Scientific & Clinical

Studies presented at ASH may offer new approaches to treating multiple myeloma

By Brian G.M. Durie, MD
Aptium Oncology
Cedars-Sinai Comprehensive Cancer Center, Los Angeles, CA

"This has been one of the most exciting medical meetings for myeloma in recent years. We believe patients with myeloma and related blood cancers will have more treatment options that could lead to a better quality of life."

– Susie Novis, IMF president and co-founder

Introduction

The 51st annual meeting of the American Society of Hematology (ASH) was held December 5 through 8 in New Orleans, LA. This important conference for the hematology community was especially exciting for the myeloma research community. Presentations covered both elderly and younger patients and, for the first time, ASH covered all stages of multiple myeloma. Studies investigated treating the disease in every possible setting, from smoldering (pre-symptomatic) myeloma to long-term continuous therapy with and without stem cell transplants, and onto promising new regimens for patients who no longer respond to existing drugs.

A large number of abstracts, nearly a quarter of the presentations submitted this year to the annual meeting of the American Society of Hematology (ASH), were for multiple myeloma, with one being presented at the prestigious plenary session. This plenary abstract dealt with the role of Velcade® (bortezomib) combinations in the frontline setting, assessing both induction and maintenance in a randomized fashion.

A new aspect of this year's ASH meeting was the focus on treatment or understanding of the disease from its earliest stages on. Below, I will briefly highlight some of the myeloma-related news coming out of the ASH meeting which appeared to generate the most interest and enthusiasm among those present at the meetings. A more detailed report is being prepared by IMF medical writer Lynne Lederman, PhD, which should be available shortly in print and on the IMF website www.myeloma.org. In addition, interviews with 55 major presenters at the ASH meeting are also available on the IMF website www.myeloma.org.

Educational symposia

The IMF's symposium -- the Super Friday Workshop -- took place on December 4. This year, the speakers included S. Vincent Rajkumar (Mayo Clinic, Rochester, MN), Mario Boccadoro (University of Torino, Italy), Philippe Moreau (Nantes, France -leader of the French myeloma study group, IFM), and Robert Orlowski (MD Anderson, Houston, TX). This particular educational session takes a practical approach to the management of myeloma, illustrating for the audience how to integrate the use of the novel agents into the management of myeloma. This is increasingly important as we now have three major novel agents in myeloma -- Thalomid® (thalidomide), Revlimid® (lenalidomide), and Velcade® -- with several promising new agents in the development pipeline. How do practicing clinicians introduce these agents into their day-to-day practice? The Super Friday Workshop reviewed how patients should be diagnosed and staged, the different myeloma prognostic categories, the role of cytogenetics and genetic profiling in identifying the best treatment for patients, the integration of novel agents along with autologous transplant for younger patients, drug combinations, maintenance, and the approach to relapsed/refractory disease.

There was also an important educational session put on by ASH that took place on Saturday afternoon and Sunday morning. Speakers Jesus San Miguel (University of Salamanca, Spain), Antonio Palumbo (University of Torino, Italy), and Keith Stewart (Mayo Clinic, Scottsdale, AZ) talked about the treatment of younger and older patients and relapsed/refractory disease.

The educational symposia at ASH are just as important as the scientific presentations of new study results. The hematologist-oncologist clinicians need guidance on how to best use the novel drugs to treat their myeloma patients. Often, because of time constraints, researchers presenting results from their studies cannot put the data into a comprehensive context. But the clinician needs to know how those results stack up against other results from other studies being presented, or against the results that have already been published. Discussions that look at both the older and the newer results in the context of day-to-day management of patients are a key component of ASH.

Smoldering myeloma

Treating patients before they show any symptoms is controversial, but a study at the University of Salamanca in Spain of Revlimid® in smoldering myeloma is an important first step toward reconsidering how patients are treated at the earliest stages of this cancer. The phase I/II study from Maria-Victoria Mateos, MD, demonstrated for the first time that early intervention treatment before clinical symptoms occur may delay the onset of active myeloma (abstract #614). In the observation-only arm of this randomized study where patients are watched closely but not treated, 50% of patients with high-risk smoldering myeloma progressed to active myeloma in 19 months, including the classic symptoms of bone disease. However, in 45 patients who began and continued active treatment with Revlimid® at this early stage, no disease progression was observed after a

median follow-up of 16 months. It is an innovation to introduce the use of an agent, in this case Revlimid®, at the earliest time point to see if early treatment reduces the complications of myeloma -- such as bone disease and kidney problems -- and improves survival. These are only preliminary data and it will take us some time to see the full impact of this type of early intervention, but obviously it is an exciting new approach.

Ongoing active therapy

A study from Antonio Palumbo, MD, at the University of Torino, Italy, (abstract #613) showed that "ongoing active therapy" may be a new option for patients with myeloma. This is the first study to show benefit from continuing treatment as long as the patient continues to respond, and it may be a first step toward revising current standards of care. The three-arm study compared patients treated with a standard combination of melphalan-prednisone (MP), to patients treated with melphalan-prednisone plus Revlimid® (MPR) who remained on ongoing active treatment with Revlimid (MPR-R). The interim data analysis focusing upon the comparison of MP versus MPR followed by Revlimid maintenance (MPR-R) presented at ASH demonstrated a 77% overall response rate for MPR-R, and a 50% reduction in risk of disease progression, versus patients treated with limited duration MP. This is the highest risk reduction reported for any phase III study in this patient group. The presentation concluded, "MPR-R (ongoing active therapy) can be considered a new standard of treatment for elderly patients." These interim results are extremely encouraging, and we certainly look forward to further analyses at the next medical meeting as the trial progresses to assess the full value of this new regimen.

Velcade combinations

Of further note, a whole series of studies presented at ASH this year indicated benefits using a wide range of Velcade® combinations. These included three-drug combinations such as Velcade®–Revlimid®-dexamethasone, Velcade®-cyclophosphamide- dexamethasone, Velcade®-thalidomide-dexamethasone, and the four-drug combination Velcade®-Cytoxan®-Revlimid®-low-dose dexamethasone ("Evolution" trial). The longer-term follow-up of the Velcade®-melphalan-prednisone combination ("VISTA" trial) was also presented and continued to show an overall survival benefit. We thus now have several very active Velcade® combination protocols. The next step is to sort through these combinations to determine which will confer the most benefit in the short-term and ultimately in terms of long-term survival. An additional aspect discussed was the use of Velcade® in a once weekly schedule, which showed promise in terms of both equivalent efficacy and reduced neurotoxicity. This approach resulted in quite a bit of discussion among attendees.

Pipeline drugs and combinations

We have come a long way in treating myeloma, but a study from the IMF's International Myeloma

Working Group (IMWG) looks at what happens when patients no longer respond to the available treatments. This makes a powerful case for continuing innovation in treatment development, while it gives us an important benchmark we can use to evaluate new drugs as they come along (abstract #2878).

Some of the most exciting ASH presentations for the future treatment of myeloma are the results of studies of new drugs. Carfilzomib (a new proteasome inhibitor), pomalidomide (the third generation IMID, after thalidomide and lenalidomide), elotuzimab (with lenalidamide) and vorinostat (which can enhance the efficacy of both lenalidomide and bortezomib) are showing efficacy in the treatment-resistant patient population. These new drugs are being studied as single agents, with steroids, as well as in combinations that include existing drugs such as Velcade and Revlimid. There are indications that patients will respond to the new drugs even when they no longer respond to other drugs in the same class (abstracts #301-306, #429, #430).

Novel combinations versus transplant

A study which caught attention was the randomized study comparing MPR versus high-dose melphalan with autologous stem cell transplant. These results demonstrated that oral drugs in the MPR arm had a 91% progression-free survival at 12 months, identical to that seen in the transplant arm of the study. This raises the possibility that at some point novel combinations could substitute for autologous stem cell transplant in the myeloma treatment paradigm. Obviously further follow-up and additional studies are required to evaluate this type of approach.

Side effects and predicting outcome

Studies from the IMWG and the IMF gene bank, Bank On A Cure®, suggest a combination of chromosome abnormalities coupled with stage of the disease are a better predictor of outcome when evaluated together than either factor alone (abstract #743). A second study finds specific genetic changes may be responsible for side effects of treatment such as neuropathy, making it possible to build a data base that anticipates adverse events (abstract #1800). Another interesting presentation showed that kidney toxicity, which is important in myeloma, can be reversed with the use of Revlimid® and dexamethasone. There were also a number of presentations on new supportive care drugs, including a new type of drug for the treatment of bone disease, ACE-011, which has a unique mechanism of action in enhancing bone repair.

Myeloma setting the stage for new treatments for other cancers

What is happening in myeloma research is feeding into developments in other areas of hematologic malignancy. Multiple myeloma has been setting the stage for new treatments for a range of cancers, and several presentations at ASH highlighted this fact. Revlimid®, developed for use in myeloma and also approved for use in myelodysplastic syndromes (MDS), is now the subject of Phase III

studies in a variety of cancers including diffuse large B-cell lymphoma, chronic lymphocytic leukemia, and pivotal studies in mantle cell lymphoma (abstracts #206, #944, #1676, #1679). Likewise, Velcade® is approved in mantle cell lymphoma and is also the subject of Phase II studies in follicular lymphoma (abstracts #933, #1661). The results achieved in myeloma are stimulating broader interest and serving as a model in hematologic malignancies overall.

Conclusion

I hope that this brief overview gives you a flavor of what is coming out of ASH. While myeloma cannot be cured at present, using new therapies in combination and in sequence can provide the potential for long-term remissions with a good quality of life for patients. MT

出典：「Myeloma Today」FALL/WINTER 2009/2010, Volume 8, Number 1: Page5
http://myeloma.org/pdfs/MT801_b4.pdf