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Myeloma Today

A Publication of the International Myeloma Foundation

Highlights

Dear Reader,

Here we are in what are supposed to be the dog days of summer, the month of August. It's the time of year when people are on vacation and not much is happening except hot sticky weather. But here at the IMF, a lot of activity is taking place this month.

On August 10, the IMF clinical conference – Challenging Cases in Multiple Myeloma & Related Plasma Cell Disorders – was held in New York City. The IMF partnered with Network for Oncology Communication & Research (NOCR) to present this exciting and interactive program, which was made possible by sponsorship from Novartis, Celgene, Millennium, CTI, and NeoRx.

This invitation-only meeting was open only to hematologists and oncologists from across the country who treat myeloma. They were presented with 10 case studies of actual patients and had the unique opportunity to share their thoughts on how they would treat each case and to debate particular treatment recommendations of the panel of myeloma experts that included Chairman, Dr. Brian Durie, Dr. Raymond Alexanian, Dr. Bart Barlogie, Dr. Bill Bensinger, Dr. Robert Kyle, and Dr. Vincent Rajkumar. The program format made for a very lively and stimulating meeting.

On August 15, Dr. Durie and I traveled to Toronto for a meeting with the local myeloma support group. This was our second visit with the group and, once again,

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PS-341: The Patient Experience*

Over the past year, there has been great excitement among callers to the IMF Hotline and postings on the internet list serve about the new drug VELCADE™ (Millennium Pharmaceuticals). It was decided that it would be of great interest to interview participants in the recent phase II trials to give readers a better direct knowledge of the impact of VELCADE™ therapy in patients with relapsing/refractory myeloma.

**Compiled by Dr. Brian G.M. Durie from patient interviews*

Alta Bates Cancer Center in Berkeley, California, and the team of doctors, nurses, and coordinators in the clinical trials group were major contributors to the phase II experience with PS-341 (now known as VELCADE™) in multiple myeloma. Patients relapsing and refractory to prior therapy were entered into the Millennium-sponsored phase II multi-center study, which accrued 201 patients.

Because of early evidence of benefit in the phase I study conducted at the University of North Carolina at Chapel Hill, there was tremendous interest and excitement among patients. The stories of 3 patients highlight the impact for patients typically in desperate need of a new treatment that will work well without too much toxicity.

SP, a retired 50 year-old African-American lady, was one such patient. Diagnosed in 1998, she had previously had a stem cell transplant with remission that lasted for about a year. When the myeloma grew back so soon, she was keen to try something new and different. So 6 months ago, treatment started with the PS-341 being administered intravenously over 3-5 seconds, twice/week for 2 weeks, followed by a 10 day rest period in each cycle. In her case, dexamethasone was added eventually to the PS-341 treatment. After 2-3 months she was responding well and has achieved an excellent remission. Her bone pain was much improved, anemia better, and myeloma protein level substantially reduced. A follow up bone marrow test showed complete remission. She is clearly a believer that PS-341

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The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure.

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PS-341 – continued

works. In her case, she had not taken thalidomide in the past, so she did not have neuropathy to contend with. There has been only slight tingling in her toes. Her main complaint was she got extremely bored, sitting around all the time, waiting for follow-up testing, and the like. She strongly recommends that anyone considering new treatment look into possible PS-341 protocols in their area.

RA is a 72 year-old retired real estate agent first diagnosed in June 1999. His initial therapy was melphalan/prednisone plus radiation treatment to an area of bone disease. Because of his age, it was felt that he was not an ideal candidate for stem cell transplant. So when he was not responding well, alternate therapy was sought. Starting in 2001, it has now been over a year since the first dose of PS-341. He tolerated it well and like SB has had an excellent response. Follow-up bone marrow showed dramatic improvement. No added dexamethasone was needed in his case. He did develop some neuropathy in his feet and takes neurontin for that. The problem with his feet consisted of what felt like "electric shocks" plus some numbness in between. He received a total of 5 cycles of PS-341 and has been followed on pamidronate (Aredia®) treatment alone since then. The treatment course was complicated by an episode of pneumonia, as well as a strange, unexplained episode when he unexpectedly fell out of a chair. But now he is active and doing very well. His very good response also makes him a strong advocate for VELCADE™ for any other patients in need of new treatment. He is particularly pleased that he continues to be in remission, without any additional therapy.

CB is a 69 year-old retired computer operator diagnosed in 1995. She had multiple therapies over the years, including VAD and other types of chemotherapy. She had also been on the Dendreon vaccine clinical trial, which was not helpful in her case. Unfortunately, her treatment is complicated by her diabetes. Prior to the PS-341 she was taking thalidomide (Thalomid™) 400mg a day and "felt like a zombie." In May 2001, she enrolled in a trial with PS-341 on the recommendation of Dr. Jeffrey Wolf. She was very excited to have a chance to "get into the new trial." When research coordinator Beth Davis told her that the next patient number in the protocol was 13, she knew it would be lucky 13 for her! After one month she was already responding very well. No additional dexamethasone was needed. Her main problem was the worsening of the neuropathy, which she had because of the prior thalidomide. The bone pain, anemia, and myeloma protein levels all improved. After 6 cycles of treatment, bone marrow testing showed complete remission. Since then, she has continued on Aredia maintenance. Currently, she is back to normal mentally, but physically she is upset because she just can't get rid of the neuropathy caused by the thalidomide. The important fact is that her remission continues, and that makes her happy.

These three patient experiences highlight participation in a Millennium sponsored PS-341 phase II clinical trials. It is important to note that not all patients responded. Preliminary analysis indicated that around 10% of patients in the first cohort were complete responders with another 30-40% of patients achieved good partial responses. Other patients have noted additional side effects including some fatigue, especially with an increased number of cycles of PS-341. Mild diarrhea and some reduction in blood counts including anemia and reduced platelet count levels have occurred. The opportunity to have access to PS-341 was welcomed by patients all needing "something to really work" to "get the myeloma into remission." There is no doubt that already PS-134 has been a success for the responding patients. How long will their remissions last? We don't know. However, we know that several patients in the meantime have relapsed and needed alternate therapy. Only time will tell what the average length of remission will be. Looking to the future there is great excitement that up front use of PS-341 can provide a greater benefit. Patients who have not had thalidomide can hopefully avoid the neuropathy. Combinations with other drugs, including the thalidomide analog Revimid™, which is <u>not</u> neurotoxic and/or melphalan, can potentially give added benefit. At this point, the outlook is promising in a disease, for which until recently there were so few drugs that could really make a difference.

Neuropathy and Monoclonal Gammopathy

By Norman Latov, M.D., Ph.D.

Introduction

Peripheral neuropathy causes numbness, pain, weakness in the arms and legs, with incoordination and difficulty walking. The neuropathy can be severe and sometimes debilitating. The causes of neuropathy are diverse, but approximately 10% of patients with neuropathy of otherwise unknown etiology also have a monoclonal gammopathy, which can be non-malignant or associated with myeloma or Waldenstrom's macroglobulinemia. Several different syndromes can be recognized based on the type of monoclonal gammopathy and neuropathy. In evaluating the neuropathy, the physician typically performs Electromyography and nerve conduction studies which measure the electrical properties of the nerves, and draws numerous blood studies to make sure that the neuropathy is related to the monoclonal gammopathy rather than to another cause. A nerve biopsy may also be needed to elucidate the pathophysiology in some cases.

Neuropathy Syndromes Associated with IgM Monoclonal Gammopathies

Sixty to seventy percent of the IgM monoclonal gammopathies that are associated with neuropathy have antibody activity to sugar-like molecules, called oligosaccharides, that are attached to fatty molecules (glycolipids) or proteins (glycoproteins), that are concentrated in the peripheral nerves. The neuropathy is these cases is thought to be caused by the antibodies attacking the peripheral nerves. The most common antibody, which is found in approximately 50% of patients, is the MAG (myelin associated glycoprotein) antibody, which is associated with demyelinating neuropathy. Other antibodies include: a) GD1b and disialosyl ganglioside antibodies, GM1 ganglioside antibodies, GD1a ganglioside antibodies, sulfatide antibodies, and GM2 ganglioside antibodies. These can be tested for by the physician. In addition, some of the monoclonal gammopathies, called cryoglobulins, can precipitate in the cold and damage the blood vessels in the nerves. In the malignant monoclonal gammopathies, the malignant cells can invade the peripheral nerves (lymphomatosis) and cause neuropathy.

Therapy is directed toward reducing the IgM concentration. The response varies between patients, depending on the degree of reduction, the type of neuropathy, and the damage already present. In general, it is easier to prevent progression than recover function, so early intervention is preferred. Several chemotherapeutic agents have been reported to be beneficial, including chlorambucil, fludarabine, and cladrabine. In less severe cases, rituximab (Rituxan™), a humanized, recombinant monoclonal CD20 antibody directed at B cells, can result in a gradual reduction of IgM concentration and clinical improvement. The combination of fludarabine and Rituxan™ is more effective than either one alone. Intravenous gammaglobulins or plasmapheresis are beneficial in some, but not most patients.

Neuropathy Syndromes Associated with IgG or IgA Monoclonal Gammopathies

Neuropathy is associated with IgG or IgA monoclonal gammopathies in the osteosclerotic forms of myeloma, with amyloidosis, and in the POEMS syndrome where patients have polyneuropathy in addition to organomegaly, endocrinopathy, myeloma, and skin changes. Osteosclerotic myeloma constitutes approximately 3% of myelomas, but 50% of these have peripheral neuropathy. Patients with the POEMS syndrome, as well as with others myelomas, have been reported to exhibit highly elevated titers of vascular endothelial growth factor (VEGF). In primary amyloidosis, the amyloid deposits consist of fragments of monoclonal antibody light chains that can be detected in the urine as Bence Jones protein.

Treatment for myeloma-related neuropathy is directed at the underlying myeloma using melphalan and prednisone. Eradication of solitary plasmacytoma by irradiation or surgery can sometimes be curative, with substantial improvement in the neuropathy. High dose chemotherapy with stem cell transplantation may be helpful in some patients with widespread myeloma. Thalidomide, which is sometimes used to treat myeloma, can also cause neuropathy as a side effect, aggravating the condition.

Treating the Symptoms of Neuropathy, Self Help, and Education

Aside from treating the underlying cause for the neuropathy, or the monoclonal gammopathy, therapy is directed at alleviating the symptoms and helping cope. Neuropathic pain, which can be debilitating, can be treated with tricyclics such as Amitriptyline or Nortriptyline, anti-seizure agents such as Gabapentine, or opioids. Physical and occupational therapy can also help patients increase strength, walk better, and do more with their hands. Sharing information and experiences with other patients that have neuropathy helps people cope, both emotionally and in practical matters. More information about neuropathy can be obtained from The Neuropathy Association at *www.neuropathy.org*.

Dr. Latov is currently Professor of Neurology and Neuroscience, and Director of the Peripheral Neuropathy Center at the Weill Medical College of Cornell University. He also serves as Medical and Scientific Director, and founding Board member of The Neuropathy Association. Dr. Latov's clinical and research interests are in the areas of peripheral neuropathy and neuroimmunology, focusing on the mechanisms and treatment of autoimmune neuropathies. His laboratory is credited with discovering antibodies as a cause peripheral neuropathy, and for developing diagnostic tests that are widely used in the evaluation and management of patients with neuropathy. He has lectured widely, and has over 200 publications, including research articles, reviews, editorials, chapters, and books.

Classification of Neuropathic Syndromes Associated with Monoclonal Gammopathies

Neuropathies associated with IgM monoclonal gammopathy:

- Demyelinating neuropathy associated with IgM MAG antibodies
- Motor neuropathy associated with IgM GM1 or GD1a ganglioside antibodies
- Ataxic neuropathy associated with IgM GD1b or disialosyl ganglioside antibodies
- Sensory neuropathy associated with anti-sulfatide antibodies
- Neuropathy associated with IgM GM2 ganglioside antibodies
- Neurolymphomatosis
- Cryoglobulinemia

Neuropathies associated with IgG or IgA monoclonal gammopathy:

- Neuropathy associated with osteosclerotic myeloma
- POEMS syndrome
- Chronic axonal neuropathies
- Amyloid neuropathy

IMF WORLD EVENTS

Joerg Brosig, Ilse Hein, Michael Plankert, Johan Creemers, Prof. Heinz Ludwig, Dr. Sabine Schock, Dr. Janischewski, Ruth Baehler, Susie Novis, and Volker Filipp

VIENNA, AUSTRIA

On April 27 and 28, 2002, the IMF held its 3rd Patient & Family Seminar in Vienna, Austria. The meeting was once again chaired and organized by IMF Scientific Advisor, Prof. Heinz Ludwig. The seminar began with welcome addresses from Prof. Ludwig, IMF President Susie Novis, and Jorg Brosig, who was representing the APMM Support Group from Nordrhein-Westfalen, Germany. We were honored to have a distinguished faculty for this meeting, which included Dr. Johannes Drach, Dr. Brian Durie, Dr. Hermann Einsele, Dr. Hartmut Goldschmidt, Prof. Heinz Ludwig, Dr. Johannes Meran, Dr. Kathrin Strasser, Jutta Hellan and Birgit Suszdorf. The two day seminar format allowed the attendees to hear lectures and participate in discussions covering a broad range of topics, including myeloma for beginners, conventional chemotherapy, auto and allo transplantation, supportive therapies, treatment possibilities after relapse, myeloma bone disease, biologic and genetic factors, novel therapies and new technologies, treatment for fatigue, as well as complementary medicine and the art of living.

At the seminar, representatives from many of the myeloma support groups in Germany, Belgium, Austria, and Switzerland were recognized for their outstanding work in reaching out to members of the myeloma community. The IMF congratulates these groups and applauds their hard work and dedication. They inspire us all and remind us how important it is to help make a world of difference for patients and their families.

TOKYO, JAPAN

The IMF was pleased to welcome IMF (Japan) member Masahiro Namai to our Los Angeles headquarters. We had the pleasure of meeting Mr. Namai in November 2000 at the first IMF (Japan) Patient & Family Seminar. His visit to the headquarters allowed us to exchange ideas and to explore ways in which we can continue to work together in the future. Mr. Namai also attended a meeting of the Los Angeles Support Group. On June 15, he accompanied the group's invited speaker, Dr. Brian G.M. Durie, Susie Novis, and IMF staffer Tanisha Hall to the meeting. Los Angeles Support Group leader, Janet Johnson, invited Mr. Namai to say a few words to the group. His emotional message reinforced the IMF's committment to reach out to people, no matter where in the world they live, to offer support and let them know that they are not alone in their battle with myeloma.

For many years, IMF (Japan) founder Aki Horinouchi was the driving force behind the organization. He inspired IMF (Japan) members to support myeloma research and raised funding to benefit a research grant. Aki also had a dream to hold a Patient & Family Seminar in Japan. Tragically, Aki died just before he saw his dream become a reality in November 2000. However, IMF (Japan) has picked up where Aki left off, and today keeps his vision and spirit alive. In December 2001, the IMF was proud to award the grant sponsored by IMF (Japan) to Dr. Masahiro Abe of the University of Tokushima School of Medicine. An award was presented in memory of Aki to his wife Midori along with the IMF Outstanding Service Award.

SYDNEY, AUSTRALIA

IMF Scientific Advisor, Dr. Douglas Joshua, will be holding the 3rd IMF Patient & Family Seminar in Australia. The IMF is proud to continue its partnership with Dr. Joshua and Novartis Pharmaceuticals in bringing the Patient & Family program to our members in Australasia. The meeting will be held on Friday, September 13, 2002 at the Crown Plaza Hotel, Coogee, NSW. Joining Dr. Joshua and participating as faculty for this meeting are IMF Scientific Advisors and IMF Board members, Dr. Brian Durie and Dr. Greg Mundy. Also participating will be Dr. John Gibson, Dr. Gordon Cook, and Dr. Stuart Dunn. Mr. R. Moran will speak about support groups in Australia.

Skeletal Targeted Radiotherapy in Patients with Multiple Myeloma

What is Skeletal Targeted Radiotherapy?

Skeletal Targeted Radiotherapy (STR) is an experimental therapy that is being developed by NeoRx Corporation for the treatment of patients with multiple myeloma. The scientific name of the drug is ^{166}Ho-DOTMP.

How does STR work?

There are two important components of ^{166}Ho-DOTMP. The first is DOTMP, a chemical that collects in bones. The other is ^{166}Ho, a radioactive holmium particle that is bound to the DOTMP. Certain types of cells in the body, such as many cancer cells, are sensitive to radioactivity and can be killed if they are close to a radioactive particle such as ^{166}Ho. These properties make ^{166}Ho-DOTMP a potentially useful drug for the treatment of cancers in the bone. When the drug collects in the bone, it will expose cells there to ^{166}Ho, killing cancer cells.

What diseases can be treated with STR?

Right now, clinical trials are being done to test whether STR is a useful treatment for myeloma. The cancer cells in myeloma are often found in the bone or bone marrow, and are sensitive to radiation, so STR might be able to kill the cancer cells. In the future, it is possible that STR could be used for other types of cancer that are found in bone, such as Ewing's sarcoma or osteosarcoma.

What are the steps of treatment with STR?

First, a tracer is given to be sure that enough ^{166}Ho-DOTMP goes to the bone in each patient. To test this, a small dose of ^{166}Ho-DOTMP is injected into the patient, and tests are done to show where the ^{166}Ho ends up. After this step, patients are treated with a larger dose of STR, and with melphalan, a drug often used in treating myeloma. The combination of ^{166}Ho-DOTMP and melphalan will hopefully kill cancer cells, but will also kill other bone marrow cells. Because of this, patients who receive STR in clinical trials will receive a stem cell transplant to replace their bone marrow cells. After treatment, the patients will be carefully monitored for side effects and to see how their cancer responds.

Have other patients been treated with STR?

Yes. 83 patients were treated with STR in two clinical trials performed by NeoRx. 64% of these patients had reduced cancer after the treatment, and 35% of them had no detectable disease for at least a while after treatment. The improvements lasted different lengths of time in different people.

What are the risks and side effects of STR?

In the clinical trials performed by NeoRx, some people experienced bladder problems. Almost all of the patients who experienced these problems did not have a procedure called "continuous bladder irrigation," that helps flush extra radioactivity from the body. All patients who are treated with STR will now get continuous bladder irrigation. Some patients also experienced kidney problems. Most of the kidney problems happened at the highest doses of STR, and these high doses will not be used anymore. Still, STR is an experimental drug and other unexpected side effects could occur. Other side effects, such as nausea and vomiting, could also occur. If you decide to participate in a trial of STR, you will be completely informed of up-to-date information on side effects.

By Richard G. Ghalie, M.D.

Multiple myeloma is a radiosensitive malignancy, but current methods of delivering large-field radiation, such as total body irradiation (TBI), can result in high exposure to non-target organs that may limit the ability to deliver an effective dose. ^{166}Ho-DOTMP is a bone-seeking tetraphosphonate agent chelated to a beta-emitting radioisotope that demonstrates general skeletal uptake, enhanced uptake in areas of active bone turnover, and no uptake in non-skeletal tissues. ^{166}Ho-DOTMP thus has the potential to deliver large doses of radiation to the bone surfaces and marrow, and may be an effective component of conditioning regimens for transplant for myeloma.

^{166}Ho-DOTMP has been evaluated in both preclinical experiments and in clinical studies. Preclinical studies demonstrated the rapid renal clearance of ^{166}Ho-DOTMP and high efficacy uptake into the skeleton. A Phase I study in 9 patients with myeloma was performed at the MD Anderson Cancer Center. Patients were treated with a calculated dose to the red bone marrow of up to 50 Gy, followed by autologous marrow or blood stem cell transplantation. Recovery in granulocyte and platelet counts occurred in all but one patient within 3 weeks after transplant. Evidence of a positive response was seen in 3 patients, one of whom received ^{166}Ho-DOTMP in combination with thiotepa, busulfan, and cyclophosphamide, and achieved a complete response (CR) with a duration of approximately 5 years.

Two other Phase 1-2 studies were designed to test the safety and efficacy of ^{166}Ho-DOTMP in combination with high-dose melphalan, with or without TBI, followed by peripheral blood stem cell transplantation. Results from these studies are highlighted below. A second Phase II study is ongoing at 5 centers in the U.S. This study is designed to further characterize the efficacy, distribution, dosimetry, and safety of ^{166}Ho-DOTMP in preparation for a multicenter, randomized, Phase III trial planned to begin in early 2003.

Results from 83 patients treated in Phase I/II studies

Responses

- 35% of patients achieved a complete response (CR) defined as two sequential negative immunofixation electrophoreses. The overall response rate (CR + PR) was 69%.
- 30% of patients treated with a dose of ≤ 30 Gy to the marrow achieved a CR.
- Patients with advanced disease also achieved a meaningful objective response, including a CR of 23% in 22 patients with primary refractory disease.

Survival

- Median survival time has not been reached; patients have been followed for a median of 29 months (minimum 21 months).
- 100% of 37 patients treated with a dose of ≤ 30 Gy to the bone marrow were alive at 1 year. As of June 2002, 27 patients (73%) are still alive, and 19 have ≥ 3 years of survival.

Engraftment

- The time to engraftment is comparable to that which is reported with high-dose melphalan alone. The median time to sustained ANC ≥ 500/mm^3 and platelets ≥ 20,000/mm^3 was 10 days. This suggests that marrow toxicity is not dose-limiting with ^{166}Ho-DOTMP.

Adverse Events

- 27% of patients in these studies experienced hemorrhagic cystitis (HC). This toxicity occurred predominately in patients who did not receive continuous bladder irrigation (21 of 51 patients; 41%) and in only one patient who did receive continuous bladder irrigation (1 of 32 patients; 3%). To reduce the incidence of HC, all patients in current and future trials will be required by protocol to receive continuous bladder irrigation during and following ^{166}Ho-DOTMP treatment.
- 7 (8%) patients exhibited a syndrome compatible with thrombocytic thrombo-

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DEVELOPING THE SECOND GENERATION MYELOMA CHIP

Progress Report from 2002 IMF Junior Research Grant Award Recipient Jaime O. Claudio, Ph.D.

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With a new biomedical research tool known as cDNA microarray, medical research has fundamentally changed the ways we look at diseases. It is now possible to analyze patterns of expression of thousands of genes in a single experiment and use this expression profile to classify diseases and stratify patients. Applying this technology to multiple myeloma as a tool for the study of the disease gene expression, we have been using our 4.3K Myeloma Chip to analyse cell lines and patient samples and identify genes that are differentially expressed between multiple myeloma and non-myeloma cell lines, and between malignant and non-malignant plasma cells. We have also been using *in silico* data mining to augment the diversity of genes to be printed on the second generation myeloma chip. Since funding support was granted, the following activities had been initiated:

1. Myeloma Gene Index

The Myeloma Gene Index, which is our intended repository of microarray data, has been updated. In order to make the Myeloma Gene Index more interactive, we have updated the site by adding a search engine. Any genes of interest can be queried from the Myeloma Gene Index using three choices of databases: (1) genes identified by sequencing (2) genes identified by microarray hybridizations and (3) genes present in our 4.3K Myeloma Array. In the future a search engine for the expression patterns of a particular gene based on microarray data will be incorporated into the website's search function. Currently, our microarray hierarchical cluster analysis results (2D heat maps) are only available from the Myeloma Gene Index's Supplement page in a non-searchable format. To access the Myeloma Gene Index, go to *www.uhnres.utoronto.ca/akstewart_lab/mgi.html*

2. Relational Database for microarray images

Because of the generation of a significant amount of image data files, we have set up our own relational database system that supports the storage of acquired microarray images. Our system of choice is the GeneTraffic Microarray Database and Analysis System (Iobion Informatics, La Jolla, California) which supports complete annotation of data based on current Minimum Information About a Microarray Experiment (MIAME) standards for microarray research (*www.mged.org*).

3. In search of a highly discriminatory gene dataset

We have generated a molecular portrait of 18 myeloma cell lines and 6 hematopoietic non-myeloma cell lines using a total of 5,460 quality controlled spots corresponsing to 152,880 datapoints. Statistical analysis of our microarray data from myeloma and non-myeloma cell lines identified 34 genes that are significantly up-regulated (after immunoglobulin lambda, kappa and J chain genes were filtered out), and 18 genes that are down-regulated in the myeloma cell lines. Among the significantly up-regulated genes in this analysis include heat shock 70 kD protein 5 (also called immunoglobulin heavy chain binding protein), a gene known to be important in the folding and oxidation of antibodies *in vitro*. The interferon regulatory factor 4 (*MUM1/IRF4*) is also significantly but not uniquely associated with the myeloma cell lines. *MUM1/IRF4* gene expression has been suggested to relate to the stage of differentiation of malignant B plasma cells and has been identified as an oncogene transcriptionally activated by t(6;14)(p25;q32) chromosomal translocation in multiple myeloma. Additional genes also include those involved in B cell biology such as syndecan, BCMA, PIM2 and XBP1. A number of genes that we identified that appear to be differentially expressed between myeloma and non-myeloma cell lines are novel uncharacterized genes matching sequences only in the draft sequence of the human genome. The most significantly up-regulated gene in myeloma cell lines and patient samples was hypothetical protein MGC3178. Further sequence analysis showed that this gene encodes for a protein that contains thiroredoxin domains, a sequence motif present in protein disulfide isomerases (PDI). Therefore, hypothetical protein MGC3178 may be involved in rearrangement of both intrachain and interchain disulfide bonds in proteins, but may also act as a cysteine-type endopeptidase, phospholipase, or a combination of these functions (SOURCE Database).

4. In silico data mining of published microaray data to identify genes useful in the molecular classification of myeloma

We have also been doing *in silico* data analysis to mine publicly available microarray datasets in order to identify genes that may be included in the second generation Myeloma Chip. Using Statistical Analysis of Microarray software, a freeware from Stanford University, we are currently mining raw data published by J. Shaughnessy's laboratory to identify gene signatures in patients with either cyclin D1 or FGFR3 translocations.

5. Microarray hybridizations using patient samples

Using patient samples, we have optimized our methodology for use in a limited amount of RNA samples. To date, we have analyzed 29 patient samples using this technique on our 4.3K Myeloma Chip. In the following months, we will attempt to analyze more patient samples as they become available.

6. Gene set for Myeloma Chip 2

We have to date identified close to 250 candidate genes that we plan to print in our second generation Myeloma Chip. In the following months, we will refine our data set based on additional information from analysis of our hybridizations using patient samples. The question is how many genes are necessary to

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THE PATHOPHYSIOLOGICAL RELEVANCE OF VEGF IN MULTIPLE MYELOMA

Six-month Progress Report from 2002 IMF Junior Research Grant Award Recipient Klaus Podar, M.D.

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Specific Aim 1:

1.1. The effects of a neutralizing Flt-1 antibody (Genentech) on (1) VEGF-triggered ERK-activation and (2) VEGF-induced migration were investigated. VEGF-triggered ERK activation was inhibited in a concentration- and time-dependent fashion in the presence of the neutralizing Flt-1 antibody. Furthermore, VEGF-triggered migrational activity was also inhibited in a concentration-dependent manner. These results further support the specific activation of the VEGFR Flt-1 I have suggested previously (Podar et al., 2001; Podar et al., 2002).

1.2. After having shown the efficacy of this drug in MM cell migration, I further investigated whether PI3-kinase activity is blocked. I observed a partial block of PIP2 phosphorylation.

1.3. As proposed, I am now investigating the role of the small Rho/ GTPases (Rho, Rac, Cdc42) in MM cell adhesion, migration, and invasion, also focusing on participation of cytoskeletal proteins.

1.4. Since the inhibitory effect of this neutralizing antibody is only partial, I will also test another VEGFR-inhibitor, newly developed by GlaxoBeecham Kline.

Specific Aim 2:

Raf-1 expression was shown in several MM cell line cells and patient MM cells. Furthermore, I confirmed the 3-fold increase of Raf-1 activity upon stimulation with VEGF, and an ~ 8-fold increase of Raf-1 activity upon stimulation with IL-6. Interestingly, the use of the PI3-kinase inhibitor LY, although blocking Raf-1 activity, did not block MEK and ERK-1,2 phosphorylation. These preliminary data suggest that Raf-1 might not be the major MEKK in MM cells. I am now attempting to identify a possible alternative MEKK. I have available the Raf-1 antisense oligonucleotides (ISIS 5132/ CGP 69846A) to specifically block Raf-1 activation. In ongoing studies I will investigate the role of Raf-1 in MM cell proliferation, survival, and migration in more detail.

Specific Aim 3:

As proposed, I investigated whether VEGF, like IL-6, can protect against Dex- and IR-induced apoptosis. Preliminary results show no/ weak antiapoptotic effects of VEGF on Dex- and IR- induced apoptosis in MM cells. In ongoing studies including also other apoptotic triggers, I will confirm these results. Furthermore, I will investigate the effects of antisense-Raf-1, RAFTK and SHP2 on IL-6- , IGF-I- , and VEGF- treated MM cells after exposure to IR, Dex, and different drugs that are currently investigated in this lab.

In order to investigate VEGF-induced expression pattern in MM cells, I additionally isolated mRNA at different times after VEGF stimulation to perform oligonucleotide microarray analysis. By clustering the data, I aim to define further genes that are involved in VEGF-induced MM cell growth, survival, and migration.

New Specific Aim 4:

In extension to Specific Aim 3, I investigated in more detail the initial events of IL-6- and IGF-I- mediated signal transduction pathways leading to MM cell survival. Caveolae, specialized flask-shaped lipid rafts on the cell surface, are mainly composed of cholesterol, sphingolipids, and structural proteins, termed caveolins; functionally, these plasma membrane microdomains have been implicated in signal transduction and transmembrane transport. My preliminary data show for the first time the existence of caveolae, usually absent in blood cells, in MM cells by RT-PCR, western blot, and transmission electron microscopy. My results also seem to indicate a possible role of caveolin-1 as a diagnostic and prognostic factor in MM, as previously suggested for some solid tumors (prostate cancer, esophageal cancer, …). Fractions of plasma membrane rafts obtained by a discontinuous sucrose gradient contain the IL-6-receptor signal transducing chain gp130 and IGF-IR, as well as Caveolin-1. The constitutive complex-formation of gp130 and IGF-IR with Caveolin-1 was further supported by co-immunoprecipitation. The functional relevance of these lipid raft microdomains in IL-6- and IGF-I- signal transduction was next investigated. Importantly, IL-6- and IGF-I- treatment triggered the recruitment of PI3-kinase to caveolae. To disrupt caveolae-biogenesis I first targeted cholesterol and second, caveolin-1. Cholesterol depletion by b-cyclodextrin inhibits PI3-kinase/ receptor/ Caveolin-1 complex-formation and eventually the activation of PI3-kinase by IL-6 and IGF-I. Consequently, b-cyclodextrin and inhibition of cholesterol biosynthesis by lovastatin also cause blockade of IL-6- and IGF-I- triggered Akt-1/ PKB activation, leading to a decrease in overall MM cell survival. With the use of an inducible antisense-caveolin-1-containing vector, I am now trying to support these data demonstrating a key role of caveolae in the regulation of IL-6- and IGF-I-triggered survival mechanisms. Optimal plasmid concentrations and transfection timepoints were determined by usage of an eGFP-vector. Co-transfections with eGFP and Caveolin-1 will be performed next. After sorting positive cells, I will either develop stable cell lines or use transiently transfected cells directly.

ADVOCACY UPDATE: Connecting the Dots

By Greg Brozeit

How much of the big political and legislative picture should we be concerned with when we advocate for more federal funding for cancer research? Funding for myeloma research? Cancer research? Medical research? The congressional appropriations process? What about tax cuts?

I have made the point numerous times in previous *Myeloma Today* articles and discussions with many IMF members around the country: if we are serious about achieving the goal of more federal funding for myeloma research, we must advocate on behalf of all cancer research funding. Specifically, we must be active in coalitions like One Voice Against Cancer (OVAC) to support full funding for the National Institutes of Health (NIH) and educate our members of Congress about the National Cancer Institute (NCI) Director's Bypass Budget. It is only by working with others with similar goals that we will achieve our specific goal of more funding for myeloma research.

IMF Advocacy Consultant, Greg Brozeit, confers with NCI Director Andrew von Eschenbach at the May 2002 meeting of the National Dialogue on Cancer in Washington, D.C.

During our most recent OVAC Advocacy Day in June 2002, however, I was strongly advised by one member of Congress and other staff members that advocating for a bigger slice of the funding pie for NIH and the Bypass Budget overlooked another stark reality. It was not enough, according to these individuals, to ask for more funding. In fact, it could be counterproductive in the long term.

What was needed, they argued, was an understanding and appreciation of how the political and appropriations processes were dependent on each other. How, for example, could the appropriations committees begin to fulfill the wishes of the competing funding constituencies if tax cuts diminished federal resources by $600 billion?

Under these conditions, no constituency should expect to fulfill their wish lists, or, in a more likely scenario, the future of appropriations would translate into a process of perceived winners one year becoming losers in the next. For example, this year, it seems likely NIH will achieve or come near to the five-year doubling pledge goal of $27.3 billion.

That might translate into education programs not being funded at the levels promised in previous years. It also may translate in reductions or stagnant funding levels for other health programs such as the Health Resources and Services Administration (HRSA) or the Centers for Disease Control and Prevention (CDC).

And in boom-and-bust funding cycle scenarios, it may mean that next year's medical research funding figure will barely rise while other programs, the perceived losers of the current cycle, will experience greater increases. It will be the legislative metaphor of moving around the deck chairs on the Titanic.

What is the subtext to this debate? Part of the answer, in a case made strongly to me by one member of Congress, is if we are vocal about increasing funding levels for NIH and NCI, we should also be vocal and concerned about tax cuts limiting the funding streams for those agencies. The two are related.

This argument is one component of the historic political tensions that have underscored the American political process. But instead of "guns or butter" the mantra for advocates may be "tax cuts or cancer research" or "tax cuts or education funding."

On the other side of the discussion, there would be no guarantee that research funding would automatically go up if tax cuts were defeated and the federal funding stream remained uninterrupted. Those decisions would again be left up to the various appropriations subcommittees and there are no guarantees that link tax income with funding for programs.

The moral of the story is that advocates must be vigilant and assertive no matter the political environment. We should always vigorously support our goals. We shouldn't take for granted success in the good times. Nor should we expect lesser results in tight fiscal times.

But we should expect winners and losers in the appropriations process. Although the NIH part of the equation looks promising for cancer research advocates this year, the other parts do not look as promising. The outlook for the next few years is even more nebulous, especially for NIH.

And remember to connect the dots. At least then it is easier to explain the final results. And remember that it is more likely to be on the losing side of the appropriations process when the income of the federal government is constricted by tax cuts.

2002 IMF CALENDAR

August 6, 2002
*Coping with Lingering Side Effects and Impact of Cancer Treatment***
Nationwide Teleconference
1:00pm to 2:00pm (Eastern Time)

August 10, 2002
Challenging Cases
New York, New York

August 13, 2002
*Therapeutic Updates in Oncology**
Nationwide

August 16-17, 2002
IMF Patient & Family Seminar
Chicago, Illinois

August 20, 2002
*Coping with Lingering Side Effects and Impact of Cancer Treatment***
Nationwide Teleconference
1:00pm to 2:00pm (Eastern Time)

August 26-September 1, 2002
Myeloma Awareness Week
Nationwide

September 12-14, 2002
IMF Patient & Family Seminar
Sydney, AUSTRALIA

October 5, 2002
IMF Ribbon of Hope Annual Gala
Washington, D.C.

October 10-13, 2002
IMF Support Group Leaders Retreat
Durham, NC

November 8-9, 2002
IMF Patient & Family Seminar
Seattle, WA

December 6-10, 2002
ASH (American Society of Hematology) Annual Meeting
Philadelphia, PA

*This audio conference is being offered by MEI, a multidisciplinary continuing education provider that promotes lifelong learning for oncology health care professionals. IMF Chairman of the Board, Dr. Brian G.M. Durie, will present the "Supportive Care in Multiple Myeloma" lecture between 12 noon and 1:00 pm (EST).

**This free teleconference series is being presented by CancerCare Inc. No phone charges apply. To register, visit *www.cancercare.org* or call (800) 813-4673.

For more information about IMF events, please check the IMF website at www.myeloma.org or contact the IMF at (800) 452-CURE.

Multiple Musicians for Multiple Myeloma

Top row: Jason Bergman, Roxanne Bergman, Leo Huppert, Russell Seeger, Lee Grayson, Don Olsen, Naomi Margolin, Maag Stanley, Angela Ford. Bottom row: Suzanne Mueller, Drew Olsen, Peter Aronoff.

By The Unknown Patient

There are lots of very special people all over the world fighting myeloma. Each brings to this fight their own special talents and personality. One such special person is Lee Grayson, a musician by trade. Lee is an incredibly talented man with a heart of gold. Time and time again, Lee has gone beyond his personal battle with myeloma to help the entire patient community. Once again, Lee has stepped forward to make a difference with *Multiple Musicians for Multiple Myeloma*, a joyous and innovative fundraising event that was the brainchild of Lee and his friend and fellow musician, Naomi Margolin.

Lee and Naomi's band, Bees Neez, performs regularly at Tupelo Honey, a beautiful club tucked away in a corner of the Long Island village of Sea Cliff. Having watched Lee fighting myeloma for the past few years, the owners of the club graciously agreed to host a fundraising event for multiple myeloma and managed to secure the necessary permissions from the village of Sea Cliff. Lee and Naomi lined up a veritable army of bands, all of whom donated their services to perform at the event. Among the bands perfoming were Jason 'n Grayson, Zen Trio, Sean Grace, Kathy Kreger Band, Rose Gunter and the Hysterical Angels, Russel Sieger, Mark Newman, The Jewish Beatles, Bees Neez, Maag Stanley, Gretchen Cryer, and Funk Filharmonik.

Lee with his doctor, Sundar Jagannath, chief of the Multiple Myeloma Center at the St. Vincent's Comprehensive Cancer Center

Add to all this good music a large crowd of fellow musicians and friends, myeloma patients and caregivers, and curious passers-by, and you've got a really fun day ahead. Attendees were given buttons emblazoned with a sentiment we've all shared at some point, "Myeloma Sucks," setting a bit of an irreverent tone. Inside, the mood was infectious, with good music and good people in abundance. Lee, Naomi, and the other performers sang, danced, and played their hearts out, while the crowd sang, clapped, drank, and shmoozed. The music ran the gamut from a nostalgic review of the Beatles era to current pop.

Kelly Martinsen of Celgene Corporation joins the celebration

The crowd had many children and there were clowns in attendance to show them the many creatures that could be fashioned out of balloons while their parents were preoccupied with good friends and good music. The bartenders were kept quite busy serving up waters and more potent potables to keep everyone cool and well-hydrated.

Between sets, the crowd heard from people who'd helped Lee in his personal battle. Dr. Sundar Jagannath attended with his family and spoke to the group about current research in myeloma and the hope that it holds for the future. Carol Bakst, a fellow myeloma patient and transplant veteran, came with her new twin grandchildren and shared some of her experiences with the group. IMFer Michael Katz, who serves on the IMF's Executive Board and leads the New York support group that Lee attends, spoke about the importance of grass roots fundraising efforts and thanked everyone for stepping forward to make a difference.

Naomi Margolin adds her voice to the festivities

The owners of Tupelo Honey, already heroes for donating the use of their beautiful club, pledged donations for every drink purchased during a number of intervals throughout the day. At one point, swept up in the spirit of the event, they began giving away drinks to save time and maximize their

Please see page 10

Jay Haberman with Carol Bakst and the twins

Myeloma Chip – continued

explore reasonably well the expression portrait of myeloma. In a report of breast cancer classification using microarray, careful selection of variably expressed genes of only 486 was able to generate clusters that was used to classify the tumors (*Perou CM et al., (2000) Nature; 406:747-52*). This study suggests that careful scrutiny of the dataset and selection of variably expressed genes of as low as a few hundreds can produce a meaningful classification. Therefore, printing a limited but well-chosen set of genes on our second generation Myeloma Array is not only feasible, but may lead to the development of lower cost expression array that can be used to study large set of clinical samples.

7. Publication

A manuscript related to this work has been accepted in a peer-reviewed journal and it is currently available on-line as a *Blood* first edition publication.

STR – continued

cytopenic purpura or hemolytic uremic syndrome (TTP/HUS), 6 to 14 months after ^{166}Ho-DOTMP. Six of these patients were treated with a targeted bone marrow dose of ≥ 40 Gy; none occurred at ≤ 30 Gy. In several patients, biopsies confirmed that the features of this nephropathy were consistent with thrombotic microangiopathy suggestive of radiation nephritis.

- Renal toxicity was more common at doses ≥ 40 Gy to the bone marrow; the incidence of Grades 3-4 renal toxicity of any cause was 33% in patients treated with ≥ 40 Gy and 11% in patients treated with ≤ 30 Gy to the bone marrow.

Conclusions

- Skeletal Targeted Therapy with ^{166}Ho-DOTMP is a promising therapeutic approach for the management of patients with myeloma.
- Its efficacy profile in combination with melphalan at 200 mg/m^2 compares favorably with other transplant conditioning regimens.
- Using peripheral stem cell transplant, hematologic recovery is rapid and sustained.
- Future trials will use a target marrow dose of ≤ 30 Gy as the therapeutic dose because of the lower risk of renal toxicity and TTP/HUS-like symptoms, as well as maintained favorable response rate, long-term survival and disease-free survival.

A ^{166}Ho-DOTMP trial is going on at 5 transplant centers across the US. Another study at more centers is planned to begin in early 2003. For more information, please visit www.neorx.com.

Multiple Musicians– continued

donation. They, like most of the crowd, were really thrilled to be able to salute Lee for his courage in battling the disease and moving beyond that battle to help others.

The flyer for the event said that it would start at 3pm and go on Till Theres A Cure. The festivities continued that day until just past midnight, when, though there was not yet a cure, there was a clear need to close up shop to avoid a clash with the village of Sea Cliff. Undaunted, Lee and Naomi turned their regular performance the next evening at Tupelo Honey into an extension of the prior day's fundraiser, receiving an enthusiastic and generous response.

Lee and Naomi are wonderful examples of people who turn a bad situation into something very positive and remind us how wonderful people can be. When Lee had his stem cell transplant last fall, they made quite an impression at the hospital, shuttling from room to room playing the guitar and singing for fellow patients and caregivers. Lee volunteers for the IMF, calling newly-diagnosed patients and making sure they've got what they need and have all of their questions answered. Their devotion to helping others, particularly in the face of the challenges presented by myeloma, is exemplary.

At a recent Patient & Family seminar, Lee received the IMF Francesca Thompson Outstanding Service Award. Dr. Thompson, an orthopedic surgeon diagnosed with multiple myeloma, was an early benefactor to the IMF. She underwrote the hotline, donated her time as a faculty member at Patient & Family seminars, and provided counsel to the many patients and caregivers who sought her advice. Lee and Naomi follow in her worthy footsteps by giving of themselves to help win the battle against myeloma. Bravo Lee and Naomi!

Rock on, Lee!

Dear Reader – continued

group leader Marion State did an excellent job of organizing our visit and making us feel welcome. We enjoyed the opportunity to meet with the group members and share the latest information about what's new in myeloma research and treatment.

We left Toronto the next morning for the Chicago IMF Patient & Family Seminar, held on August 17. We were looking forward to being back in the windy city and meeting old friends and making new ones. The IMF once again brought together an expert faculty for the full day seminar. A highlight of this meeting was an announcement about our exciting new partnership – The Inspired Venture Partnership in Multiple Myeloma. This program, co-sponsored by the IMF and the Goldman Philanthropic Partnerships, is designed to seek out high risk/reward research from a range of disciplines (oncology to computer science, to mathematics, to integrative medicine). You'll be reading more about this program in future issues of Myeloma Today.

But the month is not over yet! The IMF is about to launch our CME-accredited CD-ROM web-based program: Expert Opinions on Multiple Myeloma. This program, made possible by a generous grant from a patient, provides physicians with the chance to watch world-renowned myeloma specialists share their knowledge, discuss their treatment choices, and compare their perspectives on controversial issues in multiple myeloma and related diseases.

And if that's not enough, we will end August with our first ever national Myeloma Awareness Week, which takes place August 26 through September 1, 2002. It's an excellent opportunity for members of the myeloma community to unite in our fight against myeloma.

Myeloma never takes time off and neither does the IMF. We are here to serve you. And remember – "Until there is a cure…There is the IMF."

Susie Novis
President

If you or someone you know has a story that might be of interest to our readers, please contact:

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News & Notes

OMNI Network

The OMNI Network, a collaborative effort between the IMF and oncology nurses, is designed to provide ongoing support to those affected by myeloma. This community outreach effort educates patients and their caregivers about the link between myeloma and bone health. Presented by a nurse chosen from the local community, the 45-minute interactive session shares current information on bone metastases and healthy bone. Through discussion, myeloma patients and caregivers can talk about healthy living with an oncology nurse who understands the challenges they face in living with the disease. This nationwide special education program is offered to support groups serving myeloma patients and caregivers. To date, 60 oncology nurses have completed OMNI training. As of this printing, OMNI presentations have taken place around the country. If your support group would like to participate in The OMNI Network, please call (800) 437-3033.

Strength For Caring

Sponsored by Ortho Biotech Products, *Strength For Caring*™ is a community-based education and support program for cancer caregivers. The program is designed to help families cope with the emotional and physical challenges of caring for a loved one with cancer. To participate, all you need is a desire to learn and get support, and the date and time of an event near you. Programs are held throughout the year at hospitals and other medical facilities, and at local community centers and cancer advocacy organizations. *Strength for Caring* programs are free of charge and open to anyone who is, or will become, a cancer caregiver. For more information about the *Strength for Caring* program, or to find out the times and locations near you, call (888) I-CARE-80 or visit *www.strengthforcaring.com*.

Making a Worls of Difference

The IMF 12th Anniversary Gala is being held in Washington, DC on October 5th, 2002. This year, we are thrilled to be presenting awards to Guest of Honor Daniel E. Smith, Nationa Vice President, Federal and State Government Relations, American Cancer Society and founder of One Voice Against Cancer, Sen. Kay Bailey Hutchison, Sen. Barbara A. Mikulski, Geraldine Ferraro, and Tom Bay. The evening promises to be filled with joy, hope, and celebration, with attendees dancing to the exciting music of "Escapade," and bidding on such auction items as an African safari, a trip to Paris, a week in St. Lucia, an original Nicole Miller gown designed especially for the IMF, restaurants, dinner parties, jewelry, fantastic kids' items, and much more. To attend, please contact Suzanne Battaglia at (800) 452-2873 ext. 227 or *SBattaglia@myeloma.org*. Remember, it's YOUR time to celebrate too!

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