stratification at this time should be to update prognostic factors in the era of novel therapies, not to make a decision about treatment. Because there is evidence that risk factors change at relapse, patients can be reassessed, and if they have acquired high risk features, they should be reclassified. He also said that the International Staging System (ISS) needs to be validated for newer agents, and some modifications in the future should be expected.

Although the Durie-Salmon staging system for determining tumor mass is still the standard, it could be replaced by CRAB (calcium elevation, renal insufficiency, anemia, bone lesions) criteria. Using MRI for response evaluation requires further study.

Genomic studies, including gene expression profiling (GEP), single nucleotide polymorphism (SNP) arrays, and comparative genomic hybridization (CGH) have their place in research, but are not sufficiently validated for general clinical use.

Guidelines for Standard Investigative Work-up in Myeloma

Dr. Robert Kyle reviewed the minimum tests required at diagnosis and for prognostic evaluation for patients. These include a history and physical, which should detect any co-morbidities such as heart disease, thrombosis, hypertension, renal, liver, or lung disease, or other conditions that would affect treatment. Blood tests include a complete blood count (CBC), differential, and peripheral smear; chemistry panel with calcium, creatinine, electrolytes, liver function tests, urea, albumin (preferably using nephelometry), serum protein electrophoresis (SPEP), immunofixation electrophoresis (IFE), and serum FLC; and urinalysis, including a 24-hour urine test for protein, creatinine clearance, urinary protein electrophoresis (UPEP), and IFE. Bone marrow aspirates or biopsies are mandatory to confirm a diagnosis of multiple myeloma (>10% clonal plasma cells).

Beta-2-microglobulin is needed to determine the ISS stage, and LDH is also useful for risk assessment. Other useful tests include standard cytogenetic, and FISH on sorted bone marrow plasma cells. Imaging tests include a skeletal survey; MRI of the spine and pelvis are mandatory, particularly to rule out spinal compression. There is no definite role for PET-CT, which may be helpful for extramedullary disease.

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Editor's Note: Lynne Lederman, PhD, is a medical writer based in Mamaroneck, NY. To read the full text of her report, please visit the IMF website at www.myeloma.org.