



*Accelerating
the
Search
for a
Cure*

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MYELOMA FOCUS

Newsletter of the
MMRF

SPECIAL EDITION MMRF REPORTS FROM **The American Society of Hematology (ASH) Meeting in Orlando**

The Multiple Myeloma Research Foundation (MMRF) is proud to present this special edition newsletter. Events covered in this newsletter include the 43rd Annual Meeting of American Society of Hematology (ASH) and an educational symposium, *Advances in Multiple Myeloma: Pathogenesis to Treatment*, sponsored by the Strategic Institute for Continuing Health Care Education and supported by the MMRF. ASH and the symposium were held December 7-11 in Orlando, Florida.



This issue presents the following information:

- b New insights into myeloma staging and profiling
- b The latest information on current therapies
- b An update on novel therapies being evaluated in Phase I-III clinical trials, including the promising preliminary results of clinical trials of the proteasome inhibitor PS-341 and the immunomodulatory drug Revimid™
- b Emerging therapies in preclinical testing in the laboratory
- b The status of transplantation in myeloma

This is truly an exciting time in myeloma research. The MMRF is proud to be a sponsor of the most cutting-edge research projects, and is recognized world-wide for contributing to these positive developments.

**–Scott Santarella
Executive Director, MMRF**

Special Thanks to Our Guest Editors

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STAGING AND PROFILING

Staging and Prognostic Factors

Researchers continue to try to identify patient characteristics that can help stage myeloma and determine prognosis, yet be easy to measure in clinical practice. For example, the Southwest Oncology Group (SWOG) developed a staging scheme based on data from four recent myeloma trials. The simple system is based on beta-2 microglobulin (B2M) and albumin levels (see table below). The utility of such new systems will have to be confirmed.

Proposed SWOG Myeloma Staging System		
Stage	B2M($\mu\text{g/mL}$)	Albumin(g/dL)
I	<2.5	≥ 3
II	2.5 - 5.4	≥ 3
III	≥ 5.5	≥ 3
IV	> 5.5	<3

Chromosomal abnormalities, such as deletion of chromosome 13 and various translocations ("swapping" of chromosome segments), when looked at individually or in combination, were reported to provide prognostic information. Several studies showed that both conventional cytogenetic analysis (karyotyping) and the newer FISH technique are important complementary tools in chromosome analysis. The expression of certain genes associated with cancer (oncogenes) also appears to provide important information. An example is the expression of a certain variant of an oncogene known as RHAMM, which appears to be predictive of aggressive myeloma, whereas the loss of the p53 oncogene is associated with a poor prognosis.



Chromosome abnormalities are identifying distinct new disease entities.

– Dr. Bergsagel

Genetic Profiling

Genetic profiling is becoming an invaluable tool in our arsenal for our fight against myeloma.

– Dr. Shaughnessy



Genetic profiling, the process of looking at the expression patterns of large numbers of genes, is becoming an invaluable tool in our fight against myeloma. By comparing gene "profiles" of myeloma cells with normal plasma cells, the specific genes involved in the disease process can be pinpointed. A number of investigators presented data from several avenues of genetic research currently underway. According to John Shaughnessy, Jr., PhD (University of Arkansas), there are four ultimate goals for using gene analysis in myeloma:

1. Differentiate between normal and malignant plasma cells
2. Identify distinct genes whose "pattern" can be used to diagnose myeloma
3. Identify distinct genes whose "pattern" can be used to stage disease and predict prognosis (outcome)
4. Identify new drugs that can target the specific genetic defects in myeloma

We appear to be well on our way to achieving several of these goals. Dr. Shaughnessy and his colleagues have identified 14 genes that can discriminate between normal and myeloma cells and 24 genes that can stage myeloma and provide prognostic information. Other groups have identified specific genes that appear to be involved in the malignant transformation of plasma cells into myeloma cells.

Genetic profiling is beginning to be incorporated into clinical trials to better characterize genes that may affect response to therapy and serial analysis is being used to identify genes associated with development of drug resistance. Genetic profiling will ultimately lead to individualized treatment regimens. According to Dr. Shaughnessy, it will be like going to a "molecular medicine cabinet" -- drugs will be chosen based on a patient's genetic profile.



CURRENT THERAPIES

Thalidomide

Studies continue to confirm the efficacy of thalidomide in refractory and relapsed disease, with about a third of patients achieving durable responses. The optimal dosing of thalidomide in this patient population has not yet been defined (see box below). Adding dexamethasone to thalidomide therapy appears to increase its efficacy in refractory and relapsed disease. Ongoing study will help determine optimal use of this agent.

Thalidomide Dosing

Usual starting dose: 200 mg/day

Average dose in most studies: 200-400 mg/day

Higher doses (>200 mg/day): may be associated with higher response rates and longer survival; greater toxicity

Lower doses (\leq 200 mg/day): may be effective in earlier stages of the disease, in various subsets of patients, and in combination with other agents

In addition to its use in advanced disease, thalidomide is rapidly moving toward first-line therapy in newly diagnosed patients. Dr. S. Vincent Rajkumar (Mayo Clinic) presented data showing that the combination of thalidomide and dexamethasone is an effective first-line therapy. It can potentially be used in place of VAD (intravenous vincristine, adriamycin, and dexamethasone), the current standard induction therapy for myeloma, prior to stem cell transplant. In a study of 50 newly diag-

Thalidomide is moving along as a critical player in the up front management of myeloma.

– Dr. Barlogie



nosed patients, 32 (64%) of the patients responded to thalidomide (200 mg/day) and 26 patients went on to receive stem cell transplants. The ongoing Total Therapy II trial, which will include a total of 660 newly diagnosed patients, will provide important information regarding efficacy of thalidomide as induction therapy prior to transplant.

Although the incidence of reported side effects with thalidomide has remained fairly stable with more widespread use, one concern has been reports of deep venous thrombosis (DVT).

DVT is the development of blood clots in veins deep below the skin surface. Although it is a common occurrence in myeloma disease, certain risk factors and drug regimens -- particularly those that include adriamycin -- can increase the possibility of DVT. This risk can be reduced in patients receiving thalidomide with the use of anticoagulants, which prevent blood clotting, and by avoiding adriamycin.

Myeloma Bone Disease

Bisphosphonates play a major role in supportive care in myeloma. The potent bisphosphonate zoledronic acid (Zometa®, Novartis), which is under FDA review for use in the treatment of bone complications in myeloma, inhibited the development of bone lesions in a mouse model of the disease. It also exhibited an anti-myeloma effect and increased disease-free survival. Data also show that zoledronic acid, which is administered as a 15-minute infusion, is safe for use in cancer patients with bone metastases who have mild or moderate impairment of their kidney function.



The hope is that now we can develop zoledronic acid not only as an effective agent to prevent skeletal problems, but also as a new anti-myeloma agent.

– Dr. Berenson

NOVEL THERAPIES

Many will agree that we have reached a new treatment paradigm in myeloma. There is growing evidence that agents that target both the myeloma cell and its "neighborhood" -- the bone marrow -- are highly effective therapies. This section summarizes the key results of several clinical trials of novel therapies.

Proteasome Inhibitors

Proteasome inhibitors (PIs) inhibit the growth of tumor cells and induce programmed cell death (apoptosis). PS-341 (also known as LDP-341, Millennium) is the first PI to enter the clinic. A recent Phase I trial of PS-341 showed some notable responses to the drug. Promising preliminary data from a multicenter Phase II trial in relapsed and refractory myeloma reported by Paul Richardson, MD (Dana-Farber) generated much excitement.

Two hundred patients were enrolled in the trial. Patients received PS-341 intravenously twice a week for 2 weeks, followed by one week off (1 cycle). The cycle could be repeated up to eight times and dexamethasone could be added if there was a low response.

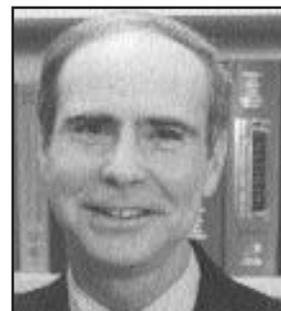
Preliminary reductions in M protein for the first 54 of the 200 patients treated with PS-341 alone are shown in the table below. Altogether, 52% of patients responded according to standard criteria and 33% had stable disease after two cycles of therapy. Responses were rapid and appeared to be independent of the number of prior therapies and baseline beta-2 microglobulin levels.

The safety and efficacy data from this study continue to be collected and analyzed, and Phase II trials in patients in first relapse are ongoing. Trials will soon begin adding PS-341 to low doses of chemotherapy based on preclinical findings that this combination is more effective than either alone

IMiDs™

Immunomodulatory drugs (IMiDs, Celgene) are derivatives of thalidomide that are 1000 to 5000 times more potent in the laboratory. They have anti-myeloma activity and anti-angiogenic effects with a better side effect profile than thalidomide. The IMiD known as CC-5013 (Revimid™) is a once-a-day oral agent. Results of two Phase I/II studies

The treatment of myeloma is at a new threshold... We now have at least two new drugs – the IMiDs and PS-341 – that have disease activity where no other drugs have previously.



– Dr. Anderson

of Revimid in patients with relapsed and refractory myeloma show that the agent has significant anti-myeloma activity.

Preliminary data on 24 of the 27 patients enrolled in a study at Dana-Farber who received Revimid at doses of 5 to 50 mg/day for at least a month are shown in the table below.

Altogether, 19 of 24 patients (79%) of patients had stable disease or better and 63% of patients had a ≥25% reduction in M protein.

Preliminary M Protein Reductions After Two Cycles of PS-341		
Result	Decrease in M Protein	Percentage of Patients
Reduction in M Protein	≥90%	11%
	75% - 89%	6%
	50% - 74%	24%
	25% - 49%	11%
Stable Disease	<25%	33%
Progressive Disease	none	15%

Revimid Study at Dana-Farber: Reduction in M Protein Levels				
Dose	# Patients	≤25	25% - 49%	≥50%
5	3	0	2	1
10	5	0	0	1
25	3	1	2	0
50	13	3	5	4
All patients	24	4 (17%)	9 (37%)	6 (25%)

NOVEL THERAPIES cont.

The Revimid study at Arkansas included 15 patients and showed similar results. Eight patients experienced a >25% reduction in M protein and one patient achieved a complete response. The drug was well tolerated with a manageable side effect profile, which included some instances of reduced blood cell counts at higher doses. Data from these studies continue to be analyzed and longer term follow-up will be necessary.

Arsenic Trioxide

Arsenic trioxide (ATO) acts in a variety of ways to induce apoptosis, inhibit angiogenesis, and stimulate the immune system. Several presentations detailed these mechanisms of action and preliminary trial results were reported for this intravenous agent.

A phase II trial of ATO is being conducted at the Cleveland Clinic in patients with relapsed and refractory disease that involves higher, less frequent dosing of

the drug. Preliminary results showed some responses in about a third of the patients treated but reductions in M protein were lower than 50%. Combining ATO with ascorbic acid (vitamin C) appears to protect the drug, increasing its efficacy and lowering its toxicity. A Phase I/II study of the combination is being conducted at the University of Miami and involves six patients with refractory disease. Early results using lower, more frequent dosing suggest that similar percentages of patients respond to the combination but the degree of the response may be improved over ATO alone. These findings point to the rationale for testing ATO as part of combination therapy with agents such as thalidomide, chemotherapy, and dexamethasone, as well as other dosing schedules.

Bcl-2 Antisense

The Bcl-2 protein is a critical factor in resistance to therapy in myeloma and is a key target for new therapeutic strategies.

Bcl-2 antisense therapy (Genasense™, Genta) displays both anti-angiogenic and anti-myeloma activity and reverses drug resistance.

Osteoprotegerin (OPG)

Bone loss occurs in myeloma as a result of excessive stimulation of bone-destroying cells known as osteoclasts. Researchers have found that the body normally produces a substance known as osteoprotegerin (OPG) that interrupts this stimulatory process and serves to keep bone destruction in check. An engineered version of OPG (AMGN-0007, Amgen) shows promising early clinical results.

Other novel therapies continue to be investigated in myeloma. The current status of several novel agents is summarized in the table below.

Novel Therapies in Clinical Trials

Agent	Phase	Description
PS-341 (Millennium)	II	A randomized Phase III trial comparing PS-341 to current therapies should begin by the end of first quarter 2002
CC-5013 (Revimid, Celgene)	II	Studies planned in newly diagnosed patients and relapsed patients, and use as maintenance therapy
Arsenic trioxide (Trisenox™ Cell Therapeutics)	II	Ongoing single-agent and combination trials
Bcl-2 Antisense (Genasense™, Genta)	III	Reverses drug resistance; being tested in combination with dexamethasone in relapsed or refractory disease
AMGN-0007 (Amgen)	I	Engineered OPG being tested in patients with various cancers, including myeloma
2-methoxyestradiol (2ME2) (Panzem, EntreMed)	II	Preclinical data show both direct and indirect anti-myeloma activity; may help overcome drug resistance
AE-941 (Neovastat, Aeterna)	II	Anti-angiogenic agent; trial initiated in patients with refractory or early relapsed disease
rhuMab VEGF (Avastin™, [Bevacizumab], Genentech)	II	Anti-angiogenic agent -- a monoclonal antibody directed against vascular endothelial growth factor (VEGF)

EMERGING THERAPIES

IN PRECLINICAL TESTING

Results from early studies of a number of new agents being investigated in the laboratory were reported at the meeting. The table below lists some of the most promising agents. These preliminary findings set the stage for future clinical trials.

Agent	Description
β -Lapachone	This plant-derived product has a variety of direct and indirect anti-myeloma effects, including activity against drug-resistant cell lines.
PTK-787 (Novartis)	This agent, which inhibits cell signaling pathways involved in angiogenesis, demonstrated anti-myeloma and anti-angiogenic activity in the lab.
Thiazolidinediones	Certain agents in this class of diabetes drugs prevent growth and induce apoptosis of myeloma cell lines and patient cells. Upcoming clinical trials are planned.
TRAIL (Apo2L, Genentech)	TRAIL is a marker found on the surface of various immune cells that plays a role in tumor cell killing. A soluble form of TRAIL triggers apoptosis of drug-resistant myeloma cell lines and patient cells. Phase I trials are expected soon.
B Lymphocyte Stimulator (BLyS™, Human Genome Sciences)	BLyS is a naturally occurring protein that binds to and regulates the development of B cells; radiolabeled BLyS, which targets myeloma cells and certain B cell cancers is being investigated as a treatment for these disorders.

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UPDATE ON TRANSPLANTATION

Single versus Double Autologous Transplants?

High-dose therapy with autologous stem cell transplant (HDT/SCT) has increasingly been used in the treatment of myeloma because of the increased numbers of complete responses achieved with this approach. Double (tandem) autologous transplants evolved as a potential means to increase the response rates achieved with single transplants, but the question remains as to whether this technique is superior to single transplants. The French IFM 94 trial had shown superior event-free and overall survival with double transplants over single transplants at the 5-year follow-up, although there was no significant difference in complete response rates between the two groups. However, other recent trials comparing single versus double transplants (ie, the French MAG95 and the Dutch HOVON study) have shown no difference in survival or only marginal benefit of double over single transplants. For example, in the French MAG95 study, no significant difference was noted at 40 months.

Other potential ways to improve the results of HDT/SCT include the use of various conditioning chemotherapy and maintenance regimens, including the addition of thalidomide or newer agents. The best conditioning regimen is currently high-dose melphalan (200 mg/m² IV). The use of melphalan and a therapeutic radioisotope linked to a compound that binds to bone (153-Samarium EDTMP, Berlex) as a conditioning regimen appears promising. Although purging stem cell transplants of tumor cells has been identified as a potential means of improving outcome, three randomized studies have shown no survival advantage of purging the graft with CD34 selection.

survival at 1 year. The study, conducted at the Fred Hutchinson Cancer Research Center, showed that the mini-transplant improved on the responses achieved with autologous transplants alone. The regimen is feasible in older patients up to 70 years of age, who are more representative of the myeloma population.



Mini-Transplants Promising

A mini (non-myeloablative) transplant is a promising treatment offering the anti-myeloma benefits of allogeneic transplants with fewer side effects. A pilot study of 41 patients receiving a tandem transplant -- an autologous followed by a mini-transplant -- showed high response rates (see table below) and 85% overall

The future of autologous transplants is not in further intensifying the treatment, but in maintaining remission with use of newer drugs.

– Dr. Harousseau

Tandem Autologous/Mini-Transplants Improve Response Rates

Disease Activity At Study Entry (# patients)	Response Post-mini-transplant (# patients)
6 CR	6 CR
15 PR	9 CR, 5 PR, 1 SD
20 relapsed/refractory/SD	10 CR, 6 PR, 1 SD, 2 PD

CR=Complete response; PR=Partial response; SD=stable disease; PD=progressive disease

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