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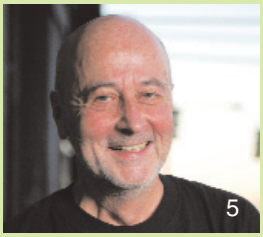
A Publication of the International Myeloma Foundation

Dedicated to improving the quality of life of myeloma patients while working towards prevention and a cure.

Highlights



Bart Barlogie, MD, PhD

Prof. Hervé Avet-Loiseau

Robert Orlowski, MD, PhD

Gary S. Jacob, PhD

Message From IMF President

Dear Friends,

On behalf of the International Myeloma Foundation, I would like to thank you for your support and update you on our progress with the IMF's research project, Bank On A Cure®.

This past year has been very busy. There are two labs that process the DNA samples and are doing the studies: one in the UK and the other in the US. Our two Co-Chairs are Dr. Brian Van Ness, Head of the Department of Genetics, Cell Biology, and Development, whose lab is in Minneapolis, and Dr. Gareth Morgan, Head of the Myeloma Group at the Royal Marsden Hospital in London.

All of the data-gathering and statistical analysis is being conducted by John Crowley's group, CRAB (Cancer Research and Biostatistics). CRAB is highly respected throughout the world for their myeloma expertise and sophisticated data analysis.

We also are pleased to announce that Dr. Dalsu Baris, a leading NCI-based epidemiologist, and ethicist Dr. Jeff Kahn, Professor of Medicine, Center of Bioethics, University of Minnesota, have joined our Bank On A Cure team.

All of the administrative paperwork is ready for final approval by the Institutional Review Board (IRB) at the University of Minnesota. This is an extremely important facet of this exciting project.

We are pleased to confirm that collaborations have been established with several important myeloma research groups. They are: SWOG (Southwest Oncology Group), ECOG (East Coast Oncology

PLEASE SEE NEXT PAGE.

This issue of MYELOMA TODAY is supported by:
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International Myeloma Foundation

Dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure.

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IMF President — continued

Group), Mayo Clinic, IFM (Intergroup Français Myelome), University of Arkansas, the German Myeloma Study Group, The Japanese Myeloma Study Group, Central Europe Myeloma Group, HOVAN (the Netherlands), the Nordic Myeloma Study Group, JEM, Pethema (the Spanish Groups), the Italian Group, the South American Study Group, Fundaleu (the Argentinian Group), the Canadian Group at the Toronto General Hospital, and the National Canadian Cancer Group. Bringing these groups together to work collaboratively is truly a milestone in myeloma research and shows the scope, breadth, and belief in the importance of Bank On A Cure!

So, our research teams are in place and, thanks to your support, we have purchased a DNA extractor. This is the most critical (and a very expensive) piece of equipment needed for this project. We've also begun our research and have run tests on over 2,000 DNA samples from patients who have already consented to correlative analyses as part of ongoing clinical trials. Initial observations include correlation between benefit with high-dose melphalan as part of stem cell transplant and the gene-regulating body metabolism of melphalan. In addition, gene regulation of TNF-alpha production, a crucial body cytokine (or hormone), correlates with response to thalidomide treatment. The goal of identifying personal gene expression patterns that correlate with treatment benefit is well within grasp!

I look forward to keeping you posted on the progress of Bank On A Cure. A truly heartfelt thank you from all of us here at the IMF and from our Bank On A Cure team. We couldn't do it without you!

Warmest regards,
Susie Novis

Why Bank On A Cure®?

EVERY MYELOMA PATIENT IS UNIQUE. TREATMENT SHOULD BE TOO.

What is the purpose of the Bank On A Cure study?

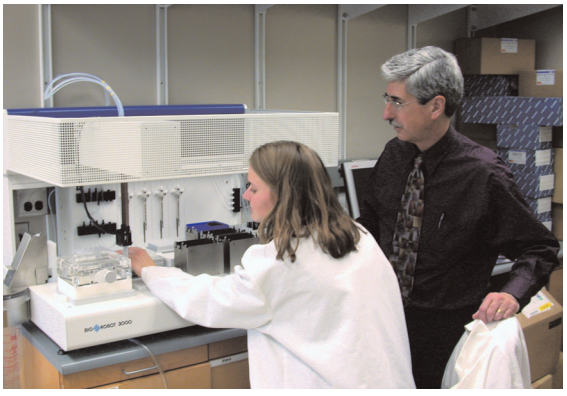
Doctors and researchers around the world are united in the opinion that the potential cure for cancer lies somewhere in the better understanding of the genetic makeup of patients. The Bank On A Cure study aims to provide a unique opportunity to develop genetic and clinical correlations that will allow better treatment response and performance, improved treatment choices, and possibly future preventative and curative strategies for patients with multiple myeloma.

Who is organizing and funding Bank On A Cure?

This project is being organized by the International Myeloma Foundation. The IMF is working closely with two labs, one based in the USA and one based in the UK. The Bank On A Cure study is being funded through generous donations from IMF members and supporters.

Who has reviewed this study?

This study was designed by a multi-disciplinary team of doctors, researchers, patients, and lay people. It has been reviewed and approved by appropriate ethics committees.



Dr. Brian Van Ness and grad student with the dedicated robotic DNA processing machine.

Who is taking part in this study?

Worldwide, up to 10,000 individual DNA samples will be collected from persons diagnosed with multiple myeloma who fit the entry criteria required to take part in this study.

Do I have to take part?

No. The decision is entirely yours. If you choose not to take part, this will not affect your current treatment and it will not affect the relationship you have with your doctor. Even if you decide to take part now, you are free to withdraw at any time in the future without giving any reason and again, this will not affect the relationship you have with your medical team.

What will happen if I do take part?

After you have read all the information you need and have agreed to take part in this study, you will be required to provide a DNA sample derived from a simple mouthwash. If you have already provided a DNA sample as part of another clinical study, you will be required to give consent to allow some of that DNA to be used in this study. Regardless of when you have given your DNA sample, you will be required to complete a simple patient questionnaire. You might be asked to provide follow-up information when required. Your doctor will also receive a questionnaire regarding your medical history and current treatment.

What is being tested?

Your DNA will be tested and analyzed to determine the characteristics of the behaviour of a number of specific genes that are known to be implicated in the onset of myeloma and which may influence treatment outcome and performance in individual cases.

What are the alternatives?

Due to the nature of this type of study and in the absence of a suitable similar or comparative study, there is no alternative. However, this puts the patient at no disadvantage or harm whatsoever, and will not affect treatment in any way.

What are the disadvantages of taking part?

There are no side effects at all from taking part in this study and there are no disadvantages that have come to light to date.

What are the benefits of taking part?

As with most studies, results cannot be guaranteed. However, it is hoped that results from this study will allow doctors to tailor treatments specifically to individual patients based on their genetic makeup. This will help to maximize response and outcome and to reduce side effects. It is also hoped that this study will lead to preventative and curative strategies in the not-too-distant future.

What if new information becomes available?

New information will only add value to this project and will not affect DNA donors in any way.

What happens when the research stops?

It is hard to predict when a research project like this will stop—if ever. DNA banks will provide a continual source of information and it is likely that this type of research will become standard clinical practice and will be integrated into everyday care of patients.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you which is used or leaves the hospital will have your name and address removed so that you cannot be identified from it. It is important to understand that specific results and information about your own case will not be available.

What will happen to the results?

The results of this study will be published in scientific journals and presented at scientific meetings. MT

IMF Calendar

April 17-18	IMF Patient & Family Seminar in Vienna, Austria
April 19-20	IMF participates in OVAC in Washington, DC
April 22-24	IMF participates in the Myeloma 2004 Conference in Torino, Italy
April 29-May 2	IMF participates in the ONS Conference in Anaheim, CA
May 8	Robert A. Kyle Lifetime Achievement Award Dinner Honoring Dr. Bart Barlogie in Little Rock, AR
May 14-16	IMF Scientific Advisors Retreat in Bermuda
June 5-7	IMF participates in the ASCO conference in New Orleans, LA
June 11	Multiple Musicians Against Myeloma, Sea Cliff, NY
July 2-3	IMF Physician and Patient Seminar in Ankara, Turkey
July 9-11	IMF Annual Support Group Leaders Retreat in Durham, NC
July 16-17	IMF Patient & Family Seminar in San Jose, CA
September 20	IMF Patient & Family Seminar in Barcelona, Spain
September 24	IMF Patient & Family Seminar in Paris, France
October 1	IMF Patient & Family Seminar in Torino, Italy
October 8-9	IMF Patient & Family Seminar in Teaneck, NJ
November 12-13	IMF Patient & Family Seminar in San Diego, CA
November 6	IMF 14th Anniversary Ribbon of Hope Gala in Los Angeles, CA
December 3-6	IMF participates in the ASH Conference in San Diego, CA

IMF(Japan) and IMF(UK) events are not included above.

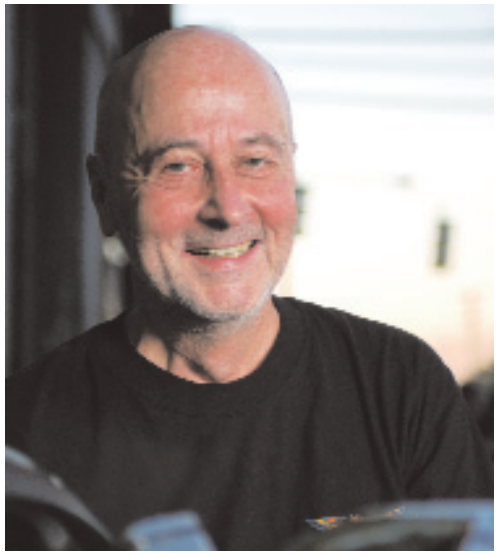
Collaborative Group meetings (i.e. ECOG and SWOG) are not included above.

THE LITTLE ROCK APPROACH

Bart Barlogie, MD, PhD

INTRODUCTION

Peripheral blood stem cell (PBSC)-supported high-dose melphalan 200 mg/m^2 is now considered standard therapy for patients with symptomatic or progressive myeloma. During the last five years, additional new agents effecting salvage rates of 30% - 50% have been discovered and patient outcomes improved.



Bart Barlogie, MD, PhD
University of Arkansas for Medical Sciences
Myeloma Institute for Research and Therapy
Little Rock, AR

Standard Therapy for Myeloma

Pursuit of dose intensity with melphalan had markedly increased the frequency of complete remission and, consequently, disease-free and overall survival. The dose-limiting toxicity of melphalan as a hematopoietic stem cell-damaging agent is irreversible bone marrow damage. A procedure commonly referred to as stem cell transplant can rescue patients from the harmful effects of prolonged myelosuppression. For this purpose, patients' own peripheral blood stem cells, collected upon induction therapy with non-stem cell-toxic regimens such as VAD, are infused back into the patient 24 hours after melphalan therapy, effecting rapid recovery of blood counts with an average duration of neutropenia < 500/dL not exceeding 7 days. As a consequence, treatment-related mortality usually does not exceed 1% to 2%. In comparison to standard-dose chemotherapy with melphalan and prednisone or combination therapies with additional alkylating agents, a single melphalan 200 mg/m^2-based autotransplant has been shown to increase complete response rates from < 5% to 25%, usually associated with extension of event-free and overall survival by at least one year. Thus, despite similar total cumulative doses of melphalan with low-dose chronic versus high-dose administration, the reduction of tumor burden is substantially lower with standard dosing due to ineffective cell kill, resulting in additional gene mutations and further drug resistance.

While stem cell transplantation overcomes the harmful effects of bone marrow damage inflicted by high-dose melphalan, other side effects have become dose-limiting, especially mucositis, or inflammation of mucous membranes such as the lining of the mouth. In an effort to achieve further reduction of myeloma tumor burden, we started applying two cycles of stem cell-supported melphalan at 200 mg/m^2 given within two to four months of each other for a total melphalan dose of 400 mg/m^2. Such tandem autotransplants have now been shown, in a randomized clinical trial conducted by French investigators, to extend the duration of disease control and survival, while allowing mucous membrane recovery after the first transplant. With Total Therapy 1 performed at Arkansas in 231 patients, 40% achieved complete remission with an overall survival at 10 years of 35%. The dominant adverse prognostic feature was the presence of cytogenetic abnormalities prior to initiation of therapy, noted in one-third of patients. The two-thirds of patients presenting without cytogenetic abnormalities enjoyed a 10-year survival of 45%, compared to < 10% among those with cytogenetic abnormalities.

Salvage Treatment

At the time of disease progression, we distinguish between primary resistance (failure to respond to initial therapy) and relapse following at least partial remission. In this latter setting, salvage therapy may not have yet been performed (untested relapse), or may have been effective (sensitive relapse) or ineffective (resistant relapse). In planning salvage therapy, these issues have to be considered along with the duration of remission, the circumstances of relapse (whether or not it occurred during therapy), and the number of autotransplants the patient has received. In addition, marrow examination, especially for cytogenetics and for evaluation of any normal marrow damage, and the possibility of secondary myelodysplasia/early leukemia must be considered. In anticipation of potential relapse after one or two autotransplants, there is a need for sufficient peripheral blood stem cell collection prior to the first transplant so that all treatment options remain open for relapse management. In our case, we typically attempt to collect 20 million CD 34 cells/kg body weight prior to first transplant.

Traditional salvage therapies include the VAD regimen, dexamethasone pulsing, thalidomide alone or combined with dexamethasone pulsing, or a highly effective regimen referred to as DT PACE, comprising dexamethasone, thalidomide, and 4-day continuous infusions of cisplatin, adriamycin, cyclophosphamide, and etoposide.

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The Genetics of Multiple Myeloma

Prof. Hervé Avet-Loiseau

Multiple myeloma is characterized by the accumulation within the bone marrow of large amounts of malignant plasma cells. This accumulation is responsible for the most common features of the disease, like painful lytic bone lesions, or inhibition of the normal hematopoiesis(1). However, despite these common characteristics, patients differ from each other in many aspects, including number of bone lesions, response to treatment, or duration of response. These differences probably reflect heterogeneity(2) in the disease, heterogeneity that can also be recognized at the cellular or molecular levels.

Extensive genetic lesions, both at the chromosome and gene levels, characterize malignant plasma cells. Although most patients present with a large number of malignant plasma cells at diagnosis (up to 1,000 billion malignant cells), chromosomal analyses are still a difficult art in multiple myeloma. Because plasma cells are quiescent(3) rather than proliferant, and because cytogenetics(4) requires the passage through mitosis(5), chromosomes are difficult to obtain in myeloma cells. Despite these difficulties, several studies have shown that several chromosomal patterns can be identified, mostly based upon the ploidy(6) mode (i.e., the modal number of chromosomes), and on a few specific chromosomal abnormalities. The first classification distinguishes myelomas on the basis of the number of chromosomes, i.e., 46 chromosomes or less (hypopseudodiploidy), and more than 47 chromosomes (hyperdiploidy). These two categories represent about half of the patients each, and seem to differ by several parameters, including other chromosomal changes and prognosis; those patients with hyperdiploidy presenting a better outcome. Other important chromosomal rearrangements involve the 14q32 region. Such rearrangements are observed in 50% to 70% of the patients with myeloma, depending on the studies and the techniques used. Although a wide variety of chromosomal partners have been described, two specific translocations involving the 14q32 region are observed with a higher frequency: the translocation t(11;14) and the t(4;14). This latter translocation is invisible using classical cytogenetics and requires other techniques like FISH (fluorescence in situ hybridization) or molecular techniques. The identification of these chromosomal changes is important in order to define the prognosis of the patients, t(4;14) being associated with a poor prognosis, whereas t(11;14) is associated with a longer survival.

Professor Hervé Avet-Loiseau
Laboratory of Hematology
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Nantes, France

Finally, and probably most importantly, about half of the patients present a loss of part or all of chromosome 13. This abnormality has also been related to a poorer prognosis, even though the technique to use to identify it (classical cytogenetics or FISH) is still a matter of debate.

What is the role of these specific chromosomal abnormalities in the occurrence and/or the evolution of multiple myeloma? This important question is so far unresolved, albeit some recent studies have started to address this issue. The major related question is whether multiple myeloma is a unique disease, or several diseases. In other hematological malignancies, genetics have identified novel entities, leading to adapted therapeutic strategies. Similar implications can be envisaged for multiple myeloma. For instance, the two major 14q32 translocations, t(4;14) and t(11;14), might identify two different forms of myeloma, possibly requiring different therapeutic approaches. The development of more global genomic analyses should enable investigators to further decrypt the disease. The recent use of microarray(7) technology has opened the door to a new understanding of diseases, based on the definition of pathological entities on molecular signatures. The analysis of large numbers of patients presenting different forms of multiple myeloma should modify our knowledge of myeloma, and possibly should modify the way to manage patients.

In conclusion, multiple myeloma is probably entering a novel era, the genetic era. The systematic evaluation of the chromosomal and gene aberrations should modify our view of the disease, leading to individual disease-adapted therapeutic management. MT

TERMS & DEFINITIONS

(1) The normal production of peripheral blood cells.
(2) Diversity, nonuniformity.
(3) A resting cell, not dividing, but not dying.
(4) Study that relates the appearance and behavior of chromosomes to genetic phenomena.
(5) Cell division in which the nucleus divides into nuclei containing the same number of chromosomes, all of which are genetically identical to each other.
(6) The number of sets of chromosomes within a cell or organism.
(7) Sets of miniaturized chemical reaction areas that may also be used to test DNA fragments, antibodies, or proteins.

Note: Prof. Avet-Loiseau is the recipient of 2001 and 2002 IMF Senior Grant awards.

OVERCOMING MULTIPLE MYELOMA DRUG RESISTANCE BY INHIBITING THE PROTEASOME

Robert Orlowski, MD, PhD

There are many difficult hurdles to overcome in the treatment of multiple myeloma, but one of the most important is a phenomenon called drug resistance (recently reviewed in (1)). Myeloma cells that have this property can evade the effects of many chemotherapy drugs, allowing them to survive and even flourish in the face of such treatment. The impact that such drug resistance can have on the outcome of therapy may be seen in many different ways. Some patients have disease that, when it is first treated with chemotherapy, does not respond well, and occasionally may even progress, which is sometimes called primary refractory disease. If this happens, patients are usually switched to a different chemotherapy regimen, which hopefully is more effective. Other patients have disease that responds well and may even enter a complete remission, but after some period of time the disease relapses, and they need additional therapy. This usually occurs because a small fraction of the original myeloma cells were resistant to treatment, and once the majority that were sensitive were killed by chemotherapy, the remaining resistant cells had room and space to grow. Finally, many patients receive several different treatments for their disease, and may find that each successive regimen results in a briefer, and less dramatic benefit. One reason that this occurs is that some of the resistance pathways are active against several drugs, and therefore myeloma cells may survive therapy with one agent because a previous therapy activated a resistance mechanism that blocks the action of both. Fortunately, there are new ways emerging to overcome such drug resistance that may improve the effectiveness of myeloma therapy, but first let's look at the molecular mechanisms by which this whole process occurs.

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University of North Carolina at Chapel Hill, School of Medicine
University of North Carolina, Lineberger Comprehensive Cancer Center
Leukemia, Lymphoma, and Myeloma Program

Inherited Chemoresistance

In thinking about the mechanisms of chemotherapy resistance important in myeloma, it is convenient to divide them up into several categories. The first is inherited chemoresistance, which is something that is present right from the beginning in the very first myeloma cell, and is passed down to all of the cells that arise later. Sometimes this genetic change may even contribute to the process of cancer formation itself. An example of this is the so-called Bcl-2 protein, which is expressed at higher levels than normal in plasma cells from many patients with myeloma. This protein is usually found in the membrane of mitochondria, which are the energy-generating organelles of cells. One of the ways that chemotherapy and radiation kills cells is by damaging mitochondria and inducing them to release a protein called cytochrome c into the cytoplasm, which then activates a process known as apoptosis, or programmed cell death. Bcl-2 is found in the membrane of mitochondria, and is thought to work against apoptosis by preventing the release of cytochrome c. Cells that overexpress Bcl-2 are resistant to a variety of therapies used in multiple myeloma, including anthracyclines like doxorubicin, alkylating agents like melphalan, and also steroids like dexamethasone. Such overexpression can account for the resistance of myeloma cells to the first therapy that they receive.

Acquired Chemoresistance

Another mechanism of resistance can be called acquired chemoresistance, because it is not present in every cell from the beginning, but appears in cells only after therapy has begun. An example of this is the so-called P-glycoprotein, which is not often found in myeloma cells initially, but after some types of chemotherapy its expression increases, and may be seen eventually in all plasma cells. The P-glycoprotein has a useful normal function, which is to recognize toxic chemicals in the cell and, from its position in the cell membrane, to pump them out, thereby saving the cell from damage. Unfortunately, many of the chemotherapy drugs used against multiple myeloma are also recognized as being toxins by this pump. By removing them from myeloma cells, the P-glycoprotein reduces the chances that the drugs will have their intended effect. Cells that overexpress P-glycoprotein are resistant to drugs such as doxorubicin and vincristine. Such overexpression can account for the ability of myeloma cells to resist treatments that they haven't previously been exposed to, because the P-glycoprotein acts against many drug classes.

Inducible Chemoresistance

One last mechanism can be called inducible chemoresistance, and is one of the more recently described ways that this process of resistance can occur. Chemotherapy drugs are

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Education Initiative

COLLABORATION BETWEEN THE IMF AND MILLENNIUM PHARMACEUTICALS, INC. BENEFITS NURSING AND OTHER HEALTHCARE PROFESSIONALS AND PATIENTS

The International Myeloma Foundation (IMF) and Millennium Pharmaceuticals, Inc., of Cambridge, MA, the developer of VELCADE® (*bortezomib*) for Injection, are collaborating on a national medical education program designed for oncology nurses. VELCADE is a new and novel agent approved by the FDA in May 2003 for the treatment of relapsed and refractory multiple myeloma patients.

Through an unrestricted educational grant provided by Millennium, the IMF is developing a multifaceted approach to reach as many health professionals as possible. The initiative includes a series of accredited Continuing Education (CE) programs. These programs will include roundtable discussions for oncology nurses delaing with their clinical experience in treating patients with VELCADE, frequently asked questions about the therapy, and case studies around nursing issues. In addition, nurse speakers are available to speak at support group meetings, and there will be presentations by oncology nurses from key trial centers on the VELCADE mechanism of action, clinical and safety data, and additional educational information regarding strategies for effective patient management. Facets of the program will be available through multiple venues including the IMF website, CD-ROM, support group meetings, and Patient & Family Seminars.

A listing of these initiatives will be featured on a web-hosted portal accessible through the IMF website at www.myeloma.org. In addition to educating health care professionals and patients about the risks and benefits of proteasome inhibition therapy, this exciting initiative will also introduce new prospects for treatment and symptom management.

The website, which will be accessed from the IMF website, www.myeloma.org, will include a page of *Frequently Asked Questions* for health professionals and patients in addition to programs for CE credit for nurses and pharmacists. Some of the programs currently in production include a *Video Roundtable* of oncology nurses discussing their experience with VELCADE and outlining expectations for nurses and patients involved in treatment. *Case Studies*, approved for CE credit, will also be available on the website and on CD ROM. Topics will cover real life situations in which health professionals have opportunities to address the concerns of patients suffering from multiple myeloma.

The website, which will be accessed from the IMF website, www.myeloma.org, will include a page of Frequently Asked Questions for health professionals and patients in addition to programs for CE credit for nurses and pharmacists.

The *Speakers Bureau* is made up of experienced oncology nurses who have received special training to speak to professional and patient groups on the mechanism of proteasome inhibition, the safe administration of VELCADE, and the best way to advise patients on the management of symptoms associated with VELCADE. To date, hundreds of practicing oncology nurses have been reached during programs throughout the United States.

In addition, a VELCADE Nurse-on-Call program is available within the U.S. in all time zones, Monday through Friday, 9 a.m. to 4 p.m. Six nurses with extensive experience using VELCADE are available through this service to answer questions from other nurses about their concerns in administering VELCADE and to share their experiences in managing side effects. Nurses calling outside the staffed hours may leave a message; they will receive a call back as soon as possible.

This educational initiative is unusually comprehensive and innovative. From one-on-one conversations between oncology nurses, to education programs, to a continually updated website, health professionals and patients alike will be able to learn about the latest developments in treatment options for multiple myeloma. MT

Atiprimod

A NEW DRUG CANDIDATE IN EARLY-STAGE DEVELOPMENT FOR MYELOMA

Gary S. Jacob, PhD

These are encouraging times for patients with multiple myeloma. After three decades of clinical trial research involving thousands of patients with multiple myeloma, the last few years have seen encouraging advancements in new therapies to treat the disease. New drugs such as VELCADE® (Millennium Pharmaceuticals, Inc.), the proteosome inhibitor recently approved by the FDA, and antiangiogenic agents such as Thalomid® and Revlimid® (Celgene Corp.) are providing doctors with additional ways to treat the disease. Additionally, advances in our understanding of the basic biology underlying the course of this disease are creating new targets for research scientists to explore as new potential treatments. A number of drug candidates at various stages of clinical development are currently being evaluated as both cytotoxic agents and as treatment for bone pain associated with the disease. One of these drug candidates, Atiprimod (Callisto Pharmaceuticals, Inc.), is just about to enter the clinic.

Gary S. Jacob, PhD
CEO, CSO
Callisto Pharmaceuticals, Inc.
New York, NY

Atiprimod has a very interesting history, providing yet another example of a drug candidate that begins its story as a potential treatment for a wholly different disease indication. Other examples of this phenomenon include Thalomid®, approved for the treatment of leprosy; Viagra™ (Pfizer Inc.), originally developed as a cardiovascular drug and approved for erectile dysfunction; and even further afield, Nutrasweet™ (aspartame), originally developed at G.D. Searle as a potential cardiovascular candidate before finding its present use as an artificial sweetener.

In the case of Atiprimod, the drug was originally developed by SmithKline Beecham as a treatment for rheumatoid arthritis (RA) and successfully completed three Phase l clinical trials[1] in RA patients. These trials included single-dose studies, one-month multiple-dose studies and an open-label[2] extension study in which patients were on the drug for as long as one year. The results of these studies showed the drug to be well-tolerated at the administered doses, with no observed dose-limiting toxicity. These Phase l clinical trials, along with an extensive preclinical package of data, were a significant benefit to Callisto Pharmaceuticals, Inc., providing considerable clinical and preclinical safety data which were used to facilitate the September 2003 filing of an Investigational New Drug (IND) Application for Atiprimod to treat multiple myeloma patients.

Initial animal model studies with Atiprimod by SmithKline scientists showed that the drug lowers serum levels of interleukin 6 (IL-6) and tumor necrosis factor (TNF). Because IL-6 is generally recognized as the primary growth factor in the bone marrow environment driving multiple myeloma (Figure 1), Callisto Pharmaceuticals began to further explore development of Atiprimod for treatment of this disease. These recent exploratory and preclinical studies on Atiprimod have been conducted at Dana-Farber Cancer Institute (Laboratory of Dr. Kenneth C. Anderson), at the University of Texas M.D. Anderson Cancer Center (Laboratory of Dr. Zeev Estrov), and at Callisto's research laboratory in Princeton, New Jersey. These studies demonstrate that Atiprimod inhibits the growth of human multiple myeloma cells.

Atiprimod's actual mechanism for inhibiting the growth of human multiple myeloma cells is unknown, although scientists have been able to show that the drug turns on programmed cellular death (apoptosis) within these cells. Scientists also know that tumors need to support their growth by stimulating formation of new blood vessels, a process referred to as angiogenesis (see Figure). In cellular assays Atiprimod has been shown to inhibit secretion of the growth factor that promotes angiogenesis, referred to as VEGF, and to directly inhibit angiogenesis in a developmental blood vessel model performed in chicken eggs.

Finally, a separate set of experiments initially performed by SmithKline research scientists provides an additional potential benefit of Atiprimod to treat multiple myeloma. Atiprimod was found to inhibit the action of human osteoclasts (white blood cells that break down bone) from dissolving bone in *in vitro* cellular assays of bone resorption. This effect of Atiprimod appears to be selective against osteoclasts, with little or no effect on the bone marrow cells.

Loss of bone mass due to the effects of multiple myeloma is a common occurrence in this disease, and despite the advent of new treatments, such as more potent bisphosphonates and

See Atiprimod, Page 19

Cancer Research and Medicare: Political Pork?

Greg Brozeit

An ominous climate is developing around the cancer community and threatening to stick around. But unlike the weather, everyone can talk about it and do something to change it. And change it we must, otherwise we will have denied our children a legacy free of death and suffering due to cancer.

The end of the last appropriations cycle—with the lone exception of funding for the Centers for Disease Control cancer programs—and the passage of the Medicare reform bill, represented potentially momentous setbacks for all current and future cancer patients.

Congress and the administration approved the smallest increases in recent memory for medical and cancer research funding. In the long term, this will result in the loss of hundreds of research grants.

The new Medicare laws have lowered reimbursements for oncology drugs and promise to lower other reimbursement rates within a year. Recent reports call into question if and how many off-label drugs for cancer patients will be covered under the new prescription drug benefit scheduled to take effect on January 1, 2006.

Greg Brozeit

All of this comes at a time when congressional critics on the left and right have deplored the extent of pork barrel projects contained in the most recent omnibus appropriations bill—the same legislation with only minor increases for cancer research; increase that will be wiped out by cost of living adjustments and obligated funds. Moreover, these cuts and policy changes are coming at a time of unprecedented progress in the development of genetically targeted drugs—arguably the greatest development in the history of cancer research.

The failure of the cancer community to win big victories last year both in the appropriations process and in the Medicare reform bill must be reversed. The silver lining may be that these actions will motivate the cancer advocacy community to be more vocal and reverse these trends.

Pork Barrel Spending: the Lord's Work?

A former colleague of mine who served as director of a senator's state projects used to introduce himself by saying: "Some people say what I do for a living is pork barrel spending, but I like to think I'm doing the Lord's work."

Pork barrel spending sums up how members of Congress prioritize much of their political decision making process. In most cases it transcends traditional or ideological affiliations. Critics of pork often ignore the fact that patrons usually have very sound reasons for support and approval of their projects.

A project in the home district or state translates into something tangible: a known number of people—constituents—who care enough about it which, in turn, makes it a priority for them too.

That highway bridge that needs to be built to ease congestion and create safe bypass zones for families and children also creates jobs. This after-school community program which takes kids off the street and reduces truancy and vandalism can improve their in-school performance. And those scientific research projects on marine parasites actually help the seafood industry in your town to provide more plentiful supplies to benefit fishermen, cooks, and restaurant goers alike.

Of course, if that highway is built in a sparsely populated area and is named after a congressman, many may call it pork. Should that after-school program focus on recruiting kids through the use of midnight basketball leagues and rap music, some might be skeptical about why the federal government should support it. And those far-out projects looking into the mating behavior of coastal jellyfish might just seem like some sort of payoff for a well connected university. It depends on your perspective.

In other words, political pork, like beauty, really is in the eye of the beholder—or, to stick with the theme of this piece: the eye of the constituent. Pork barrel spending is not always as bad as it is made out to be. Individual projects, duly considered on their own merit, can withstand the charge of being frivolous or inappropriate. Moreover, there are members of Congress who are willing to go to bat for programs and promote alliances to assure funding for them.

The questions remain: How can we apply the rules of pork to the cancer patient and family community? Is it possible for a critical mass within Congress to identify with the National Institutes of Health, the National Cancer Institute, and Medicare funding in the same way that they do for public works projects in their states and districts? How do advocates work together to form a collective vision of cancer issues as accountable political pork?

See Political Pork, Page 26

IMF Kicks Off 2004 Seminars with Florida Retreat

Stephen Robertson

On January 23-25, I attended my first IMF Patient & Family Seminar at the Wyndham Bonaventure in the city of Weston just outside Fort Lauderdale, Florida. For weeks prior to this weekend, I'd had the pleasure of speaking to myeloma patients, family members, caregivers, and support group leaders, as well as local Florida nurses and physicians. As a new addition to the IMF family, I approached my first Patient & Family event with a tremendous feeling of excitement and anticipation. I wasn't disappointed.

Friday morning, as attendees began arriving at the Registration Desk, I had the pleasure of meeting our invaluable board members Mike Katz and Don Woodward, and Don's lovely wife Annette. There was a real sense of community and excitement as everyone assembled to hear IMF president and founder Susie Novis welcome all the attendees and introduce the retreat's distinguished faculty of Myeloma experts: Drs. Brian Durie, Robert Kyle, Maurizio Zangari, Mohamad Hussein, and Lewis Mehl-Madrona.

Terry Nalband and Susie Novis

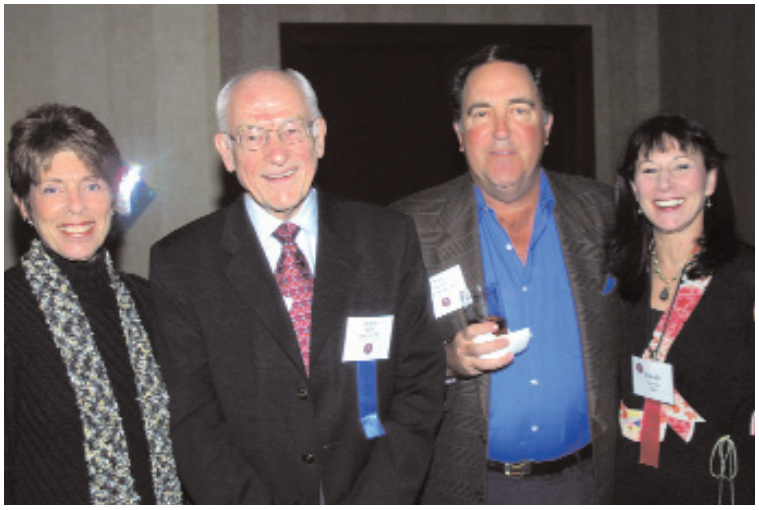
The topics covered by this renowned group over the next few days included Myeloma Overview, Initial Therapy, Transplantation, Novel Therapies, Supportive Care, Combination Drug Therapies, and Alternative Healing.

As participants continued to arrive throughout Friday and Saturday, I was delighted to at last meet long-time IMF supporters Kerri and Anthony Marioni, who successfully launched the *Hair Cares* member fundraiser, as well as Terry and Howard Herman, who helped turn the *Mail For A Cure* campaign into a resounding success.

Dr. Mohamad Hussein

At Friday evening's Cocktail Reception and Welcome Dinner, I finally got to meet IMF board member Rich Saletan and his wife Suzanne, as well as IMFers Joe and Melissa Vaccaro and their adorable daughter Marisa.

Myeloma support groups from all over the country were also very well represented. At the donor Recognition Dinner on Saturday evening, Susie expressly thanked support group leaders Chuck and Pat Koval from Madison, WI, Andy and Cathy Lebkuecher from Atlanta, GA, and Ken and Mary Makowka of Wilton, CT. Representing the many local Florida support groups were leaders Vicki Anderson of Miami, Terry Nalband of Palm Beach, John and Dorothy Russell of Inverness, and Jean and Bill Brady of Broward County/Fort Lauderdale.



Suzanne Saletan, Dr. Robert Kyle, Rich Saletan, and Susie Novis

Besides working tirelessly as support group leaders, many of those mentioned above have also been staunch supporters of IMF programs. Susie and I (with the help of little Marisa Vaccaro) were pleased to pay tribute to these IMFers along with Dr. Don Flatt, Jim Kilma, Martin and Kim Rubin, Melvin Bernhaut, Joseph and Frances Spaid, Beth Morgan and Barb Baxter, Bob, Cindy and Melanie Feltzin, Scheri Tamlyn (in absentia), and Wendy and Barry Breslow. Speaking of Wendy Breslow, we're very pleased that she has kindly agreed to be on the Steering Committee for IMF Gala in November. Again, we wish to thank all our members, donors, and support group leaders for their tremendous generosity. Without you, the IMF would not be able to

Mr. & Mrs. Francis Abel

Dr. Don Flatt attends his 8th IMF Patient & Family Seminar!

See Florida Retreat, Page 24

Los Angeles Area Support Group Salutes Leader

Jackie Schwartz, PhD

How could we demonstrate our love, admiration, and heartfelt appreciation for Janet, the founder of our group? This was the question that challenged our Support Group since Janet passed the baton in September after the death of her dear husband, Art. By October we had decided upon a plan. With the commitment of Dr. Brian Durie and Susie Novis to speak at our January meeting, we expected that this would lure Janet to attend. When Janet said "yes" to my seemingly casual invitation to attend the January meeting, way back in October, we could then shift into action.

Our emphasis was to honor Janet, in ways that she would feel appreciated. We knew, too, that she'd be most gratified if we also honored Art. We put out the word to all of the members of the Support Group, inviting them to contribute to gifts for Janet and a donation to the IMF in memory of Art. With everyone's cooperation and generosity, it all came together beautifully!

Janet Johnson and Jackie Schwartz

Never late for a meeting, Janet entered quietly and sat at the rear of the room. The meeting started according to plan. Susie Novis and Dr. Brian Durie spoke of the growth of the IMF and the progress being made in the field of myeloma, inspiring hope in the 96 group members in attendance.

When they had finished their presentations, I asked Sheila Wilson and Susie Novis to come forward. Sheila presented Susie $1000 in checks collected from members of the group. By the end of Sheila's remarks, noting that this money was given in memory of Arthur Johnson, I again took the microphone and asked his caregiver, Janet, to come forward.

Some people squealed, "Oh, is she here?" As Janet walked forward, the excitement in the room was palpable. By the time Janet got up to the front of the room, everyone in the room was on their feet, clapping and clapping and clapping. Honestly, it was the kind of fervor usually associated with a political convention. Janet kept asking people to sit down, and everyone continued to stand, and clap, clap, clap. She managed to keep the moisture in her eyes from rolling down her cheeks just then, but clearly, she was very touched by people's enthusiastic reception.

I brought up the first gift bag, from which Janet retrieved a beautiful plaque. When she read the words revealing our gratitude, the tears of appreciation rolled down her cheeks. More gifts followed: a big basket of fruit, spa gift certificates, plus a trip away for a deluxe spa weekend.

Janet Johnson with her award

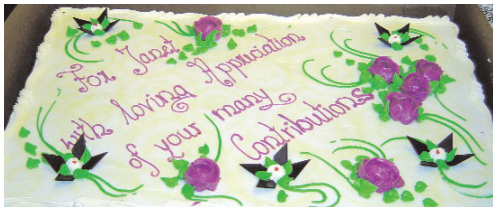
It was only when six-year-old Dempsey came forward with her own special gift for her grandma, that Janet seemed to be aware that members of her family had come to see and participate in this ceremony to honor her. Janet's daughter, Janine, had been a valuable, wise resource during the planning phase.

Characteristically gracious, Janet wanted to emphasize the members' qualities, and she asked how many had been with her at that first meeting in Marta Schwartz's (no relation) living room back in 1998. Many hands went up, and Janet told those in the audience that they are the real heroes, who keep on fighting the good fight and living their lives as fully as they're capable. Why shouldn't they? They have had Janet and Art as models, and despite the decline in Art's health over that last year and his almost daily doctors' appointments, Janet persistently carried the weight of being an unparalleled group leader.

Of course, we couldn't have had a celebration without food, so then we enjoyed a luncheon catered by a local chef and sponsored by Novartis Pharmaceuticals. That was capped off with a huge decorated cake from a local bakery.

We miss you, Janet, and at the same time, we recognize that your moving on to new involvements makes absolutely good sense. You've closed the MM chapter of your life, and you're on to new discoveries. The words on your plaque will, I'm sure, describe your participation in whatever you do:

With sincere appreciation to Janet Johnson
We honor you for your vision, caring, and dedication,
as founder and leader of our group,
from the Los Angeles Multiple Myeloma Support Group,
January 17, 2004. MT



Note: Dr. Schwartz is the new facilitator of the L.A. Area Multiple Myeloma Support Group.

IMFers Pay Tribute To Janet Johnson

On January 17, 2004, the L.A. Area Multiple Myeloma Support Group hosted a farewell bash for Janet Johnson, the first leader of the support group. Janet initiated the group and has planned and led the meetings for over six years. Her beloved husband and partner Art, videotaped each meeting despite his worsening myeloma over the years. Janet was Art's loving caregiver and upon his death this past August she felt that she had completed her mission.

Nancy Sorrenti, Sheila Wilson, and Susie Novis

Janet Johnson with Dr. Brian Durie

Almost one hundred people, including members of her family, Dr. Brian Durie, and Susie Novis, gathered to honor Janet. There were tears and there was laughter. We thanked Janet for all of the tremendous work she did during the past six years. She gave her heart to us unstintingly and left an exemplary model for us to follow as we continue the L.A. Area Multiple Myeloma Support Group.

About 3½ years ago, I attended my first support group meeting, having recently been diagnosed with myeloma. I was a basket case, ready to cry at the drop of an eyelash. Janet's adeptness at leading the group became apparent to me immediately, and my extreme anxiety eased. As the years passed, her leadership has remained something to marvel at, especially since she was Art's caregiver. Janet and Art had four grandchildren and they took full advantage of bonding with them. Two more grandchildren were added, and Art was able to see them both to his great delight. We certainly know that the demands of caregiving can be relentless, yet Janet always had an ear for those of us who needed someone to talk with.

Milo and Deedee Sutton

It is our hope to continue on the high plateau she has laid out for us with her dedication and hard work. My admiration for Janet is boundless, and I know that I am not alone in that admiration. She has our thanks and our very best wishes for the next episodes of her life.

— Nancy Sorrenti

We first met Janet and Art in 1998. They had taken on the leadership of the L.A. MM support group since its inception. Janet was a great leader: dedicated, always encouraging and uplifting, and all the while in full control of the meetings. When Art was not feeling well, and I know they both would have rather been at home, they always came anyway. Janet had many innovative ideas that raised funds for myeloma research and brought recognition to our support group. It was nice to see Janet receive the recognition she truly deserves.

— Mike & Regina Conti

Sisters Olga Beale and Dora Polk

Janet deserved all the appreciation and praise given her by those of us who have benefited so much from the dedication to the support group. Each person in attendance has been a beneficiary of her kindness, support, and encouragement. She and Art worked so hard and saw to it that every meeting was a meaningful educational and supportive experience for each one who came. Even as Art's health was failing, he held the video camera steady to record each meeting to stock the library for people that hadn't been able to attend. Janet was the ultimate caregiver, not only to her husband, but to the rest of our group. She is an encourager, always admonishing everyone to "Never give up!" We'll miss you Janet and wish you well as you go forward and have time to be with your grandchildren.

— Don & Althea Channell

The tribute to Janet was truly an uplifting experience! We all embraced this well-deserved recognition. The look on everyone's face was a wonderful thing to see... especially Janet's! It showed what the human spirit really means. We are proud to be members of this courageous organization.

— Fred & Sheila Wilson

I met Janet and Art Johnson in 1998 when I attended my first L. A. Area Multiple Myeloma Support Group meeting. Janet was an extremely caring and supportive spouse and caregiver. She was well-informed on all aspects of myeloma

See Tribute to Janet Johnson, Page 25

IMF Member Fundraisers

Suzanne Battaglia

For 14 years, the IMF has been successful in serving the myeloma community thanks to people like you, people who realize that if we're going to beat myeloma, each and every one of us touched by this disease needs to get involved! And, over the years, that's what's been happending. Many of you have joined the fight to end this disease, contributing to the cause in a variety of ways—grand and small—and making a world of difference.

Myeloma Today has been recounting these efforts: You've read about a little girl who collected pennies, children who baked cookies and sold them door to door, and IMF members who held gala benefits, walks in the park, bike rides, musical concerts, garage sales, and a host of other fundraisers too numerous to name. We're forever grateful to all of our members who have pitched in to help the IMF help others.

Your support of the IMF helps us fund research that brings us all closer to a cure. But there is still a lot of work to be done. And, while I'm thrilled to report that 2004 appears to be a banner year for member fundraisers, I'd like to ask all of you to join our efforts. We need your help. You can get involved by creating your own fundraiser or by drawing inspiration from other IMF members who have put together some terrific events.

In the last issue of Myeloma Today, we reported on the wonderfully successful fundraiser that Lisa Doyle and her family held last September in Lake Arrowhead, California. The IMF Mile High Walk-a-Thon honored Lisa's dad, Ed Davenport, whose myeloma is now in complete remission. To ensure that this special event offered "something for everyone," Lisa came up with the great idea of selling penny suckers for a dollar. This simple, fun, and original concept, along with the walk itself, raised over $8,000 for myeloma research! Flush with last years success, Lisa will offer double the fun this year, by holding the 2nd Annual IMF Mile High Walk-A-Thon in Lake Arrowhead on August 14th, while her sister Robin hosts an event in Huntington Beach.

IMFers in Arowhead Lake, CA

IMF's Suzanne Bataglia with event organizer Lisa Doyle at the Mile High Walk-A-Thon registration desk.

Such tremendous enthusiasm is truly inspirational, and has in fact inspired other IMFers to get involved. Lisa Doyle's effective grassroots approach has motivated Susan Rocchio of Staten Island, New York. Now Susan is organizing a similar event in memory of her mother-in-law, Donna Rocchio.

The IMF's most successful 2003 member fundraiser, "Fiesta for a Cure," was held by Jerry Pransky at the beautiful Mountaingate Country Club in Bel Air, California. Truly a fun fiesta, the event was complete with great Mexican food and Margaritas, not to mention the appearance of the Laker Girls! The silent auction featured fabulous items including desirable sports and entertainment memorabilia. Also on hand was auctionaire extraordinaire April Brown, who led the spirited cash prize raffle. What better way to spend a Sunday afternoon than to have a great time and raise over $50,000 in support of Bank On A Cure®! Jerry Pransky is a true champion and is planning to hold the next "Fiesta for A Cure" at Mountaingate Country Club on July 25th. We invite you to join us for a wonderful afternoon of great food, fun, and prizes.

From Coast to Coast IMFers are organizing events, and these are only two examples of the fun and creative ways to raise awareness about myeloma and much needed funding for research. If you have an idea for a fundraiser or would like to find out how you can get involved in one of the IMF events in your area, we are here to help you get started.

Here's to making 2004 another banner year for the IMF! MT

Note: Please contact Suzanne Battaglia or Stephen Robertson at 800-452-CURE (2873). You can also contact Suzanne at sbattaglia@myeloma.org and Stephen at srobertson@myeloma.org. To view a calendar of upcoming IMF events, please go to page 4 or visit www.myeloma.org.

I'm Not Leavin'

Michael Tuohy

Like all multiple myeloma patients, I was shocked and devastated when diagnosed. It was September of 2000. I was 36 years old, with a 7-year-old daughter and a 2-1/2- year-old-son. My wife Robin had given up her career as a paralegal to stay home and raise our children. I was the family's sole breadwinner. Would I be there for them? I wanted to teach my son to play baseball and to walk my daughter down the aisle. And, when the anger and fear subsided a bit, I realized that I needed my family to know that I will fight the beast known as myeloma with every ounce of my energy and with a positive attitude that I *will* be there for them. And that along the way I will do all that I can to help others facing myeloma.

Michael, Mikey, Allie, and Robin Tuohy

Robin searched the web for resources and found the IMF. When Susie Novis called and asked if we would like to go to Washington, D.C., with the IMF to represent young patients with myeloma, we were all fired up to raise awareness and ready to urge our representatives to support much-needed funding for research. That was in 2001, the year of the blood cancer hearings in which Geraldine Ferraro told of her diagnosis. While in D.C., we met other myeloma patients for the first time. We came home more inspired than ever to be proactive in fighting the beast. With the help of the IMF, we started the first myeloma support group in Connecticut.

I wrote a song for our two young children to help them to deal with what I going through. After writing the song, I decided to donate it to the IMF as a way to not only generate funding for myeloma research and education but also to create awareness about the disease. I hope that the song will inspire others to fight, to be positive, and to be proactive in their journey with myeloma. We are donating all proceeds to the IMF, an organization staffed by the most wonderful and caring people for myeloma patients and their families, to help support the IMF in their continuous efforts to find a cure for myeloma. MT

Note: The CD is available through the IMF. It is priced at $10 plus postage. In the U.S., shipping fee is $1.06 via First Class Mail. If you are located outside the U.S., please contact Kemo Lee of the IMF at klee@myeloma.org or 800-452-CURE (2873) and he will quote the delivery cost for your destination.

Excerpt from *I'm Not Leavin'*
Music and Lyrics by Michael Tuohy, ©2003

Well, the road that I've traveled is mighty uncertain
Some things in life aren't ever justified
If I could hide all my feelings simply believing
All of my sorrow would fade away

Well, I've been faced with tough decisions
But for the first time in my life
I'm looking at the future with my eyes open wide...

I'm not leavin' I have too much left to live for
I'm not leavin' gonna fight for my life
I can deal with it – I won't let it take me down
Feeling that my heart will heed the call

There are so many reasons for me to believe that
I can take anything that comes my way
I have too much to live for – and nothing to die for
All of my dreams will reach their destiny

If I could ever find a way to turn back time
Would I even realize to see the light?
In my heart I know, while my faith still grows
Waiting for that silver lining to unfold

Now I'm looking for answers to so many questions
Yearning to live, is this a test for me?
And I know I'm inspired by a spirit that's higher
All of my dreams will reach their destiny

Well I'm turning back my change of fortune
Ready for a long hard ride
lookin' at the future with my eyes open wide...

I'm not leavin' I have too much left to live for
I'm not leavin' gonna fight for my life
I can deal with it – I won't let it take me down
Feeling that my heart will heed the call.

Praise for *I'm Not Leavin'*

I received the CD a couple of hours ago. Thank you so much! As first I played it, I burst into tears: a mixture of emotions rushed to my heart. Bravo, Michael! Your lyrics are the words that every human being comes to speak one day. Your song makes me feel the courage, the strength, the thirst for understanding and acceptance, and at the same time the celebration of life with all its ups and downs. Thank you again for the precious gift of your music!

Lots of love,
Meena Annovazzi-Catellani
Torino, Italy

IMF Supports Senator Hutchison Initiative

(l-r) IMFer Carol Klein, NCI Director Andrew von Eschenbach, Geraldine Ferraro, Sen. Kay Bailey Hutchison, and IMF's Michael Katz and Susie Novis

The announcement made on March 24th by the office of Senator Kay Bailey Hutchison (R-TX) regarding funding for the Geraldine Ferraro Blood Cancer Education Program at the Centers for Disease Control and Prevention (CDC) was met with tremendous support by the IMF. We are inspired by the courage of Geraldine Ferraro in raising the awareness of multiple myeloma and the leadership of Senator Kay Bailey Hutchison to secure the financial resources needed for the education of all people fighting cancer. The important potential of the Ferraro program is also underscored by the support of One Voice Against Cancer (OVAC), a 50-plus member cancer funding coalition, and the National Patient Advocate Foundation. We believe this program will foster the creation of new partnerships and models of outreach. This will empower all blood cancer patients and provide them with increased knowledge.

Multiple Musicians Against Myeloma

IMFer Naomi Margolin is organizing the 2004 Multiple Musicians Against Myeloma event. Some of Long Island's best-known musicians and performing artists will gather on Sunday, June 11, 2004, for an all-day celebration to help defeat multiple myeloma. Please join us for an unforgettable evening at Tupelo Honey restaurant in Sea Cliff, NY. For more information, please contact Naomi at 516-487-6712.

Recipes for a Cure, Volume 2

Sharon Klein and her twin sister, myeloma survivor Marilyn Alexander, were the driving force behind our very popular cookbook. The project was a huge success and all of the copies have sold out. Sharon and Marilyn are now compiling recipes for the second volume of the cookbook. We invite you to help us with this project by contributing your favorite healthy food recipes to this upcoming publication. Please send your submissions to Marilyn Alexander at alex19115@aol.com or 8913 Alton Street, Philadelphia, PA 19115. Please include your name, city, state, and e-mail address, along with the category that your recipe would fit into (Appetizers, Beverages, Breads, Desserts, Entrees, Pasta, Salads, Soup, and Vegetables).

IMF Educational Materials In Japanese

A new Japanese version of the *IMF Concise Review* has been translated and published by the Tokyo Representative Office of the IMF. To obtain a copy of this publication, please email Ms. Ikumi Okubo at okuboikumi@nifty.com, call her at +81(426)24-9848, or fax her at +81(426)24-9864. The Japanese version of *IMF Patient Handbook* is not yet completed. However, the *MM Handbook*, the 256-page publication of the IMF Tokyo Representative Office, can be ordered from Ms. Okubo.

2003 IMF Honor Roll Omissions

Our heartfelt appologies to the Los Angeles Area Multiple Myeloma Support Group for not listing their generous gift of $1,001-$5,000 in the 2003 IMF Honor Roll.

Austrian Multiple Myeloma Support Group

Ilse Hein, myeloma survivor since 1992, is the current support group leader of the Austrian Multiple Myeloma Support Group. The group welcomes your inquiries and participation:

Selbsthilfegruppe fuer Multiples Myelom Oesterreich
Buerglsteinstrasse 21-10
5020 Salzburg
Austria
+(43) 664 1318838
myelom.shg@aon.at
www.myelom-selbsthilfe.org

Talk About Cancer With Children of All Ages

CancerCare, in collaboration with the Lance Armstrong Foundation, the National Cancer Institute, the Intercultural Cancer Council, Living Beyond Breast Cancer, and the National Coalition for Cancer Survivorship, is presenting *Cancer Survivorship: Living With, Through & Beyond Cancer,* the 2nd Annual Cancer Survivorship Telephone Education Workshop. *Talking About Cancer With Children of All Ages* workshop will take place on Wednesday, April 14, from 1-2 p.m. (Eastern Time). The faculty will be Wendy S. Harpham, MD, FACP, Attending Physician, Department of Internal Medicine, Presbyterian Hospital of Dallas; Melissa Hicks, MS, CCLS, LPC, RPT, Child Life Specialist, Program Director Camp Sunshine, President, Child Life Council, Co-Founder, Wonders & Worries, Inc.; David K. Wellisch, PhD, Professor in Residence, Chief Psychologist Adult Division, Department of Psychiatry, UCLA School of Medicine, Department of Psychiatry. The workshop is free – no phone charges apply. To register, go to www.cancercare.org and click on the *CancerCare Connect* icon.

Letters

Dallas P & F Seminar: An Open Letter To The IMF

Dear Peter,

That was a great letter and expresses how we all felt after a weekend with Brian and Susie, Mike, Greg, and staff... We are all encouraged by the IMF and their support. Yes, we like to see the advances in treatment, but we need to be carried through the process. That is what the IMF does for us. Thank you again, Peter, for expressing it so well.

Ann Waldmann

Dear Peter,

Thank you for your beautifully written letter. You expressed the sentiments of many of us who have been the recipients of TLC from the International Myeloma Foundation. My feelings of aloneness with multiple myeloma ended when I found the IMF and all of its wonderful staff, members, and volunteers.

Deborah Eller

Dear Peter,

I can only say 'amen' to what you have written (and wish I had your talent for putting thoughts and feelings into words). Thank you for sharing this with us!

Cathy Lebkuecher

Robert Reeves (center) with friend and daughter

BRAVO!!!

Very well said, and I second it. We here in Philadelphia feel the same way and can't thank all the efforts of the IMF enough! You are our true heroes!

Marilyn Alexander

Wow, Peter! Wish I'd said that. Very nicely done. And so very well deserved.

Debbie Exner

Dear Peter,

Your letter brought tears to my eyes. What can I say—the seminars are profoundly felt on both sides. It was an honor to meet you and Lucy, Marcia, and Jerry, and all the wonderful members of the North Texas Support Group. The courage of myeloma patients and their families—what some smart soul defined as their "grace under pressure"—is what gives those of us at the IMF inspiration to work harder and be better, in our jobs and in our lives. Thank YOU.

Debbie Birns

ASH 2003: An Avalanche of New Information

Just wanted to say that I found Dr. Duries's remarks very useful. His summaries are very helpful and I will be looking up many of the abstracts in the literature. Many thanks!

Jim Mutch

IMF Hotline

Dear Debbie & Nancy:

Many thanks to both of you for your caring guidance and counsel. Words cannot express what your being there to answer my many questions means. You always answer in a cheerful, positive and caring manner. Again, thanks.

The IMF website is great and provides much needed information to both patients and family. And, the "Management Guidelines" you sent me answers many questions and provides a concise analysis of the complete picture.

I am sending you photos taken at bike rides this year. One was taken at a 50 mile ride... The pictures put a face on the voice you talk to.

Robert Reeves

Dear Debbie,

I reconcile to the fact that the IMF is a true friend at all times. Your attention, concern, and cooperation enhances all the good virtues that the IMF is doing in regard to the myeloma patients, worldwide. The paradigm *"Until There is a Cure... There is the IMF"* is VERY true. Many thanks for your efforts, and to the IMF.

V.K. Varma, India

IMF InfoPack

Thank you for the information pack I received today. I think it is so generous of you to provide them to anyone, anywhere in the world. Thanks again and all the best for 2004... The Year of the Cure!!

Barbara Stewart, Australia

The Myeloma Minute Email Newsletter

Just a special thank you for the newsletter email. It gave us more information about the disease than we had been able to find anywhere else. We hope that 2004 will bring new and bright hope to all MM patients.

Jack and Wanda Wahus

ADVANCES IN MYELOMA TREATMENT: THE PAST 10 YEARS

Prognostic Factors

Several clinical factors have been linked to a poor prognosis in patients with multiple myeloma. The presence of cytogenetic abnormalities represents the most powerful adverse prognostic factor, present in one-third of newly diagnosed patients with symptomatic disease. The hazard of relapse and death with such chromosome abnormalities increases by two- to three-fold.

New Agents

Thalomid®. Thalidomide was only the third compound, behind melphalan and dexamethasone, to be recognized as an independently active treatment for myeloma. One hundred and sixty-nine patients who were enrolled in a clinical trial and received up to 800 mg of the drug per day had a partial response rate of nearly 33% and extended event-free and overall survival. Thousands of myeloma patients have since benefitted from thalidomide treatment, which can be combined with chemotherapy because thalidomide does not interfere with the bone marrow production of blood cells and platelets. However, 50-80% of patients treated with thalidomide can suffer from peripheral neuropathy, a condition in which the nerves are affected, causing pain, numbness, or weakness of the extremities. In some patients, reducing the dose of thalidomide or stopping the treatment altogether will alleviate the symptoms. In a randomized clinical trial of Total Therapy II, the 4-year estimate of grade 3 or greater sensory neuropathy was 16% among 263 patients receiving thalidomide and 5% among 280 patients receiving no thalidomide. The combination of thalidomide and dexamethasone as both induction therapy (given prior to autotransplant-supported melphalan therapy) and as maintenance therapy (given after melphalan therapy) is now being examined by the Southwest Oncology Group (SWOG).

Revimid®. The thalidomide derivative, Revimid or CC-5013, can beneficially alter the patient's immune system and kill myeloma cells both directly and indirectly by altering the bone marrow microenvironment. One-third of patients with advanced and refractory myeloma respond with at least a 50% reduction in measurable myeloma protein, typically associated with marked improvement or normalization of bone marrow. Revimid is essentially devoid of neurotoxic side effects but produces myelosuppression that is readily reversible, unless there is major bone marrow compromise from extensive prior alkylating agent therapy.

VELCADE®. VELCADE has been shown to have remarkable activity in patients with myeloma that has not responded to other regimens, including thalidomide. Also referred to as PS 341, this is one of a new class of agents for the treatment of myeloma, known as proteasome inhibitors. We are currently testing a combination of VELCADE plus thalidomide for patients relapsing after melphalan-based autotransplants. Nearly 70% of more than 60 patients with sufficient follow-up achieved at least a partial response at the end of the third cycle of therapy, including nearly 20% who achieved complete remission.

Other Agents. Arsenic trioxide is another treatment under investigation. This compound targets mitochondria, the energy power houses in our cells, and thus may be able to initiate programmed cell death of myeloma cells. Other compounds under investigation by ourselves and others include monoclonal antibodies to interleukin-6 receptor and CD20, farnesyl transferase inhibitors, and STI 571 (Gleevec®).

Immunotherapy

Interferon was the first biologically-based treatment for myeloma. Randomized trials have revealed that patients receiving interferon as maintenance therapy had slightly improved event-free and overall survival compared with those receiving no maintenance therapy. Trials are also underway to determine whether vaccinations that have been developed from patients' myeloma cells may be another means of treating the disease. We have begun an exciting trial employing cancer testis antigen peptide vaccination. These tumor-specific antigens, not present on normal tissue except testis, are expressed in over one-half of patients with myeloma, especially at the time of relapse in the high-risk setting of cytogenetic abnormalities.

Mini-Allogeneic Transplants

Allogeneic transplants use stem cells from a donor, usually from a matched sibling. Only 1 of 7 patients potentially benefit from allogeneic sibling transplant. Major complications include graft-versus-host disease and opportunistic infections, which cause high first-year treatment-related mortality of about 50%. However, survivors of allogeneic transplants may experience fewer late relapses than survivors of autotransplants. The "mini-allo" transplant differs from the standard myeloablative regimens in that lower doses of conditioning treatment are employed, such as total body irradiation at 2 Gy or melphalan at 100 to 140 mg/m^2 with or without fludarabine. Mini-allogeneic transplants are much better tolerated because of a virtual absence of mucositis and other toxicities, resulting in a marked drop in treatment-related mortality, from approximately 50% with standard allotransplants to the 10%-15% range. In view of the marked efficacy of donor lymphocytes in killing recipient myeloma cells, and in cases of cytogenetic abnormalities, we are offering this approach to high-risk patients following maximum disease control achieved safely with a single autotransplant (tandem auto/mini-allotransplant).

Targeting the Bone Marrow Microenvironment

Myeloma cell survival depends on interactions with the bone marrow "neighborhood," the microenvironment. Thus, researchers have demonstrated that with treatment targeting the microenvironment by way of 1) osteoclast-inactivating bisphosphonates (Aredia or Zometa); 2) disrupting myeloma-stromal cell interaction (thalidomide, Revimid, VELCADE); or 3) inhibiting angiogenesis; myeloma cells die and bone is preserved.

SUMMARY

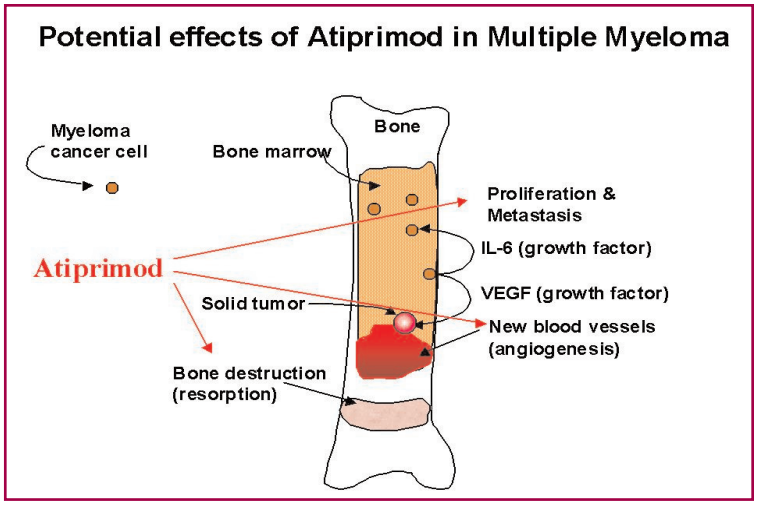
Myeloma researchers agree that, in order to control multiple myeloma, achieving a high frequency of complete remission early in the management is important for long-term benefit. Because of its potential for inducing a complete remission in nearly half of our patients, autotransplant-supported high-dose melphalan, especially in the setting of tandem transplants, has emerged as a safe platform of treatment upon which improvements can be anticipated by introducing thalidomide, Revimid and VELCADE for remission induction prior to, and for maintenance after, autotransplants. Reduced melphalan doses at 100 to 140 mg/m^2 with autologous hematopoietic stem cell support have recently been shown to be effective and safe in patients presenting with renal failure or advanced age (> 70 years), so that the majority of patients with myeloma can now be offered this highly effective therapy. We recommend that all patients with newly diagnosed myeloma be considered for appropriately dose-adjusted high-dose melphalan with stem cell support. The discovery of active new drugs, the immunomodulatory agents thalidomide and Revimid, as well as the proteasome inhibitor VELCADE, has given hope to patients with refractory end-stage disease. MT

Note: The International Myeloma Foundation is proud to present its second Robert A. Kyle Lifetime Achievement Award to Bart Barlogie, MD, PhD, Professor of Medicine and Pathology, and Director of the Myeloma Institute for Research and Therapy in Little Rock, Arkansas. Dr. Barlogie is being honored for his outstanding body of work, both clinical and research, in the field of myeloma. The IMF is giving this award to recognize his tireless work to significantly improve care, treatment, and prognosis for many myeloma patients.

The IMF's Robert A. Kyle Lifetime Achievement Award was established to honor an individual whose lifetime body of work furthers the ultimate goal of finding a cure for myeloma. The accolade is named for Dr. Robert A. Kyle, noted physician and founder of the Myeloma and Related Diseases Research Group at the Mayo Clinic in Rochester, Minnesota.

The award will be presented at a dinner at the Peabody Hotel in Little Rock on May 8, 2004. For information on participating in the evening or placing an ad in the Tribute Book being assembled in Dr. Barlogie's honor, please contact Stephen Robertson by email at srobertson@myeloma.org or by calling 800-452-CURE (2873).

Atiprimod — continued



other methods of controlling the bone disease, the effects are not totally abated, particularly in patients who relapse or become refractory (resistant) to chemotherapy. The capability of Atiprimod to control bone resorption could potentially provide a significant additional benefit in the treatment of multiple myeloma patients.

Atiprimod is about to enter a Phase l/lla[3] clinical trial in relapsed multiple myeloma patients in March 2004. These are patients who no longer respond to chemotherapy and are in advanced stages of the disease. The Phase l/lla trial will be performed at two sites, Dana-Farber Cancer Institute (Boston) and M.D. Anderson Cancer Center (Houston), with Principal Investigators Dr. Nikhil Munshi (Dana-Farber) and Dr. Moshe Talpaz (M.D. Anderson). The trial is an open label study, with the primary objective of assessing the safety of the drug, and the secondary objective of focusing on evaluating early indicators of efficacy (any responses in multiple myeloma patients). The duration of this clinical study will depend on how well the drug is tolerated and on drug response, with final results not available until the end of 2004. MT

TERMS & DEFINITIONS

(1) Phase I clinical studies generally involve a small group of people who take the same drug but via different methods of delivery or different dosages. The purpose of the study is to measure safety and dosage of the drug.
(2) An open label trial is a clinical study where each patient and doctor knows what each patient is receiving as the study drug.
(3) Phase l/IIa studies combine a Phase I study, testing the safety and dosage of a drug, with an early indication of drug response (efficacy) that is otherwise typically not explored until a classic Phase II study.

See Atiprimod, Page 26

typically thought of as only killing cancer cells, but in fact they have many effects, and sometimes can actually activate signals that promote the survival of cells. This can be a desired outcome, because it may decrease the toxicity of some drugs against normal cells, thereby minimizing side effects to the patient. However, it can also be harmful, because if it promotes the survival of cancer cells then the drugs have actually decreased their own effectiveness against the tumor. In multiple myeloma one of the most important of these mechanisms is the so-called nuclear factor kappa B (NF-κB). When activated, NF-κB opposes apoptosis in a number of ways, one of which is by inducing a family of proteins called IAPs, or inhibitors of apoptosis. These proteins are able to slow the process of cell death stimulated by chemotherapy and radiation by binding to proteins called caspases, which are the catalysts that carry out the cell death program. NF-κB is activated in cells treated with drugs that are active in multiple myeloma, such as doxorubicin and melphalan, and also by other treatments, such as radiation. Since NF-κB is found in all myeloma cells, it can contribute to resistance to chemotherapy at every stage of the disease process.

VELCADE®

The approval in May of 2003 of the drug bortezomib (VELCADE®; formerly known as PS-341) by the Food and Drug Administration after positive results against multiple myeloma in Phase-I (2) and –II (3) clinical trials was an exciting development. This drug works by inhibiting the proteasome, which is a large complex in cells that is responsible for removing damaged proteins, and also proteins that have already served their purpose for the cell and are no longer needed (reviewed in (4)). Bortezomib, made by Millennium Pharmaceuticals, was approved for treatment of patients who have had at least two prior therapies, with progression of that disease on the last of these. Its ability to induce a complete remission in 10% of patients, and either a complete or partial response in 27%, was very encouraging (3). In addition, the drug was able to double the time to disease progression in patients with multiple myeloma compared to whatever had been their previous therapy. This is different than the usual trend with additional chemotherapy regimens for briefer durations of benefit, as described above. Perhaps most exciting about this drug, however, are studies that show bortezomib can help to overcome all of the mechanisms of chemotherapy resistance described above.

Chemotherapy drugs are typically thought of as only killing cancer cells, but in fact they have many effects, and sometimes can actually activate signals that promote the survival of cells.

How VELCADE® Counteracts Drug Resistance

Laboratory studies of cells that overexpress the Bcl-2 survival protein showed that exposure to bortezomib resulted in both phosphorylation of this protein and also cleavage into small fragments (5). This reduces the Bcl-2 level in cells, and likely makes them more susceptible to chemotherapy, which accounts in part for the ability of bortezomib to induce apoptosis independent of Bcl-2 status. With regard to the P-glycoprotein pump, studies have shown that function of the proteasome is needed for normal P-glycoprotein to be made (6, 7). When the proteasome is inhibited, abnormal immature forms of this protein accumulate which cannot pump chemotherapy drugs from the inside to the outside of cells. Since this results in greater levels of these drugs inside cells, it could enhance the ability of these drugs to kill myeloma cells. Finally, in terms of NF-κB, proteasome inhibitors work at several steps of this pathway, and block both the ability to make some parts of the NF-κB transcription factor (8), as well as its ability to move into the nucleus, where it activates proteins such as IAPs that block apoptosis. Based on just these findings alone, there would be excitement about the possibility that bortezomib could enhance the anti-tumor efficacy of standard chemotherapy drugs used in myeloma

Drug Synergy

Even more optimistic are laboratory studies looking at the ability of combinations of drugs including bortezomib to kill myeloma cells. In the first pioneering work that showed the promise of bortezomib against myeloma in the laboratory (9), investigators were able to show that the addition of steroids caused more cell death than either of the two drugs by themselves. This is called drug synergy, and is not always found between drugs, because some combinations will actually antagonize each other and cause less cell death, possibly compromising their clinical efficacy if they were tried in patients. Also, cells that had previously been resistant to steroids were once again able to be killed by these drugs when they were added in combination with bortezomib. Other drugs that are used in patients with multiple myeloma have been tested with similar results (10-12), showing synergistic cell killing, and also the ability to kill previously drug-resistant cells. These studies included agents such as melphalan, doxorubicin, and immunomodulatory analogs of thalidomide, and strongly supported the testing of such combinations in patients with multiple myeloma.

VELCADE® Plus Melphalan

Based in part on the laboratory studies described above, several drug combinations either are being tested, or already have been, with a focus on myeloma, one of which is the combination of melphalan and bortezomib (13). Melphalan is also called Alkeran®, and is made by Celgene Corporation.

In the most recent update of these results, presented at the December meeting of the American Society of Hematology (ASH), Yang and colleagues showed the outcome in the first 15 patients treated. From a side effect standpoint patients tolerated the drugs well, probably due in large part to the fact that the first dose level used melphalan at 0.025 mg/kg, which is one-tenth the dose used in the melphalan/prednisone combination, and bortezomib was used at 0.70 mg/m^2/dose, or about one-half of the approved dose of 1.30 mg/m^2. Ten patients had responses, including five with partial responses, meaning that there was a 50% decrease in measurable disease burden, and some of these included patients who had previously received melphalan.

VELCADE® Plus Thalidomide

Another combination that has been studied is that of thalidomide and bortezomib (14). Thalidomide is also called Thalomid®, and like melphalan is also made by Celgene Corporation. At the ASH meeting last December results from the first 56 patients treated were presented, all of whom had relapsed after transplantation, and 81% of whom had previously received thalidomide, to which their disease had become resistant. Zangari and colleagues noted that the combination was well-tolerated, and while peripheral neuropathy was a frequent event, it generally was mild to moderate, and not severe. This is important because peripheral neuropathy is a known complication of both thalidomide and bortezomib by themselves, and one concern about combining them would be that patients would have even more of this problem. Neuropathy is caused by damage to the nerves and can present in many different ways, including numbness, tingling, burning, and pain, especially in the extremities, and sometimes can cause weakness and even impair the ability to perform activities of daily living. If such symptoms occur patients and their healthcare providers generally choose either to decrease the doses of the responsible drugs, or in more severe cases to stop the drugs altogether. There are also supportive care measures that can be used, such as supplementation with vitamins like B-complex, including B6, vitamin E, and folic acid, and also some prescription medications, like gabapentin (Neurontin) and Elavil. Neuropathy can improve over time once the drugs causing it are stopped, but the time course can be very long, and may take weeks to many months. Also, since nerve tissue does not regenerate or heal well, some patients may be left with a residual, permanent neuropathy. In addition to these findings on neuropathy from this study, more impressive was the fact that 22% of patients had a complete response, and 57% had either a complete or partial response. Such responses occurred even in patients whose myeloma had deletion of chromosome 13, which is usually a poor prognostic sign that predicts a worse response to most therapies than patients without this cytogenetic abnormality. Finally, the response rate was reported to be the same in patients receiving bortezomib at 1.0 mg/m^2/dose and the lowest dose of thalidomide, 50 mg per day, compared with those receiving higher doses up to 200 mg of thalidomide daily. This is important because it suggests that it might be possible to reduce the doses of the drugs given to patients with comparable, or maybe even enhanced efficacy, and such reductions will make the drugs better tolerated.

> Thus, it may now be possible to overcome the resistance of myeloma cells and recapture drug sensitivity, allowing the beneficial reuse of agents which would previously have not been considered options for patients because of prior exposure.

VELCADE® Plus DOXIL®

The last two-drug combination that was presented at ASH used bortezomib and pegylated, liposomal doxorubicin (15). This drug, better known as DOXIL®, is made by Tibotec Therapeutics, and is a different preparation of the standard drug doxorubicin. Pegylated liposomes are lipid bilayers similar to cell membranes, and the doxorubicin is contained inside these structures. There are several advantages to this formulation compared with regular doxorubicin. One of these is that because the drug is released very slowly from the liposomes, it can be given intravenously over one hour, but stays in the body over a long period of time, similar to the effect of a continuous infusion of doxorubicin like many patients receive with the standard "VAD" regimen. Because of this, patients do not need either a central line for these infusions of doxorubicin or an infusion pump, and instead can receive DOXIL® through a regular peripheral intravenous line. Also, the drug appears to be less toxic to the heart than standard doxorubicin which, if given at a cumulative dose in excess of 550 mg/m2, can cause a so-called cardiomyopathy, with decreased heart function that in severe forms causes congestive heart failure. In this study, which was done at our institution, bortezomib was given as an intravenous bolus dose on days 1, 4, 8, and 11 of a 21-day cycle in a range of doses, though the final study recommendation will be to start with 1.3 mg/m^2/dose. DOXIL® was given on day 4 about one hour after the bortezomib at a fixed dose of 30 mg/m^2. Patients tolerated the combination well, and the side effects were those that would be expected if either drug were used alone. Side effects that were seen in at least 25% of patients

See Drug Resistance, Page 22

included fatigue, thrombocytopenia (low platelet count), nausea, constipation, anemia, neutropenia (low white cell count), decreased appetite, diarrhea, neuropathy, and mucositis, or mouth sores. Responses with at least a 50% reduction in disease burden were seen in 73% of patients, with 36% having a complete response. Of particular interest is that there were 13 myeloma patients on the study who had previously received either standard doxorubicin or DOXIL® itself, and whose disease had either progressed despite this therapy, or at best not responded and remained stable. Out of these 13 there were complete responses in 5 and partial responses in 3, suggesting that bortezomib was indeed able to reverse resistance to doxorubicin in at least some of these patients. Also encouraging is the fact that of the two patients who went on to transplant after this treatment, both were able to have good numbers of stem cells collected, suggesting that this combination does not damage stem cells and does not close the door to later transplantation.

Avenues for Further Research

All of these studies have so far been done only at single institutions, and the number of patients treated has been modest, so larger trials done at many centers will be needed to confirm these preliminary results. Several such studies are already being planned, and hopefully some of the results will be available soon. None of the combinations have yet been tested head-to-head in a randomized fashion, which is the best way to compare them directly, so it is not possible to know which is better, or if one is better for some patients while others may benefit from another. Other two-drug combinations based on bortezomib are being tested as well, including one trial of the thalidomide analog CC-5013, which is also known as Revlimid™, and made by Celgene Corporation. Finally, some investigators are looking at three-drug combinations, hoping that there would be a further improvement in efficacy. Thus, there certainly remains much work to be done in this area. Also, it should be pointed out that there are many other agents being studied that also may be able to overcome drug resistance in multiple myeloma. One good example is oblimersen, or Genasense™, being developed by Genta Incorporated, which is an anti-sense oligonucleotide that decreases levels of Bcl-2 protein.

However, there are many encouraging results that have been obtained so far from the bortezomib studies described above. The overall and complete response rates of some of the bortezomib-based combinations appear to be higher than what would be expected with either bortezomib alone, or with the standard chemotherapy agent alone. This supports the possibility that the drugs are acting synergistically to kill myeloma cells. Some patients with disease that was previously resistant to the standard chemotherapy have had significant responses, including many complete responses, to the combination of this same agent and bortezomib. This supports the possibility that bortezomib is able to overcome drug resistance. Also, the fact that some of these responses occurred at doses that were less than what would be considered standard is encouraging. If lower doses can be used, side effects will be decreased, and more people will hopefully benefit from therapy because fewer patients will need to stop treatment due to drug-related toxicities.

What This Means to You

What does all this mean for patients with myeloma, their families, and their health care providers? First of all, these combination regimens will be tested in additional trials, and by enrolling in these studies patients can have access to cutting-edge medicine using drugs that are known to have benefits against multiple myeloma. Only by doing such studies and collecting and analyzing the data will we be able to know which combinations work best and, possibly, which regimen is better for which type of myeloma patient. This may lead ultimately to the ability to predict ahead of time which therapy would be best for each patient as an individual. For those patients who do not have access to such trials, however, since all of these drugs are FDA-approved, it is possible to receive this therapy without enrolling on a clinical study. While these regimens will probably not be the cure for multiple myeloma, they may represent a new concept in the treatment of this disease. In the older paradigm, patients were treated with certain drugs, but once their disease no longer responded that drug was never reused, because the myeloma cells retained their drug resistance to that agent by passing those genetic characteristics on to their progeny. With the availability of drugs such as bortezomib, which seems able to overcome such resistance, this treatment paradigm may need to be changed. Patients whose disease was resistant to thalidomide or doxorubicin were able to have significant responses to these agents in combination with bortezomib, as noted above. Thus, it may now be possible to overcome the resistance of myeloma cells and recapture drug sensitivity, allowing the beneficial reuse of agents which would previously have not been considered options for patients because of prior exposure. As a result, the number of treatment options available to patients may be dramatically increased, which is the next best thing to a cure. Furthermore, the enhanced complete response rates suggests that such combinations will improve survival, and ultimately may form part of a multidisciplinary approach that will bring us closer to the cure for this disease. MT

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fulfill its mission of education, research, advocacy, and support.

Dr. Maurizio Zangari

In talking with first-time participants as well as those who had attended IMF seminars previously, it is very evident that no matter how many of these wonderful weekends one has been to, there is always new, pertinent information available. But perhaps even more empowering than the medical information you gain, is the knowledge that you are not alone, that there are many, many others who share your experience and who understand what you're going through. We at the IMF know this and are committed to being there for you every step of the way.

The Feltzin Family

I had heard what an opportunity these seminars provide to patients, caregivers, and health care professionals to interact and get the latest information on myeloma in a supportive and empowering setting. But actually seeing the invaluable benefits that individual patients derived from one-on-one consultations with our expert faculty members, as well as the extraordinary sense of community and support, is something I'll never forget. I truly was not prepared for the heartfelt gratitude that so many of this event's participants extended to me and the entire IMF team.

patient and caregiver consult with Dr. Durie

Our littlest volunteer Marisa Vaccaro assists Susie Novis during award presention ceremony.

On Sunday, many of the retreat's attendees took the opportunity to participate in a variety of special activities: yoga class, nutrition class, and nature walk through the beautiful grounds. The weather was spectacular, truly Florida at its best, and these additional activities provided a really nice way to wind down the weekend. The group said their goodbyes at a farewell luncheon, having truly benefited from the memorable experience of the retreat format of this particular IMF Patient & Family seminar event.

Ken and Mary Makowka with Susie Novis

The appreciation and feedback that I continue to hear from everyone in attendance is phenomenal. I have to admit, it touches me immeasurably to feel a part of a foundation that provides a truly valuable service to those affected by myeloma, and to be welcomed and acknowledged so warmly by so many of those at my first IMF event. I look forward to attending many more IMF events in the future and look forward to seeing familiar faces as well as meeting more of our members.

Have a safe and healthy 2004 and remember:
"Until There is a Cure... There is the IMF." MT

Note: Stephen Robertson has joined the IMF staff as Development Coordinator.

Joseph and Frances Spaid

Tribute to Janet Johnson — continued

Janet Johnson and Billy Ware

and was a superbly well-organized leader of the local chapter. Through the years, I became more and more impressed with Janet's leadership skills. She worked hard to locate a variety of speakers to include doctors, nurses, and myeloma patients. Her constant strength and her positive attitude toward life while her husband was fighting cancer were admirable. Janet and Art fought together for as good a quality of life as was possible, regardless of the treatments Art endured. She inspired us to do the same in our lives.

— Bob Brown

Few local support groups could possibly hope to have as a coordinator a person such as Janet Johnson. Her faithfulness, encyclopedic knowledge, common sense, and winsomness would be very difficult to duplicate!

— Ralph D. Winter

Janet and Art Johnson will be greatly missed for all their tireless efforts to make the support group what it is today.

— Carrie Lacy

Janet Johnson with Dempsey

Thanks for the gift of Janet and Art,
Stronger than granite in the heart.

— Dora Polk

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Atiprimod — continued

Note: Included in this article are "forward-looking" statements. Such statements are indicated by words such as "expect," "should," "anticipate" and similar words indicating uncertainty in facts and figures. Although Callisto believes that the expectations reflected in such forward-looking statements are reasonable, it can give no assurance that such expectations reflected in such forward-looking statements will prove to be correct. Callisto's actual results could differ materially from those anticipated in the forward-looking statements as a result of various factors.

Callisto is a biopharmaceutical company primarily focused on the development of drugs to treat multiple myeloma, other cancers, and osteolytic bone disease. Callisto's lead drug candidate, Atiprimod, is a small-molecule, orally available drug with antiproliferative and antiangiogenic activity. In addition, Callisto has programs focused on the development of an analog of the human intestinal hormone, uroguanylin, to treat colon cancer, and drugs to protect against staphylococcal and streptococcal bioweapons and as a protection against the devastating effects of toxic shock syndrome.

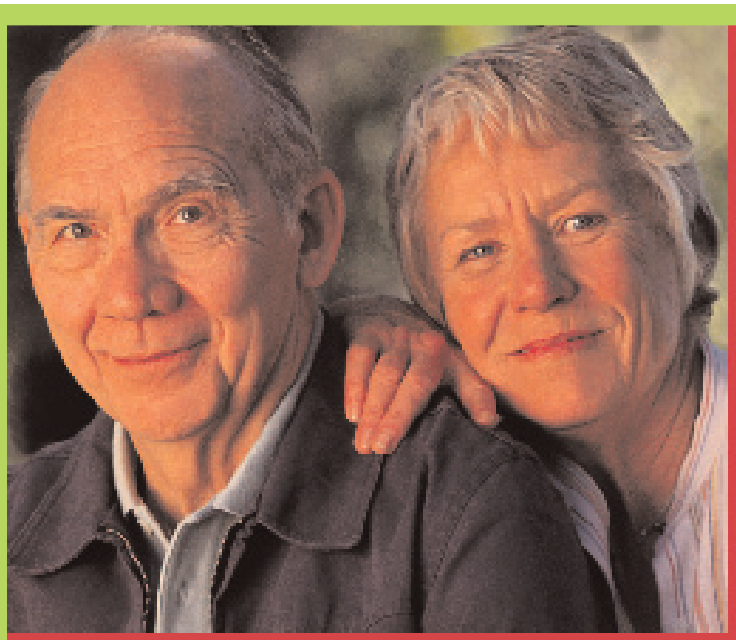
Callisto has two operating subsidiaries, Callisto Research Labs, LLC and Synergy Pharmaceuticals Inc. For additional information, visit www.callistopharma.com.

Political Pork — continued

Newsweek columnist Robert Samuelson wrote an essay titled "Medicare as Pork Barrel" shortly after the Medicare reform bill was passed by Congress. Rather than traditional definition of pork—highways, bridges, community programs, scientific research projects—Samuelson said the Medicare bill became a tool for satisfying a number of constituencies with influence over lawmakers.

The process behind the Medicare reform bill may provide a valuable lesson, but only if it can be linked to the real opportunities and probable outcomes of research. Policy makers must understand that unfulfilled opportunities in research will literally cost tens—if not hundreds—of thousands of lives over the course of the next couple of decades. MT

Note: For more information about how to become an effective advocate, please check regular updates in the IMF email newsletter, The Myeloma Minute, or contact Greg Brozeit at greg.brozeit@sbcglobal.net or 330-865-0046. To subscribe to The Myeloma Minute, please visit the IMF's website at www.myeloma.org.



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