IWMF NEWSLETTER

TORCH

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International Waldenstrom's Macroglobulinemia Foundation

INSIDE THIS ISSUE

DOCTOR ON CALL: DAVID G. MALONEY, M.D., PH.D.

David G. Maloney, M.D., Ph.D.

Dr. David Maloney is Professor of Medicine, Division of Oncology, at the University of Washington and Member, Clinical Research Division, the Fred Hutchinson Cancer Research Center. Early in the 1990's, while at Stanford University working with Ronald Levy, M.D., he conducted the initial clinical trials of the antibody rituximab in the treatment of patients with low-grade lymphoma. These initial studies ushered in a new era of treatment for patients with B-cell malignancies.

For our Doctor on Call series Dr. Maloney answers questions posed by the Torch *about the drug Rituxan (rituximab, MabThera) – possibly the drug most frequently used to treat WM, both alone and in combination.*

What is rituximab and how is it made?

Rituximab (Rituxan) is a monoclonal antibody that binds to a protein named CD20. CD20 is a molecule that is present on the cell surface of normal B-lymphocytes and on most of the malignancies that arise from B-lymphocytes, including most lymphomas and also WM. Rituximab is a chimeric antibody (from a fusion of two cell types) formed from protein sequences of mouse and human antibodies. The binding site that attaches to CD20 is murine (the mouse portion), while the rest of the antibody, which interacts with and attracts support from the immune system, is from a human antibody. Rituximab is produced by a cell line that is grown in tissue culture.

How was the dose and schedule of rituximab determined?

Rituximab was initially identified to have anti-tumor activity in the treatment of patients with indolent B-cell lymphomas based on a series of studies evaluating single doses from 10-500 mg/meter squared body surface area and then 4 weekly doses of 125-375 mg/meter squared. Because the treatment was well tolerated, the highest dose (375 mg) was selected for further study. Anti-tumor effects were observed at each of these weekly doses, and the drug was approved by the FDA in 1997 (using the 375 mg dose, weekly for 4 or 8 doses) for the treatment of relapsed low-grade lymphoma. Approximately 50% of patients had at least a partial remission lasting about 1 year. Subsequent studies have started to evaluate different doses and schedules. There is limited data that indicates some diseases (such as chronic lymphocytic leukemia) may require higher doses or a more frequent dosing schedule. In combination with chemotherapy, rituximab is usually given with each 3-4 week chemotherapy cycle. The usual doses are 375-500 mg/meter squared, but few controlled studies evaluating dosing have been done.

How does rituximab kill tumor cells?

Rituximab kills tumor cells either by interacting with the patient's own immune system or by changes induced in the tumor cells directly by the antibody binding to the CD20 on the cell

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surface. The immune mechanisms are thought to be the most important. Once the antibody is attached to the tumor cell, cells of the immune system are attracted to the cell and attach to the other end of the antibody, the FC portion (*fragment crystallizable* – the stem of the Y-shaped antibody) through specialized receptors (called FC receptors). This may then lead to the destruction of the tumor cells. There is some limited evidence that patients who genetically have cells with higher affinity FC receptors may have better responses to rituximab. Rituximab may also interact with another portion of the immune system, the complement system, that can kill antibody-coated cells by assembling a complex of proteins that poke holes in the tumor cell, leading to its death. Lastly, rituximab binding to the tumor cells may augment the effects of chemotherapeutic agents and other biologic agents used in lymphoma therapy, such as fludarabine and thalidomide.

What are the typical infusion related reactions to rituximab?

Rituximab is given by slow intravenous infusion. The initial doses are often associated with mild to moderate symptoms including fever, low or high blood pressure, allergic type symptoms of rash or wheezing or chills. These reactions are usually managed by slowing or stopping the infusion, or with medications. In some patients, however, the reactions may be severe, including, but very rarely, life-threatening. In most patients the reactions are with the initial infusions, although some patients may continue to react to subsequent treatments. The cause of the reactions is likely in part due to the killing of B-lymphocytes (normal and tumor) in the blood. Subsequent infusions are usually associated with fewer reactions, in part due to the persistence of rituximab in the blood from the prior treatment.

What is HAMA or HACA?

HAMA stands for "human anti-mouse antibody" and HACA stands for "human anti-chimeric antibody." These refer to the possibility of patients making an immune reaction against the rituximab antibody. Since rituximab has some protein sequences that are from a mouse antibody, it is possible for patients to develop an antibody response against rituximab. This is actually very rare in patients with lymphoma but more common in patients who receive rituximab for other diseases such as rheumatoid arthritis. Several of the "next generation" anti-CD20 antibodies are fully human

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3932D Swift Road • Sarasota, FL 34231-6541
Telephone 941-927-4963 • Fax 941-927-4467
E-mail: info@iwmf.com • Website: www.iwmf.com

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HAVE YOUR SAY

The *Torch* welcomes letters, articles or suggestions for articles.
If you have something you'd like to share with your fellow WMers,
please contact Alice Riginos at 202-342-1069 or ariginos@sy-thetis.org

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PRESIDENT'S CORNER

BY JUDITH MAY

Judith May, President

MEMBER SURVEY

Thank you to all of you who submitted your Member Services Survey Form. Forms were received from 8.9% of our members – not quite the 10% participation we hoped for. We do learn a great deal from your responses, and it was especially helpful that so many of you wrote comments. For example, we learned that while the website and our talk list IWMF-TALK were rated lower than our printed, hard-copy materials, the most common remark was the respondent's lack of a computer or that the information was too scientific to comprehend easily.

This very important exercise has given the Board of Trustees a better understanding of who uses the various services, and it will guide us in making some changes in the future. Your comments on weaknesses, strengths, challenges, and new services are extremely helpful. I believe the survey is something we should repeat every two years, and I hope that even more of you will respond the next time.

Member services are listed below in descending order according to your ratings, followed by the percentage of responders who indicated they had No Experience with a particular service. The percentages will not always add up to 100%. This gap is due to those who decided not to rate a particular service. I did not assume this meant No Experience as they could have chosen that rating if it were so.

Responders:

IWMF Members:	94.4%
Non-Members:	5.6%
United States:	6.4%
International:	2.5%
Total:	8.9%

Rating of IWMF Member Services:

	Rating	No Experience
Torch	96.9%	2.4%
Publications	89.5%	4.9%
Info-Pak	73.3%	25.6%
Website	60.0%	32.0%
IWMF-TALK	45.5%	49.3%
Ed Forum	43.8%	51.2%
Support Groups	41.8%	42.5%
Lifeline	23.4%	72.2%

NOTES REGARDING THE RATINGS

- The *Torch* was by far the favored service and we truly appreciate knowing this as we have made it our centerpiece for keeping you informed on a regular basis.
- Publications need no explanation. Our booklets and other written materials are very popular. We will continue to look for new topics and to update them when new information is available.
- The Info-Pak had many comments about how useful this was for newly diagnosed patients, which is the targeted group for that service.
- As stated previously, the website cannot be accessed by those who do not own computers. This fact contributed to a lower rating. Additionally there were comments from users that it needed to be updated more frequently with the latest news and sections needed to be revised to stay current. ***Presidential note:*** The last comment will soon be absolutely inapplicable because the new IWMF website (previewed on pages 6-7) is on the brink of being online and open for all, thanks to the perseverance of Vice President for Member Services Marty Glassman and Canadian volunteer Ron Ternoway, who spent the past months working closely with our contractor.
- IWMF-TALK has many self-described 'addicts,' but also there are those who find it too scientific. Others find too much social chatter.
- The Ed Forum rating was not unexpected since of our 3,000 members we cannot accommodate more than 300 at a Forum. Over half of responders reported having no experience. For those who did attend, the comments were overwhelmingly positive in regard to how much they learned and how helpful it was to meet and talk with other patients.
- The support groups' rating is influenced by the fact that 42.5% of responders have not been to a meeting. We still have vast areas of the country where we do not have sufficient numbers of WM patients to put together a support group. As our membership expands we are always looking for areas where patients are close enough to be linked as a new group.
- The Lifeline service is reported to be of use mostly to the newly diagnosed. However, there are those who don't use it because they find other ways to discuss their situations with patients (for example, in support groups). We will continue to offer this service as those who have used the Lifeline were so convincing in their support of this very helpful option for patients.

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President's Corner, cont. from page 3

In answer to the question **"How did you find the IWMF"** these were the responses:

Internet	54.2%
Doctor	19.0%
Other cancer orgs.	9.1%
Friend or relative	7.0%
SGL or member	3.5%
Arnie Smokler	2.8%

A number of you misread this to mean how you learned you have WM and we had answers such as blood test, BMB, physical exam, etc. These we had to discount. In fact, there were other misunderstandings of certain questions and realizing this will help us to be more specific in the next survey.

"Would you attend an Ed Forum held in the same year as a Summit meeting?"

Yes	28.2%
Maybe	13.8%
No	38.1%

We noted that many of the maybe's and the no's stated that they couldn't travel due to health problems, or the cost was too much to attend either one, or they would only go if it were close enough to drive to. This is not unexpected since it is our experience that the majority of WM patients do not go to conferences or meetings unless they are easily accessible.

NEW TRUSTEE

Carl Harrington of Philadelphia is a newly elected member of the IWMF Board of Trustees. Carl has a degree in history from Hamilton College, a Masters of Teaching from Brown University, and a Masters of Business Administration from the Wharton School of the University of Pennsylvania.

His career has been in marketing at some of the largest consumer-oriented companies in the U.S. In 1999 Carl and a partner formed their own marketing consulting company. Specializing in defining new strategic options, innovations, and new product development, they have handled all sorts of projects from website development to promotions to name changes. Several of his major clients have included Bausch & Lomb, Johnson & Johnson, and the American Marketing Association. Carl has worked domestically and internationally, both with clients and in consulting.

Several years ago Carl volunteered to help with pharmaceutical and foundation fundraising in hopes of using his marketing knowledge to help build IWMF's contributions. The Board has been very pleased with Carl's fundraising work and commitment to the Foundation and feels he has much to contribute to our fundraising goals.

Diagnosed with WM in July 2006, Carl is fortunate to be on 'watch and wait' since then.

IWMF EDUCATIONAL FORUM – JUNE 24-26, 2011

I'm delighted to announce that the 2011 Educational Forum will be held in Minneapolis, Minnesota, on June 24 to 26. We chose a northern, mid-western location because by moving to a different region each year we like to encourage attendance for those who may never have attended a Forum before. If you have kept track of the Forum locations you know that we continually move location – east, west, north, south, central, mid-west.

This year we will have early bird sessions beginning Friday morning at 9:00 am – to attend you will need to arrive Thursday evening. The topics of these sessions will soon be released. Friday afternoon we will hold breakout sessions beginning at 1:30 pm, and if you are there for lunch we will have box lunches available outside the meeting rooms. Friday will be a full day with the welcoming reception and dinner in the evening. This gives us the entire day on Saturday for presentations by the doctors and researchers who are continuing to do incredible research on our rare disease.

The Ed Forum hotel is the **Radisson Plaza Hotel** in downtown Minneapolis. There will be more details coming in other announcements. This hotel is in a wonderful location only five blocks from the riverwalk along the Mississippi River flowing through Minneapolis. Along the walkway you will find restaurants and shops as well as running and walking paths. The hotel is also near the large Nicoletta Mall area. Minneapolis has efficient and inexpensive transportation on the city's Light Rail service and on the covered skywalks above ground. The hotel's group rate is $119 and includes free wireless access in each room.

If you would like to see the Radisson's website, please go to: *www.radisson.com/minneapolismn_plaza*.

To make your reservation, call either 1-800-395-7046 or 612-339-4900.

There will be regular e-mails and mailings about the Ed Forum agenda as we develop the program and confirm the speakers.

I hope you will plan to join us in Minneapolis. I look forward to seeing you there.

Stay well,
Judith

TREASURER'S REPORT AS OF JUNE 30, 2010

BY BILL PAUL, TREASURER

The finances of IWMF are operated through two separate funds: the Research Fund and the Operating Fund.

The Research Fund accounts for all contributions received for research and is charged only for funds to be expended on approved research projects.

The Operating Fund accounts for contributions, from members and others, that are not designated for research, such as membership contributions. This fund is charged with all member services expenses and all operating expenses, none of which are charged to the Research Fund.

The following is a summary of the financial results for the first six months of 2010:

	Research	**Operating**	**Total**
Income	$233,000	$185,000	$418,000
Expenses	101,000	344,000	445,000
Net Income or (Loss)	$132,000	$(159,000)	$(27,000)

Income in the Research Fund was $127,000 more than during the same period in 2009. However, the Research Fund is still in a precarious position since three new research projects have recently been approved (see the report on page 8) and a greater need for funds will be evident over the next five years. Our current Research Fund bank and CD balance is just under $1,500,000 while we have research grants payable of $500,000, leaving us with a surplus of approximately $1,000,000 to apply to future grant requests. However, grants not shown on this June 30 statement total nearly $3 million. There is a great need for funding over the next three to five years to meet these obligations. On the positive side, these new financial obligations mean that IWMF is sponsoring new and exciting research projects, always searching for a cure. Your Research Committee does an outstanding job in finding, reviewing, and recommending sponsorship of these projects. It is now up to us to help with the funding.

The six-month deficit for the Operating Fund, while significant, is actually somewhat encouraging considering current economic conditions. The Operating Fund bank balances still hold enough in a cash position to meet our expenses for approximately six months, so we do have a small cushion.

Many thanks for your support in the past, and thank you in advance for your generosity in the future. IWMF needs our support now more than ever. Please continue to contribute.

If you have any questions, feel free to contact me at 901-767-6630 or *Billpaul1@juno.com*.

IWMF'S NEW WEBSITE

BY MARTY GLASSMAN, VICE PRESIDENT FOR MEMBER SERVICES

In the article below Vice President Marty Glassman compares the travails of the team working to launch the new website to sailing a ship in stormy seas. Pushing the metaphor a bit further, your editor, a crew member on the good ship IWMF Website, would like to commend Captain Marty and First Mate Ron Ternoway who stood firmly at the bridge through glitches and switches in course, eyes fixed, not on a nautical chart but on Marty's spreadsheet. Their perseverance has brought our ship into port and we can all now climb aboard.

For the last few years the challenge of developing a new IWMF website has engaged a number of IWMF volunteers. Our goal from the outset was not simply to give the old website a new look. We were set on creating a greatly improved tool to keep IWMF stakeholders as aware as possible about our illness, its treatments, and the possibility that "cure" would become part of the WM terminology.

It has not been smooth sailing all the way. Most recently those of us involved in the project experienced emotions that, from day to day, ran from high to low and back again. Some days it seemed that all the winds were blowing against us when illness hit participating volunteers or when our development vendor's company was sold. We were ready to abandon ship. Then there were the times when we would experience the elation of seeing images and text come together and we could see land in sight. We felt that if not that day then certainly by the end of a given week we would surely declare the website ready to run. At other times optimists among us even thought that once we had our new website up and running then everybody could retire from the project and we no longer would need a website committee. Of course, neither extreme was correct.

As we go to press in early September, we are still dotting all the 'Is' and crossing the 'Ts'. We have a small group of participants doing final testing. But I'll take the risk of playing the optimist and say that when the *Torch* reaches

IWMF's New Website, cont. on page 8

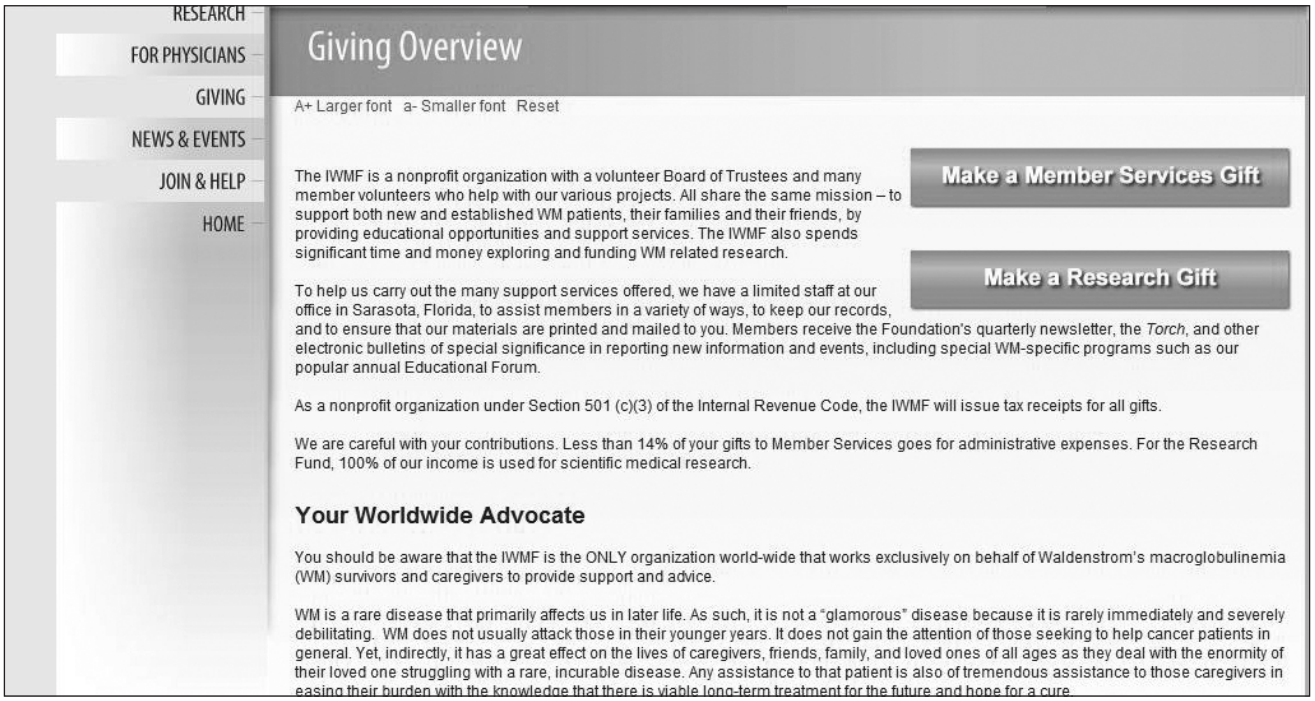
WELCOME TO THE NEW IWMF WEBSITE: A PREVIEW OF THE SCREEN IMAGES

The Home Page displays the IWMF mission statement and, to the left, the full menu of the website.

Visit the Home Page often to stay informed by messages from IWMF's President and WM-related news regularly updated.

WELCOME TO THE NEW IWMF WEBSITE: A PREVIEW OF THE SCREEN IMAGES

Giving to the IWMF – many options are now available online.



IWMF's annual Ed Forum provides education, information, and opportunities to learn and share.

you in October the website will be fully live and we will be inviting everyone to visit.

When you open *www.iwmf.com* you will see that there is a whole new look and feel. From the Home Page there are clear paths for the newly diagnosed and others who are not familiar with WM and treatment possibilities. Veteran patients will find the latest information available about new treatments and about clinical trials currently running or in the planning stage. And there is so much in between.

Most important of all, the new website demonstrates that our world of instant information and communication affords us improved opportunities together with challenges to keep on top of the fast-moving world focused on this very rare disease.

Our advice to users of the new website would be to:

- Visit the Home Page frequently
- Be especially aware of the changes and updates posted to the News & Events section
- Let us know what we can do to make the website more effective for your needs
- If you see another website that has some interesting features, either on their home page or within their content pages, that might be applicable to the IWMF website, pass that information on to us

Now for the key question: who do we thank for making the new website happen? The answer is **lots of people**. Over the past few years, lots of enthusiasm and optimism kept us going because so many individuals participated and reviewed our progress. Included are the office staff that keeps the "pieces glued together," the writers and editors who provided the content of the website, and our vendor, who not only did the technical work but also advised us how to approach the market place we were dealing with.

Even when we disagreed, we never forgot our primary goals:

To provide support, education, and information through publications and seminars to the WM "family" of patients – whether newly diagnosed or veterans – and their caregivers, physicians, and families.

To support WM related research through direct giving or active fundraising.

And speaking of fundraising – visitors to the new website will also note the expanded facilities for making a wide variety of gifts to the IWMF online.

In short, we have come a long way on the website voyage. I do expect that, when you read this, *www.iwmf.com* will be open for navigation by all who seek information about WM and about the IWMF. And already we are looking forward to developing an ever-increasing set of facilities and features to further serve our community.

RESEARCH UPDATE: IWMF AWARDS THREE MAJOR GRANTS

BY SUE HERMS

The IWMF has awarded grants for three exciting projects. Researchers in search of a cure for Waldenstrom's macroglobulinemia have for several years called for better tools in order to efficiently study the disease. IWMF has responded to their recommendations by approving three grants for providing these tools. First, in combination with the Leukemia and Lymphoma Society (LLS), the IWMF is sponsoring four scientists to develop stable and representative WM cell lines. A second IWMF-funded project is the development of a transgenic mouse model with characteristics found in WM patients. And, in addition, the IWMF is underwriting the establishment of a blood and tissue bank with samples from WM patients.

The Significance of Cell Lines to WM Research

Why are cell lines important in the study of a disease such as WM? When removed from tissues, cells (including cancer cells) will continue to grow and divide in culture if supplied with the appropriate nutrients and conditions. If the cells are derived from a single parent cell, the cell culture is a clonal cell line because all the cells are genetically identical. Cell lines can be used to investigate the physiology or biochemistry of cancer cells or to test the effects of various chemical compounds or drugs on specific cancer cell types. The major advantage of using cell lines for these applications is the consistency and reproducibility of results that are obtained from using a batch of clonal cells.

Although there are three cell lines currently used for WM research, both the validity and usefulness of these lines have been called into question. It has not been definitively established that these cell lines are genetically identical to the tumor cells of the patients from whom they were derived, and, in addition, at least one cell line has been reported to be unstable. Therefore these cell lines may not accurately represent WM.

In July 2009 the IWMF and LLS jointly submitted a request for applications to develop stable and representative WM cell lines to be made widely available to researchers. Under the agreement, four laboratories are being sponsored for up to $100,000 each in the first year of study. Further funding, potentially for up to two additional years, will be contingent on available funds and progress toward the goal of developing suitable cell lines. The four recipients of this funding are Dr. Stephen Ansell at Mayo Clinic, Rochester, MN;

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Dr. Asher Chanan-Khan at Roswell Park Cancer Institute, Buffalo, NY; Dr. Suning Chen at Jiangsu Institute of Hematology, First Affiliated Hospital of Soochow University, China; and Dr. Irene Ghobrial at Dana-Farber Cancer Institute, Boston, MA.

Transgenic Mice Are a Key to Drug Testing and Development

Transgenic mice are genetically engineered to express certain disease traits and are capable of passing these traits to their offspring, resulting in a colony of genetically identical mice. Transgenic mice are important in studying diseases because disease characteristics and effects can be studied in a complex living organism, rather than in a culture tube. Potential treatments can be tested in mouse models for both benefits and toxicities before they are approved for human use in clinical trials.

The IWMF just recently awarded a grant for the development of a transgenic mouse model to express disease characteristics of WM. The award recipient is Dr. Siegfried Janz at the University of Iowa, Iowa City, IA. Dr. Janz previously worked on the development of transgenic mouse models for multiple myeloma at the National Cancer Institute. His award amount is $540,000 for a two-year project; if successful, he will be eligible to receive additional funding for genetic studies of his WM mouse model to attempt to discover the driver genes that lead to the development of WM and to assess potential targets for new therapeutic and preventive approaches for WM. If he is successful in his mouse model development, he plans to make his model accessible to other WM researchers.

A Tissue Bank That Will Foster WM Research

The third recommendation was the funding of a tissue bank to obtain blood and bone marrow samples from WM patients and to make them widely available to other researchers. A grant for this type of project has been awarded to Dr. Irene Ghobrial at Dana-Farber Cancer Institute, Boston, MA, in the amount of $900,000 for a four-year study. Dr. Ghobrial plans to collect at least 1,000 samples of patients with WM at different stages of disease progression and will also include serial samples of the same patients during progression. Institutions as well as community oncologists are being encouraged to participate in sample collection and submission to the repository. These samples will not only be used at the Dana Farber Cancer Institute but will be made available to qualified researchers throughout the world.

Dr. Ghobrial's laboratory will use these samples to screen for common cancer mutations described in similar tumors, will perform whole genome sequencing on a subset of WM patients to better examine specific genetic changes that occur in WM, and will determine the signature of microRNAs (gene regulators) during disease progression. She also intends to develop assays that can be used to determine whether treatments hit their expected targets, their mechanisms of activity, and possible explanations for disease resistance to treatment. Dr. Ghobrial's study, including the tissue bank, is being funded by the IWMF at a cost of $900,000 over a four-year period.

The Need for These Essential Research Tools

A valid WM cell line, transgenic mice, and a tissue repository are critical research tools that are needed in the effort to find treatments that will control and/or cure WM. Recent technology advancements may well lead to breakthroughs in our understanding of WM and lymphomas.

Announcing the three new IWMF grants, Tom Myers, Vice President for Research, commented as follows: "In order to fund these important and exciting projects the IWMF must continue its drive to obtain research funds. We have come so far in understanding the disease and developing new treatments."

A LETTER FROM DR. IRENE GHOBRIAL ABOUT THE IWMF TISSUE BANK

We would like to thank the IWMF for funding our new study that will serve all patients with Waldenstrom's macroglobulinemia (WM). The purpose of this study is to obtain bone marrow and peripheral blood samples, along with clinical data, from patients with WM. These samples will become part of a tissue bank at Dana-Farber Cancer Institute (DFCI) that includes samples of other cancers related to WM.

The stored samples will be used in ongoing studies to learn more about the causes and the biology of WM, multiple myeloma (MM), and lymphoplasmacytic lymphoma (LPL); to identify the factors that result in normal cells becoming cancer. The samples will be used to determine ways to improve treatment options, to study how the immune system identifies abnormal cells (tumor cells), and to evaluate the immune function in these diseases. We will also study the tumor cells at the gene level to develop new treatment strategies, as well as to better understand how biologic differences affect patient outcomes. These studies will help us better direct our efforts in designing more specific and more effective therapies with less toxicity.

This new tissue bank has some unique features that are not present in many other studies:

1. The tissue bank will link clinical data to samples, including bone marrow and peripheral blood.

A Letter from Dr. Irene Ghobrial, cont. on page 10

For example, we can identify samples from patients who are resistant to certain therapies and specifically study genes related to this resistance.

2. The bank will allow community oncologists to obtain bone marrow and peripheral blood samples from patients with WM and send them directly to Dana-Farber. Participating WM patients do not have to come to DFCI to give bone marrow or blood samples.
3. A local doctor does not have to get IRB (Institutional Review Board) approval for this study as the study has been approved by DFCI to be posted online. Participants can also register their consent from the online postings.
4. Participants do not have to be at DFCI to sign the consent form. Participants can sign the consent form and fax it to us before tissue samples are collected or after the samples have been sent to DFCI.
5. We will promote rapid dissemination of information about WM by sharing information obtained from this study with other researchers who are working on WM. The identification of the patient providing the sample will not be disclosed.
6. We plan to obtain 1000 unique WM samples linked to clinical data so that we can perform genomic and proteomic profiling of WM.
7. The bank will allow for future collection of multiple samples from the same participant over time (both before and after each treatment, for example).
8. In the future the bank will add an epidemiology questionnaire to be completed by participants. This will allow us to study whether environmental or occupational factors can be linked to WM.

Interested in participating? Here's what you can do:

- Go to the IWMF website *www.iwmf.com* and download the consent form and questionnaire and return them to us.
- We will send information and a kit that will help your local physician collect blood and bone marrow and send the samples to DFCI. The kit contains a pre-printed FedEx form so it is easy for your doctor to ship your samples directly to DFCI with minimal paperwork and effort.
- Donate to IWMF to help fund this research.

If you have any questions, please e-mail us at: *studyofWM@gmail.com*

Finally some important clarifications:

1. The bank of WM tissue at DFCI is funded solely by the IWMF.
2. Dana-Farber will also bank tissue collected from patients with other diseases related to WM, including lymphoplasmacytic lymphoma (which looks like WM, but is marked by high levels of IgG or IgA), multiple myeloma, smoldering myeloma, and MGUS (a condition predisposing to WM and myeloma). The study of diseases related to WM is critical in the attempt to better understand the biology of WM.
3. Collection and storage of the samples of diseases related to WM, however, are not to be funded by the IWMF. Support from the IWMF is limited to the WM tissue bank.

Irene Ghobrial, MD
Dana-Farber Cancer Institute

MANY WAYS TO GIVE TO IWMF RESEARCH

The purpose of our Research Fund initiative is to raise $5 million in cash and pledges by 2011 to support research leading to a better understanding of WM, more effective treatments, and an ultimate cure.

Two major strategies have been created in recent years to meet this goal: the Research Fund campaign was established in 2005, while the initiative of $5 million to be raised in 5 years (5-in-5) was created more recently with a variety of new gifting options. The major options listed below make contributing to the Research Fund easy:

DR. ROBERT A. KYLE AND CHARLENE M. KYLE ENDOWMENT FUND:
In honor of Dr. Robert A. Kyle and Mrs. Charlene M. Kyle, the first ever endowment program for the IWMF was established in 2009.

NAMING OPPORTUNITIES FOR INDIVIDUALS:
Projects or programs in tribute to a person or in memory of a patient are usually at a comparatively lower level of giving. The 5-in-5 campaign provides a naming opportunity for individuals (patients, doctors, past and current Board members, caregivers, etc.) at a higher level.

NAMING OPPORTUNITIES FOR FOUNDATIONS, COMPANIES, AND ORGANIZATIONS:
Foundations, companies, and organizations may wish to focus their resources on specific scientific or medical research projects. This kind of philanthropic investment justifies naming the project after the leader of a company, foundation, or organization in return for its gift or grant. If your organization has an interest, please contact Carl Harrington at 215-348-5656.

Many Ways to Give, cont. on page 12

THE BEN RUDE HERITAGE SOCIETY ENROLLMENT

The International Waldenstrom Macroglobulinemia Foundation (IWMF) cordially invites you to become a member of the Ben Rude Heritage Society. Your legacy is an inspiration to others. Please indicate below your acceptance of enrollment in the Ben Rude Heritage Society. We hope also that you will consider providing information about your legacy so that we have a full understanding of your wishes. If possible, please attach supporting documentation. Thank you.

LEGACY GIFT

I/We have arranged a legacy gift for the benefit of IWMF through my/our:

❑ Will ❑ IRA/Retirement-Plan Beneficiary Designation ❑ Trust ❑ Charitable Remainder Trust

❑ Other *(please specify)*: _____

Additional Information: _____

DESIGNATION

This gift is to be used for *(please check one)*:

❑ IWMF's Greatest Need ❑ Research Fund ❑ Dr. Kyle Endowment Fund

❑ Fellowship Stipend Fund ❑ The Following Purpose: _____

GIFT DETAILS

As of this date, the value of my/our gift is: the sum of $_____ or _____% of my/our estate or other gift plan, with the current value of the IWMF portion estimated at $_____. I/we understand that my/our estate **is not** legally bound by this statement of gift value.

RECEIPT OF GIFT

This gift will be received by IWMF after the life of:

❑ The First Donor ❑ The Surviving Donor/Spouse ❑ Other Individual(s): _____

❑ Other Contingencies or Stipulations *(please specify)*: _____

BEN RUDE HERITAGE SOCIETY HONOR ROLL LISTING:

Name(s): _____

❑ Please enroll me/us in the Ben Rude Heritage Society using the Honor Roll listing above.

❑ Please do not list my/our name(s) in the Honor Roll and _____in all other publications.

❑ Typically, IWMF recognizes Heritage Society membership with a crystal recognition piece. Check here if you prefer not to receive this token of appreciation.

Donor Signature:_____ Date of Birth: _____ Date: _____

Donor Signature:_____ Date of Birth: _____ Date: _____

Please note that all information will remain confidential to IWMF. For further information about the Ben Rude Heritage Society, please contact Dave Benson at 952-837-9980 or dave@dbenson.com.

Please mail completed enrollment form to: IWMF Business Office, 3932D Swift Road, Sarasota, FL 34231.

Many Ways to Give, cont. from page 10

ESTATE OR PLANNED GIVING:
In general, estate or planned giving options fall under three categories: bequests (estate gifts), life income, and other planned giving vehicles. If you would like additional information, please call Dave Benson, senior development officer, at 952-837-9980.

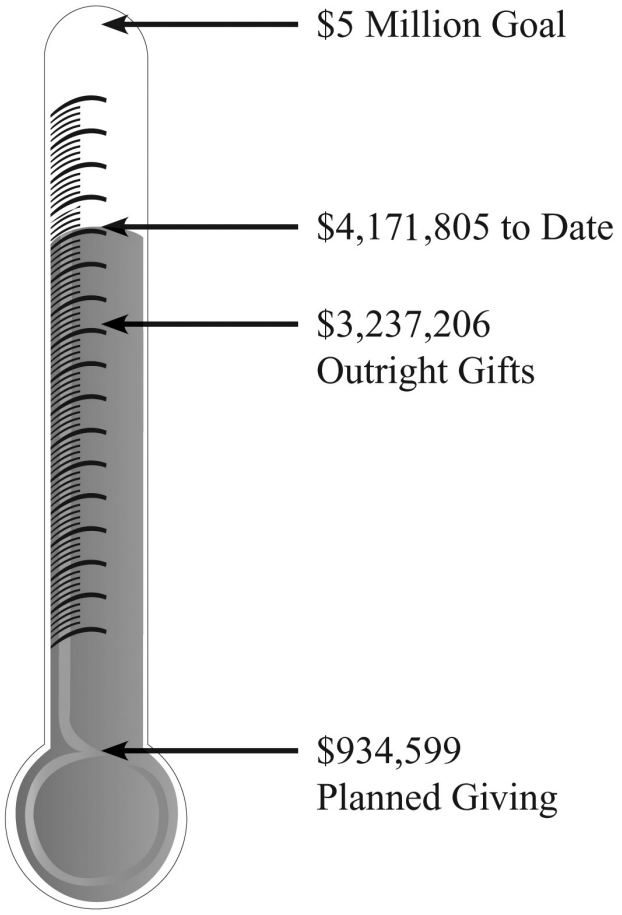
BEN RUDE HERITAGE SOCIETY:
The Ben Rude Heritage Society is so named in recognition of the second president of the International Waldenstrom's Macroglobulinemia Foundation (IWMF). Through your planned estate gift and your participation in the Ben Rude Heritage Society you can touch the lives of others as we strive to find the cause and a cure for WM. As Ben shared often, "A person's life is measured by the effort made for the benefit of others."

We are close to our goal for 2011 but we still need the help of everyone. With the new projects reported on page 8 of this issue of the *Torch* we will need almost a million dollars a year. Your participation is crucial as we strive for increased research focus on our orphan disease. It would help so much if you would use the enclosed envelope to contribute to our unrestricted Research Fund or to the giving option of your choice.

Also, please do not forget the fall drive for our Member Services Fund. It is essential that we continue to receive funding at a level that will provide you with the services, support, and information you need as we all continue to strive for a good quality of life with our rare disease.

Thanks for all you are doing to keep the IWMF alive and effective.

Judith May
President, IWMF



THE SIXTH INTERNATIONAL WORKSHOP ON WM AND THE SECOND IWMF INTERNATIONAL PATIENT FORUM ON WM

The Sixth International Workshop on Waldenström's Macroglobulinemia (IWWM6) will be held 6-9 October 2010 in Venice, Italy. Top WM researchers and clinicians from around the world will meet at this comprehensive workshop dedicated solely to basic and clinical WM research. Further information including the conference agenda for IWWM6 is now available online at *www.wmworkshop.org* The organizing chairs for this event include Dr. Giampaolo Merlini and Dr. Enrica Morra of Italy, as well as Dr. Steven Treon of the Dana-Farber Cancer Institute. Christopher Patterson of the Bing Center for Waldenström's Research at Dana-Farber is the organizing secretariat. One can only expect a spectacularly well-planned conference. The IWMF is a key sponsor of this event, and we will be on hand to report all the goings on and exciting new research developments. Note: the Workshop is open only to WM researchers.

On Sunday, 10 October, following the conclusion of IWWM6, the Second IWMF International Patient Forum on WM will be hosted by the IWMF. Internationally renowned WM experts, such as Drs. Robert Kyle, Steven Treon, Eva Kimby, and the IWWM6 conference co-chairs Drs. Enrica Morra and Giampaolo Merlini, will lecture on topics including

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The Sixth International Workshop, cont. from page 12

biological and clinical features of WM, treatment of WM, complications in WM, future directions in WM treatment, as well as answering questions in a collaborative "ask the doctor" panel (a very popular feature at annual IWMF Educational Forums!). Afternoon sessions will consist of interactive breakout sessions and a patient panel. IWMF President Judith May, as well as other IWMF Trustees, will be on hand to discuss IWMF member services and our active research program. International WM support group leaders from Holland, France, England, and other countries will also be present to discuss expansion of WM support and education services to WM patients and caregivers all over the world.

The Second IWMF International Patient Forum on WM will be held at the majestic Hotel Molino Stucky Hilton in Venice. Breakfast and lunch are provided. There are no fees for registration or to attend the International Patient Forum. The conference is filling up, so interested WM patients and caregivers are encouraged to register soon. Brochures with full details and registration form are now available through *www.iwmf.com*

Many thanks to Christopher Patterson, Sara McKinnie, and all others for helping organize what is sure to be an outstanding Patient Forum!

See you soon!

Guy Sherwood, M.D.
Chair, IWMF International Committee

THE UPSHOT ON VACCINATION FOR THE ADULT CANCER PATIENT

BY SUE HERMS

In light of all the attention focused on H1N1 influenza (swine flu) during the preceding flu season and the concerns about who should be vaccinated, this article will review the general guidelines for vaccination of adult cancer patients.

In general, cancer patients who are receiving chemotherapy, radiation, long-term or high dose steroid therapy, or transplantation, or who have a hematologic cancer such as leukemia and lymphoma, are immunocompromised, meaning that they have an impaired immune system. For this reason, vaccines that are composed of live, attenuated (weakened) bacteria or viruses are not recommended for these patients as they can potentially cause serious side effects, including the actual infection. It is also recommended that pregnant women should not be given certain vaccines.

Vaccines manufactured from killed bacteria or viruses, toxoids (inactivated toxins), or partial bacterial or viral components are usually safe for people with immune system deficiencies, with the warning that a certain proportion of the population may have allergic reactions to other substances included in these vaccines.

The Centers for Disease Control and Prevention (CDC) in Atlanta states that the following vaccines are safe for most adult immunocompromised patients: anthrax, *Haemophilus influenzae* type b, hepatitis A, hepatitis B, human papilloma virus (HPV), influenza shot, Japanese encephalitis, meningococcal polysaccharide and meningococcal conjugate, pneumococcal polysaccharide, polio shot, tetanus/diphtheria booster, typhoid shot, and rabies.

Not all of these vaccines are given on a routine basis, however. Some are only administered to health-care workers, certain age groups, after a specific exposure, or for those traveling to areas of endemic disease. Patients who have had stem cell transplantation or spleen removal should receive certain recommended vaccines. For vaccines that are **routinely** given, the CDC recommends that immunocompromised people receive seasonal flu shots yearly – note that for the 2010-11 flu season, the regular seasonal shot will now include H1N1. The pneumococcal polysaccharide shot should be administered following a cancer diagnosis and once every five years thereafter. A tetanus/diphtheria booster is also recommended every 10 years for all people, including cancer patients.

Some have questioned whether vaccination of immunocompromised patients is effective. It is true that these patients may not be able to develop a good immune response to vaccination; however, the current advice from the CDC is that any amount of immunity is better than none, particularly in the case of widespread diseases such as flu. Therefore, it is considered good practice to immunize with safe vaccines, on the principle that some benefit may be derived. Vaccinating these patients may necessitate giving an extra dose, altering the timing of doses, or selecting a different vaccine formulation. If someone with immune deficiency has received exposure to a specific disease for which a safe vaccine is not available, it may be desirable for that person to receive intravenous immunoglobulin therapy (IVIg).

Vaccines that generally should **not** be administered to immunocompromised patients include the following: chicken pox, measles/mumps/rubella, nasal flu, oral polio, smallpox, shingles, oral typhoid, and yellow fever. Patients who have

The Upshot on Vaccination, cont. on page 14

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immune system deficiencies should also avoid close contact with others who have recently received vaccines on this list for a few days following vaccination.

Shingles is of interest to many cancer patients, particularly if they are receiving immunosuppressive therapy for their disease. The shingles vaccine, as mentioned above, is not indicated and should not be given to prevent shingles; instead, these patients should receive prophylaxis therapy with acyclovir or Valtrex.

Always consult with your physician if you have any questions about vaccination.

Sue will be pleased to answer your questions and can be reached at: suenchas <suenchas@bellsouth.net>

THE 51st ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY: PART 2

BY GUY SHERWOOD, M.D., IWMF TRUSTEE

This article is the second of two summarizing some of the more interesting and informative lectures and posters from the 51st Annual Meeting of the American Society of Hematology (ASH) held December 2009 in New Orleans, Louisiana. It is impractical to review all the lectures and posters relevant to WM: this would require a rather large edition of the *Torch*! I have chosen topics that are varied, timely, and important to individuals interested in the science of WM. As before, these brief summaries are edited for scientific jargon; interested individuals are directed to the official ASH website *www.hematology.org* for more detailed information on any of the topics discussed and for further reading on other related topics. At the conclusion of this article I will attempt to give you my personal (and brief) impressions on the future of WM research.

NEWER THERAPEUTIC AGENTS

Newer therapeutic agents for WM are continuously being developed. Dr. Kasyapa Chitta and colleagues of the Roswell Park Cancer Institute, Buffalo, NY, reported on a study of the novel biological molecule At-101 which appears to induce apoptosis (cell death) in WM cells resistant to bortezomib (Velcade). In the incredibly complex world of cellular pathways the Bcl-2 protein family has the unique ability to balance cell survival. AT-101 is a biological molecule known to disrupt the anti-apoptotic functions of Bcl-2 family members. In fact, this molecule has been shown in lab studies to induce apoptosis in several tumor model systems including multiple myeloma. Velcade has been used with success in WM, particularly when combined with other traditional therapies. However, continued treatment with Velcade often results in the development of drug resistance. Having developed an *in vitro* model of Velcade-resistant WM cells (also cross-resistant to conventional therapies used for WM such as fludarabine and doxorubicin), the investigators assessed the effect of AT-101 on these resistant cells. Results from their studies suggest that the potent AT-101 molecule induces a quick cell death in Velcade-resistant cells and has a unique therapeutic potential against WM that is independent of resistance to Velcade. Dr. Chitta suggests that the Bcl-2 protein family is a potential target in WM and that AT-101 has a possible therapeutic role in the treatment of WM.

In the field of WM research, we are quite accustomed to "borrow" results from studies done in multiple myeloma (MM) and try to associate some of these with WM. This is due to the fact that not only is MM much more common than WM but also the physiology of MM parallels that of WM to a large degree. Dr. Paul Richardson and Dr. Irene Ghobrial of the Dana-Farber Cancer Institute (DFCI), Boston, MA, updated Phase I and II clinical trial results evaluating progression free survival and overall survival in relapsed and refractory MM patients previously treated with Velcade who were then treated with perifosine in combination with Velcade and dexamethasone. Perifosine is an oral agent that has been shown to inhibit Akt and activate JNK, two biological pathways important in both MM and WM. In a Phase I and II study Velcade-relapsed and refractory MM patients with advanced disease were treated with perifosine and Velcade, both with and without dexamethasone. The most common side effects (affecting 10% of patients) were minor at grades 1 and 2 and included nausea, diarrhea, vomiting, fatigue and anorexia, which were managed with supportive care and dose reductions. More severe (grade 3 and 4) side effects (5% of patients affected) included thrombocytopenia (low platelets), neutropenia (low white blood cells), anemia (low hemoglobin), hyponatremia (low serum sodium) and diarrhea. Interestingly, only one patient experienced worsening peripheral neuropathy and that was reversed after treatment discontinuation. No treatment-related mortality was seen. Progression free survival and overall survival of patients in the study have been quite impressive: 80% of patients achieved stable disease or better. The authors conclude that perifosine in combination with Velcade, with or without dexamethasone, is generally well tolerated and demonstrates impressive activity in both heavily pre-treated and Velcade-refractory MM patients. It remains to be seen whether this study will have implications for WM patients.

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A topic of great interest to many WM'ers is the use of green tea as a dietary "supplement" – but is there any merit to its use? The role of green tea extract (EGCG) when combined with fludarabine and chlorambucil in the treatment of chronic lymphocytic leukemia (CLL) was evaluated by Dr. Connie Lesnick of the Mayo Clinic, Rochester, MN. As is well known, CLL, a "sister" disease of WM, is incurable with current chemotherapy treatments. Epigallocatechin 3 gallate (EGCG), the major catechin (antioxidant) in green tea, has been shown to induce death of CLL B-cells. In a Phase I trial for patients with early stage CLL, EGCG treatment was well tolerated and resulted in a decrease of malignant B-cells and or lymphadenopathy without associated myelosuppression in the majority of treated patients. The author evaluated the effects of EGCG on the viability of CLL B-cells when combined with fludarabine, chlorambucil, or fludarabine and chlorambucil in combination. Based on *in vitro* testing in the laboratory, Dr. Lesnick concluded that safe, achievable doses of EGCG appeared to enhance the efficacy of alkylating agents (e.g. chlorambucil), purine nucleoside analogues (e.g. fludarabine), and alkylating agent and purine analogue combination therapy for the majority of CLL patients. Testing to date indicates that EGCG is an attractive agent to test in combination with purine analogue and alkylator based chemo-immunotherapy for patients with CLL.

DIAGNOSTIC AND PROGNOSTIC ADVANCES IN THE TREATMENT OF WM

Dr. Xavier Leleu, formerly of the DFCI and now with the Service des Maladies du Sang, Hôpital Huriez, Lille, France, and Dr. Irene Ghobrial, DFCI, reported on the use of positron emission tomography (PET scan) as a new marker of response in WM. It is well known that WM is characterized not only by tumor infiltration in the bone marrow but also by hepatomegaly (enlarged liver) in 20% of patients, splenomegaly (enlarged spleen) in 15% of patients, as well as lymphadenopathy (enlarged lymph nodes) in 15% of patients. Organomegaly (enlarged organs) is associated with a worse prognosis in WM. Additional clinical tests to help evaluate tumor burden and prognosis may be required in these patients. The aim of the study by Drs. Leleu and Ghobrial was to determine whether PET might be an effective tool in evaluating patients with WM. Thirty-nine WM patients who were selected for treatment with combination Velcade and rituximab in a Phase II clinical trial underwent staging evaluation by PET before and after therapy. Twenty-five (64.1%) patients had a positive PET before treatment, while 13 (37.1%) patients had a positive PET after treatment. Eleven (45.8%) of the patients with a positive PET before treatment had a negative PET following treatment. One (4.8%) patient who was initially negative had a positive PET after treatment. All other patients had no change. Before treatment there was no clinical or biological difference between positive PET patients and negative PET patients (age, gender, hemoglobin level, serum Beta2-microglobulin value, platelet count, IgM spike). A positive PET before treatment was not indicative of either response or survival. A negative PET after treatment, however, did correlate well with response. A positive PET scan after treatment was an adverse prognostic factor for overall survival. In conclusion, over 60% of the WM patients participating in the trial had positive PET scans prior to treatment, and the majority of those with positive PET scans prior to therapy demonstrated negative PETs after therapy. The authors conclude that PET positive scans after therapy correlated with poor prognosis, and thus PET scans may prove an effective tool in the diagnosis and prognosis in WM.

The use of rituximab (Rituxan, MabThera) is widespread among WM patients. Dr. Divi Cornec of the Immunology Laboratory, Brest University Hospital, Brest, France, reported on predictors of early response to single agent rituximab in patients with indolent lymphoma. The clinical and biological responses to rituximab are known to be highly variable in non-Hodgkin's lymphoma patients. The author studied a set of biomarkers in patients with indolent non-Hodgkin's B-cell lymphoma (primarily low grade follicular lymphoma) treated with a standard weekly dose of single agent rituximab for 4 weeks. All patients underwent PET scan analysis before treatment and 10 weeks after the beginning of treatment. Younger age, lower tumor burden as measured on PET scan, and the presence of the immunoglobulin receptor FcγRIIIa V/V genotype distributed on the patient's natural killer cells and macrophages are associated with a better early response to rituximab therapy in indolent lymphoma patients. The determination of these factors prior to initiation of rituximab therapy could help in adapting individual therapeutic protocols.

SURVIVORSHIP IN WM

WM patients are often concerned with the possibility of developing a new cancer secondary to treatment received for WM. Dr. Stefano Sacchi, Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy, provided a systematic review of the recorded data on the incidence of a second malignancy after treatment for non-Hodgkin lymphoma. Studies describing the risk of second malignancy in non-Hodgkin's lymphoma (NHL) survivors, including WM patients, have yielded conflicting results. Relevant observational studies published from 1985 to 2008 were reviewed in order to provide estimates of the relative risk of second malignancies appearing during follow up of NHL patients. These studies included 223,593 patients affected by NHL of whom 14,952 presented a second cancer. The development of secondary lung cancer and bladder cancer showed a statistically significant larger risk. Prostate and breast cancer did not demonstrate evidence of association with NHL therapy. An increased risk of developing Hodgkin's lymphoma was noted, particularly myeloid leukemia, including either acute or chronic leukemia or myelodysplastic syndrome (as is well known, such risks are associated with particular chemotherapeutic agents).

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In conclusion, Dr. Sacchi's analysis indicates that NHL treatment is associated with a significantly higher risk of developing a second malignancy, particularly lung and bladder cancer, as well as hematological malignancies such as Hodgkin's lymphoma and myeloid leukemia.

TREATMENT CONTROVERSIES IN WM

Dr. Steven Treon, DFCI, presented an important study on the controversial role of maintenance rituximab in WM. Rituximab (Rituxan, MabThera) is perhaps the therapy used most frequently in patients with WM, but the benefit of maintenance rituximab has not been well established in this disease. Dr. Treon and his research team assessed the impact of maintenance rituximab on a group of WM patients who had shown positive response to rituximab-based therapy. This study included 240 WM patients; 59 (27%) had been previously treated with a rituximab-based therapy while 181 (73%) were untreated at the start of the study. Of the total 240, 86 (35%) patients received maintenance rituximab following response. Between the 35% who received maintenance therapy and the other 65% who did not there were no observed differences in baseline age, serum IgM, IgA, IgG, bone marrow disease involvement, complete blood counts, Beta2-microglobulin levels, or response rates following initial rituximab-based therapy. Prior to maintenance therapy all patients in the study received rituximab alone or in combination with one of the following: bortezomib (Velcade), cyclophosphamide, an immunomodulatory agent such as thalidomide, or a nucleoside analogue such as fludarabine. The median number of rituximab infusions received in treatment was 6, while the median number of rituximab infusions received for maintenance was 8.

Maintenance rituximab was administered in one of two schedules: either one infusion every 3 months for 63 (73%) patients, or 4 weekly infusions every 6 months for 23 (27%) patients, with a median of 2 years of treatment. Both progression free and overall survival were, on the average, longer in patients who received maintenance rituximab: average progression free survival was 56.3 months for those who received maintenance rituximab versus 28.6 months for those who did not; overall survival was 120 months for those on a maintenance regime and 116 months for those who were not. Improvement in progression free survival was noted irrespective of the patient's status before the start of the study – that is, untreated or treated, treated with rituximab alone or in a combination therapy (therapy combining rituximab with either cyclophosphamide, a nucleoside analogue, or bortezomib).

Among patients who received maintenance rituximab, progression free survival was 53.3 months for those patients receiving one infusion of rituximab every three months compared to 61.3 for those receiving 4 weekly infusions every 6 months. Serum IgM response was 598 versus 1380 mg/dL and hematocrit was 40.7% versus 38.6% in patients who received maintenance versus no maintenance. Among those patients who received maintenance therapy the median serum IgG (351 vs. 461 mg/dL) and IgA (23 vs. 33 mg/dL) levels were lower and an increased number of sinus and pulmonary infections during the course of follow up were observed. Dr. Treon suggests that these results support the use of maintenance rituximab in WM patients who respond to an initial therapy with a rituximab-containing regimen. Further studies clarifying the recommended schedule and duration of maintenance rituximab therapy in WM are suggested and will be no doubt forthcoming as an increasing number of WM patients receive maintenance rituximab therapy.

FUTURE DIRECTIONS IN RESEARCH

As newer discoveries in the biology of WM are made, one wonders what the future may hold for WM patients and caregivers. I have had the privilege of attending many scientific conferences in the course of my WM "career," which began, for those of you keeping score, in 2001. It is quite clear to me that we are entering a very exciting time: although a cure for WM remains elusive, there is no question that newer targeted agents are prolonging survival and reducing unwanted side effects of therapy. The amazing explosion of knowledge, particularly in the field of genetics, will herald an increased focus on individualized therapy. One can now envision a visit to the doctor's office where not only will blood test and bone marrow biopsy diagnose WM but will also direct a tailored therapy based on the patient's particular genetic profile. We can now determine to a certain extent whether a patient will respond to certain therapies (rituximab for example) and expanded prognostic and diagnostic tools will soon permit the patient and their physicians to use the best and safest course of treatment for the individual. The astounding (in my estimation) increase in clinical trial participation by WM patients over the past 5-10 years is responsible in large measure for the markedly increased survival rates WM patients are now experiencing.

A prognosis of 5-7 years for WM patients? Ancient history, my friends …

Donate and participate.

N.B. – The 52nd American Society of Hematology Annual Meeting and Exposition will be held 4-7 December 2010 at the Orange County Convention Center, Orlando, FL.

FROM IWMF-TALK

BY MITCH ORFUSS

Summer may be vacation time, but there was no vacation regarding TALK. The issues and discussions were as frequent and varied as ever as so many WM patients gave and received support and information. The following excerpts from ten major topics of discussion give *Torch* readers who choose not to follow TALK online a wide-ranging peek into what's on the minds of TALK subscribers. Interestingly, perhaps the most frequent topic since the last *Torch* was "T-shirts" – which illustrates both humorously and seriously that there are more ways than one can imagine for TALK readers to provide support and comfort to each other. T-shirts aside, what follows are some of the more popular discussion topics prominent on TALK over the last three months.

About Rituxan:

Given that Rituxan is successful for half the patients that try it, **Stephanie K** asked whether anyone had ever done the test that predicted Rituxan's effectiveness. **Billie Evans** responded that in advance of a consultation with Dr. Treon she had the PgxPredict: Rituximab test. The result of the test is not a numerical score but rather placement of the patient within a tier of probable response. Billie thought that, armed with this predictive information, if she were found to be in the top tier, she could "get away with" solo-Rituxan, whereas if she were in second tier she would probably go with a "Rituxan combo" of drugs. As it turned out, Billie was placed in the second tier, which predicted 62% chance of Rituxan monotherapy putting her into complete or partial remission. When Billie went for her consultation at DFCI she was surprised the find that she was the first patient to come to Dr. Treon for their appointment with predictive results for rituximab in hand! For the time being the decision of a next treatment was postponed because Dr. Treon felt that Billie's current symptoms were the result of an IVIg flare and not disease progression. Returning home, she saw her local oncologist the next week who said that he and Dr. Treon had spoken about future treatment, which would likely include Rituxan and a second drug to be determined, which Billie felt was not different from what would have been prescribed even without the test. Billie, however, preferred knowing that she and her oncologists were making the best-educated choice they could about how to proceed in terms of treatment. The cost of this extra assurance? Billie reports that the published cost of the test is $2,500 but (at the time she looked into it) that it was being offered to WM patients for a maximum of $500 out-of-pocket.

Guy Sherwood added that some researchers – Dr. Treon's team in particular – have noted that the addition of another agent, say thalidomide for example (there are others),"evened out" the effectiveness of Rituxan for all patients, irrespective of such "predictive" status. This, says Dr. Guy, cuts both ways as the addition of a second chemical agent also adds risk. Guy personally added Neupogen at (almost) every Rituxan maintenance infusion. He does not have reams of data but believes it helped, as has been demonstrated in the literature. There are so many different varieties of WM out there, and, given our biological "individualism" (to a point), it is difficult, Guy feels, to find the ideal treatment. This is why he believes in the critical importance of basic research in addition to drug trials. Slow and steady wins the race (but it is difficult to be forever patient!).

Dexamethosone and Decadron:

Pat O'Brien requested input about this drug. A palliative-care doctor suggested this med for Pat's husband, and his hematologist subsequently prescribed it. The indication was that it would help with his lack of energy and appetite. Pat's husband took it for a week and seemed to start enjoying better energy and good spirits. Pat became concerned, however, because dexamethasone is a steroid. Their pulmonologist was okay with that. Their internist expressed a little hesitation due to possibility of increase in blood pressure as well as the possibility of increased glucose levels. None of the concerns materialized. Pat's husband has always had safe levels of blood pressure and glucose.

Janet Braley advised that we should learn all we can about dexamethasone, as it is one of the more powerful steroids. Janet's WM includes central nervous system involvement, Bing Neel syndrome. She was put on dex when she started her treatment to help with inflammation. The problem started when she was weaned off it. Janet's adrenal glands began to fail. She nearly died not once but twice. Her doctors did not know why she'd fall asleep and not awaken. They kept her on the steroid until they figured out what to recommend. In

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HOW TO JOIN IWMF-TALK

Here are two ways to join:

1. Send a blank e-mail to: *iwmf-talk-subscribe-request@lists.psu.edu*

   Make sure to enter the word "subscribe" as your subject, and do not sign or put anything in the message area (make sure you do not have any signature information in there). Also, do not put a "period" after "edu" or it will reject. Once approved you can post by sending e-mail to *iwmf-talk@lists.psu.edu*
2. Contact Peter DeNardis at *pdenardis@comcast.net* and provide your full name

the meantime Janet's weight ballooned to over 200 pounds (whereas she usually weighs between 110 and 115). Doctors advised that she would not lose the weight until she stopped the drug and that it would likely take a year. Janet's doctors decided to inch her off her dex. Yes, she did lose the weight – and more quickly than anticipated: about four months.

Gerry Wergland had dex as part of his chemo last year, receiving 21 infusions over 5 months. While Gerry's appetite increased, he did not recall a change in energy. Dex also provided temporary relief from back pain from a ruptured disk. The downside was muscle weakness in the legs. He found it difficult to climb stairs and walk for distance. Gerry was able to recover after stopping the dex and beginning physical therapy and exercise. His understanding is that dex is a corticosteroid, not the same as steroids abused by some athletes. Gerry strongly advises caution.

Dr. Tom Hoffman said that patients in palliative care should be given any drug that makes them more comfortable, without concern about side effects. The dex prescribed was not a large dose. Tom said that the power of steroids mostly derives from the given dose, not the drug prescribed. Dex is used today mostly because it is associated with lower incidence of accompanying side effects than many other steroids.

Scott K wrote that he had recently been put on 40 mg of dexamethasone a week, taken all in one day. Scott had been symptomatic and, as he understands it, the dex was prescribed to help him deal with symptoms while he continued the Rituxan treatment he was undergoing. Plasmapheresis helpfully relieved most of Scott's symptoms. Dex seems to have created a roller-coaster effect in that a few days after Scott took the dose he had a lot of nervous energy and did not sleep well. Then he began to tire. After that, the symptoms that the dex had been combating crept back. In addition, Scott had had unusual pain on the top of his head with some numbness that tended to pulse as it worsened. The possible longer-term side effects of dex had Scott concerned.

"Chemo for Life" (Maintenance):

Mike Dewhirst quoted an article from the New York Times raising three concerns about maintenance therapy: 1) The data (which are taken from studies on multiple myeloma and follicular lymphoma) do not reveal whether such treatment improved the rate of overall survival in such patients. Both multiple myeloma and follicular lymphoma are diseases in which people can live a decade or more following diagnosis. So it is too early to say that longevity is increased or that doctors are simply changing the shape of the curve leading to death. 2) We do not know what the adverse effects would be of taking these drugs for long periods of time. There may be side effects that might reveal themselves only after prolonged use. **John Eldridge** suggested that the point might be a bit more complex than that. Studies show that symptoms are less likely to recur (i.e., blood labs staying "good"), but they do not demonstrate extended life. One would think that fewer symptoms would lead to longer life, but that has not been clinically demonstrated. 3) If maintenance therapy does not increase life expectancy, is it ethical for society to support it? **Pat Marsala** replied with a resounding *Yes*, pointing out that society supports diabetics and those with autoimmune diseases such as rheumatoid arthritis and lupus. **LClark5488** questioned whether cost means a life is not worth saving. Her husband has been a WM patient for 14 years and is still earning and paying taxes, and she hopes that society would evaluate his life as still being worth it. Otherwise, we are on a slippery slope. Her husband's doctor said he has a patient from England with WM. After seven years his treatment is no longer paid for: incurable, hence no treatment. The real issue is how we reduce the cost of treatment. **Stuart Alper** added: What next? Will society eventually stop paying for treatment of diabetes because it's incurable? There are hundreds of diseases that are chronic but manageable with treatment. **Lois Smith** contributed that she doesn't expect anyone to be able to "afford her" past some undefined final point...and that is okay with her. Lois thinks that Americans expect more than anyone or any government can afford. At some point, we can't be "saved from death." **Gerry Wergland** summarized his take on the recent Dana-Farber study of 240 patients who responded to a Rituxan-based therapy. Of the 240 patients, 86 received maintenance Rituxan. Of the 86 patients receiving maintenance Rituxan, 63 had a maintenance infusion administered every three months, and 23 had four weekly infusions every six months. *Progression-free survival* was found to be about twice the duration for those receiving maintenance Rituxan as those who did not (56 vs. 29 months), though *overall survival* was about the same (120 vs. 116 months)! Progression-free survival was somewhat better (61 months) for patients on the six-month cycle compared with the three-month cycle of maintenance infusions (53 months).

Cryoglobulinemia and Cold Agglutinin:

Billie Evans queried: How are cryoglobulinemia and cold agglutinin diagnosed? Are there blood tests? Fay Langer, who always signs off as "a cryo patient" so that readers are reminded of her disease status, replied that there is a blood test for cryo. The results are "positive" or "negative," not a value (such as 11.3 hemoglobin, for example). When Fay was diagnosed, her doctor put a vial of Fay's blood in a refrigerator and saw that it thickened. When the blood returned to room temperature, it also reverted to normal consistency. Fay suggested that when one has cryo and undergoes plasmapheresis, one should be sure the blood is warmed before it's returned to the body. Fay did not know the test for cold agglutinin, but offered that in both cases it is important to know whether you are positive for either or both conditions so that blood is handled properly for testing purposes at the lab, a "BIG" issue to use Fay's emphasis.

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From IWMF-Talk, cont. from page 18

Green Tea and Resveratrol:
Janet Westrich writes that polyphenols have been shown to help increase the white blood cell count, which is responsible for fighting infection. She adds that the high vitamin C content in green tea also contributes, as is well-studied and accepted, helping in preventing and fighting colds. **Liane Stafira-Cochrane** replied that there is no scientific evidence for vitamin C's preventing colds or helping to get over the symptoms. The data, she says, suggest no benefit. Liane did say that, on the other hand, there may be some benefit to drinking green tea based on the experimental data.

"Magic Mouthwash":
Jack Whelan wrote that he is currently taking a Dana-Farber-prescribed drug for mouth sores attributed to his therapy (Rituxan weekly and RAD001 daily): a mouth rinse of lidocaine 2% and Kaopectate giving him immediate pain relief from a numbing effect; Jack says it feels like the effects of novocaine. He understands that extra-effort oral hygiene, particularly for immunocompromised WM patients, comes recommended. Prior to treatment, Jack's dentist recommended a "magic mouthwash," a mix of a teaspoon of Cherry-flavored Children's Benadryl and three teaspoons of Maalox. This combination of numbing from the Benadryl and the acid-neutralizing effect of the Maalox really helped. **Paul Rippas** is on a drug trial and also experienced mouth sores. The solution Paul found was a prescription for dexamethasone.

Disability Benefits:
Julie Frey is an RN who quit her job when diagnosed due to her lowered immune system and fatigue. She and her husband are now living on her husband's salary. Given that Julie's job involved taking care of sick people, she asked whether TALK readers had insight into the availability of benefits. **Peter Sissman** suggested that Julie check with the human resources department of her former employment about whether she has a disability insurance policy through work (or other sources). Further, Peter advised that if she hasn't reached either social security age (62 and up) or Medicaid age, Julie should consider filing a claim under Social Security Disability Insurance. In addition to a monthly payment, after two years she would be eligible for Medicare. She might even be entitled to benefits retroactively. Peter urged Julie not be discouraged if she is initially denied benefits. There is a multi-level appeals process for which the rate of denial reversal is high. At that level, Peter recommends consulting an experienced social security law lawyer. There are no direct legal fees. If successful in gaining approval for benefits, fees capped at $4,000 will simply be deducted from back benefits, unless the information is dated.

Further examples of the extraordinary range of additional topics raised in TALK over the past three months include: the meaning of M-spike, whole-body/low-dose radiation, leg cramps, serum viscosity and exercise, plasmapheresis, shingles, bendamustine, RAD001, foot pain and dehydration. The range and depth of interest and support never fail to impress.

COOKS' HAPPY HOUR

BY PENNI WISNER AND NANCY LAMBERT

For many of us, a very hot summer is now past and we, with Penni and Nancy leading the way, are ready for autumn. Our cooks happily return to their ovens and slowly roast that remainder of seasonal bounty – the tomato – in all of its glorious variety. But something more unusual is also roasting in their now cozy kitchens – read on to savor the potential of shiitake mushrooms in the happy hours to come.

Oven-drying, the lazy person's preferred preserving method, tames the sometimes overwhelming bounty of the fall. You don't need special equipment – no canning pots and tools, no dehydrater. Though of course, if you have those, do give them full employment.

And since it is once again the end of tomato season (the season most of us look forward to so eagerly and all too soon must mourn its passing), let's focus on tomatoes. Oven-drying intensifies their flavor. Caramelizes it. The tomatoes turn into candy. Especially if you decide to oven-dry cherry tomatoes – Sun Golds, perhaps, or Sweet 100s – then, oh dear, yes, you have candy. I wonder if anyone makes tomato caramels?

Halve the tomatoes – all of them, all varieties. I've oven-dried cherry tomatoes (yes, halving them, too), heirlooms, Early Girls (my favorite tomato for its rich and tart tomato flavor balance), and San Marzanos, the classic sauce tomato. Arrange them in a single layer on a baking sheet. Season them with salt and pepper and, with a very light hand, drizzle with a little balsamic vinegar, and then a lot of olive oil. Toss around some peeled whole garlic cloves and some chopped fresh herbs such as rosemary, oregano, and thyme. Tuck in a few bay leaves. You could also use some dried herbs and mixes such as Herbes de Provence but be careful here not to go overboard and add too much, just a tablespoon per baking sheet should do it. You could also add a couple of dried hot peppers. That would be fun.

Put the sheet in a slow oven, 200°F to 250°F. The higher the temperature, the more attention you must pay. I know this

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Cooks' Happy Hour, cont. from page 19

from bitter experience. Set the timer for an hour; take a peek and see how the tomatoes are doing. They first release their juices, and then these begin to evaporate and the natural sugars begin to caramelize. The tomatoes are done when they have lost perhaps 3/4 of their volume, are still pliable, and very intensely flavored. This can take an hour or two for cherry tomatoes and up to overnight for larger tomatoes. You and your oven need a trusting relationship to stay overnight.

Scrape the tomatoes into a bowl and let them cool. Then pack them in 1/2-cup size jars or containers and freeze. Add some of your dried tomatoes to tomato sauce to give it a real flavor kick, or put them on crostini spread with ricotta whipped with a little olive oil. Or serve the tomatoes with fresh mozzarella. Make sure to use that delicious olive oil for salad dressings and such. Or just as a dip for bread. You will not regret it.

My newest enthusiasm also involves oven-drying – shiitake bacon: mushrooms sliced, seasoned, and then oven-dried until their flavor has been so amped up that, yes, they taste like bacon. You could easily call them "umami power bites." Make a big batch to have on hand for everything from egg dishes, pizza and grilled or melted cheese sandwiches, polenta, sautéed greens, to salads, and eating out of hand or adding to soups and stews. Even if you're a vegetarian, you, too, can enjoy BLT's in the summer. Yours will be SBLTs and, if you share with meat-eating friends, they won't miss the real thing. And if you had been to Michael Recchiutti's (the San Francisco chocolatier) mushroom-and-chocolate tasting with me last year, you would know for sure that mushrooms go with everything.

High and Fast or Low and Slow: You can make the bacon by roasting the mushrooms at 400°F for 10 to 20 minutes or low and slow, 250°F, for an hour or two or until not quite stiff. The low-slow option gives you more control and you do not want to burn the mushrooms. If you want something like bacon bits, chop the mushrooms into 1/2-inch pieces instead of slicing. When done, the mushrooms should still be pliable; they get crisper as they cool. If you prefer to eat gluten-free and make the soy-sauce version (below), use gluten-free soy sauce. You can increase the amount of soy and fish sauces to produce a stronger flavor, but be careful as both are salty.

You need: 8 ounces of large shiitake mushrooms, 1 1/2 tablespoons extra-virgin olive oil, 1 teaspoon soy sauce, and 1/2 teaspoon fish sauce. Preheat the oven to 250°F. Cut the mushrooms into 1/2-inch slices (stems removed and saved for stock). Gently toss the slices in a bowl with the olive oil, soy sauce, and fish sauce until evenly coated. Lay out on a cookie sheet, leaving space between the pieces. Bake until they are very shrunken and not quite crisp, about 2 hours. As they cool, they will get crisper. Turn over after 1 hour. This gives you an opportunity to judge how quickly the mushrooms are cooking and to adjust your timing, if necessary.

Vegetarian variations: Instead of soy sauce and fish sauce, coat the mushroom slices in teriyaki sauce and bake them at 250°F for about an hour, checking at 45 minutes. The teriyaki caramelizes onto the mushrooms making them almost like candy. (Am I exposing my sweet tooth too much?)

Yet another variation that mimics bacon's smokiness involves hickory salt (or another smoked salt such as Celtic smoked sea salt). Toss the mushrooms with 2 tablespoons olive oil and smoked salt to taste.

If jalapeno bacon is your passion, dust the mushroom slices with a pinch of cayenne before baking. Hey, why not go all the way and try a pinch of cinnamon, too!

Our motto: Eat Well to Stay Well

MEDICAL NEWS ROUNDUP

BY SUE HERMS

Anti-Fungal Drug Impairs Rituximab Activity – Researchers from the Technical University of Munich, Germany, reported that the antifungal treatment itraconazole impairs the activity of rituximab-containing therapy when given concurrently. Itraconazole inhibits the recruitment of CD20 to lipid rafts in the cell membrane and interferes with calcium influx, both of which are crucial for rituximab-mediated cell death. In contrast, the antifungal drug caspofungin does not appear to adversely affect the activity of rituximab.

Phase II Trial Evaluates Lenalidomide and Rituximab Combination Therapy – A Phase II study evaluated the efficacy and safety of lenalidomide (Revlimid) and rituximab in 28 patients with untreated, indolent non-Hodgkin's lymphoma. The overall response rate was 86%. Complete responses (complete absence of disease markers) occurred in 79% and partial responses occurred in 7%, while 14% had stable disease. At follow-up of 14.1 months, one patient experienced disease progression. Adverse effects included rash, neutropenia (low neutrophils), myalgia (muscle aches), neuropathy, infection, fatigue, and thrombosis (blood clots).

New Drug Tested in Phase I Study of Multiple Myeloma and Chronic Lymphocytic Leukemia – Investigators at John Theurer Cancer Center at Hackensack University Medical Center in New Jersey reported on a Phase I clinical trial of SNS-032, one in a new class of drugs that inhibit cyclin-dependent kinases. Cyclin-dependent kinases are proteins involved in cell metabolism, renewal, and signaling,

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and are thought to play key roles in cancer growth. This study involved 37 patients with multiple myeloma or chronic lymphocytic leukemia, and its primary purpose was to test the maximum safe dose that could be given; the drug also appeared to indicate some anti-tumor activity and additional studies are planned.

Vitamin C May Adversely Affect Responses to Certain Chemotherapies – Memorial Sloan-Kettering Cancer Center reported that vitamin C supplementation during cancer treatment may detrimentally affect therapeutic responses. Mouse models of leukemia and lymphoma received vitamin C before treatment and then were administered doxorubicin, cisplatin, vincristine, methotrexate, and imatinib. Examination of the mouse tumors showed a decrease in apoptosis (programmed cell death) that led to a substantial reduction in therapeutic efficacy.

Results Reported for Long-Term Impact of Rituximab Maintenance on Immune System – Another study from Memorial Sloan-Kettering Cancer Center released results on the long-term impact of rituximab maintenance therapy on the immune system. This retrospective study looked at 215 lymphoma patients. Rituximab maintenance was associated with a higher risk of developing hypogammaglobulinemia (low immunoglobulin level) – 55% compared to 33% who received standard rituximab monotherapy or combination therapy. Also, a higher percentage of patients on rituximab maintenance received IVIg for treatment of symptomatic hypogammaglobulinemia – 20% vs. 10% who did not have maintenance.

Alemtuzumab (Campath) Assessed in Lymphoplasmacytic Lymphoma – Dana-Farber Cancer Institute and the University of Wisconsin in Madison, WI, examined the activity of alemtuzumab (Campath) on 28 lymphoplasmacytic lymphoma (LPL) patients. Alemtuzumab targets the CD52 antigen widely expressed on lymphoplasmacytic cells and mast cells. This therapy resulted in an overall response rate of 75% and a major response rate of 36%; the median time to progression was 16 months. Hematological toxicities were common among patients who had received prior treatments. These included neutropenia (low neutrophils), thrombocytopenia (low platelets), anemia, rash, and infection. Cytomegalovirus (CMV) reactivation and infection were also common among previously treated patients. Long-term follow-up revealed late-onset idiopathic thrombocytopenia in four patients at a median of 13.6 months following treatment.

Polish Study Evaluates Rapid Infusion Rates for Rituximab – The Maria Sklodowska-Curie Oncology Institute in Warsaw, Poland, performed an exploratory non-randomized study on 125 patients to evaluate the safety of rapid rituximab infusion rates. Patients received their first rituximab dose by standard procedure; subsequently, some patients received either rapid doses or standard-rate infusions. The median infusion time for the rapid dose was 111 minutes. A small percentage of patients (6.5%) experienced infusion reactions during their first standard-rate delivery. No patients who received subsequent standard-rate infusions had reactions while 2.7% of patients who received subsequent rapid infusions did. The study was unable to identify factors predicting the occurrence of infusion reactions. With a one-year follow-up, the study concluded that rapid rituximab delivery starting from the second cycle is equally as safe as a standard-rate infusion and may be routinely used in clinical practice.

Reduced Intensity Allogeneic (Mini-Allo) Stem Cell Transplantation Feasible for Older Patients – Among patients 60-71 years of age, reduced-intensity allogeneic hematopoietic stem cell transplantation (mini-allo) was well tolerated and associated with reasonable survival. This study by Dana-Farber Cancer Institute retrospectively analyzed outcomes in 158 older patients with hematological malignancies. Two-year overall survival and progression-free survival were 46% and 35%, respectively; incidences of acute and chronic graft vs. host disease were 19.6% and 45.9%, respectively. The study concluded that this type of transplantation should not be excluded solely based on advanced patient age.

Parental Age Has Effect on Development of NHL in Offspring – Although advanced parental age at one's birth has been associated with increased risk of breast and prostate cancers, few studies have examined its effect on adult-onset hematologic malignancies. A study published by the Beckman Research Institute in California examined the association of parent's ages with the development of these malignancies in a group of 110,999 women. Paternal age greater than 40 years was associated with an increased risk (approximately 1.5 times) for development of non-Hodgkin's lymphoma in offspring. No association of either paternal or maternal age was observed for development of acute myeloid leukemia or multiple myeloma in offspring.

Micromet Updates Phase I Results for Blinatumomab – Micromet, Inc. announced updated results from a Phase I trial of its monoclonal antibody blinatumomab (MT103) in patients with relapsed non-Hodgkin's lymphoma. Blinatumomab is designed to direct the body's T-cells against CD19, a protein expressed on the surface of B-cells and is the first in a new class of agents called BiTE antibodies. Of those patients evaluable, 100% achieved a response, with median response duration of 21 months. The most frequent side effects were leukopenia (low white blood cell counts) and fever. Less common adverse events included transient neutropenia (low neutrophils), transient thrombocytopenia (low platelets), transient increase in liver enzymes, and central nervous system events, all of which were fully reversible following treatment cessation. Micromet is developing a different dosing schedule to minimize neurological events.

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Italian Study Assesses Resveratrol and Simvastatin in IgM-MGUS and Smoldering WM – The U.O. di Oncologia, Ospedale N. Giannattasio, in Rossano, Italy, issued a one-year follow-up report on the use of resveratrol and simvastatin to decrease IgM secretion in both IgM-MGUS and smoldering WM patients. The six patients in this small study received 40 mg/day of resveratrol and 20 mg/day of simvastatin for at least 180 days. The IgM-MGUS patients all had a reduction between 30-50% of their IgM monoclonal peak after 6 months of therapy, a result that is still being maintained at 14 months of follow-up. The IgM reduction was approximately 25% in the smoldering WM patient and is also still being maintained.

Orphan Drug Designation Received for New Treatment That Enhances Stem Cell Engraftment – Tarix Pharmaceuticals has received orphan drug designation from the FDA for TXA127, its drug used to help patients recover their stem cell population following stem cell transplant. The designation applies to myelodysplastic syndrome, and the drug is currently in a Phase II clinical trial to test the safety and efficacy of platelet recovery in patients with Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma.

New Oral HDAC Inhibitor Undergoes Testing for Hematologic Malignancies – The Ohio State University is assessing the safety and activity of a new oral drug AR-42 in a Phase I/II clinical trial. AR-42 is a histone deacetylase (HDAC) inhibitor designed to treat relapsed or treatment-resistant multiple myeloma, chronic lymphocytic leukemia, or lymphoma. The drug has been licensed to the biopharmaceutical company Arno Therapeutics, Inc., for clinical development.

Fludarabine and Rituximab Effective for Treating Chronic Cold Agglutinin Disease – Many patients diagnosed with chronic cold agglutinin disease (CAD) have a clonal lymphoproliferative bone marrow disorder such as WM. Treatment with rituximab leads to 45-60% partial responses, but with rare complete responses and a median response duration of only 11 months. A multi-center trial in Norway tested combination oral fludarabine and rituximab on 29 CAD patients and reported a 76% response rate, with 21% achieving complete response. Estimated median response duration was more than 66 months. Fludarabine toxicity may be a concern, and benefits should be weighed against risks in patients who are very old or who have other health issues.

Hyperglycemia During Chemotherapy May Increase Treatment Toxicity – A multi-center study reported in the American Journal of Clinical Oncology that hyperglycemia (high blood sugar level) during chemotherapy for hematologic and solid tumors correlates with increased toxicity of treatment. A total of 349 patients participated in this retrospective study – 162 had non-Hodgkin's lymphoma (NHL) and 187 had prostate cancer. For NHL patients, hyperglycemia was associated with an increased incidence of neuropathy, fever, and fatigue. A similar, although less clear pattern, was suggested in prostate cancer patients. The authors suggest that additional studies are needed to assess whether better glycemic control during chemotherapy can improve toxicity and outcomes.

Modafinil Evaluated for Relief of Fatigue Due to Chemotherapy – The University of Rochester Cancer Center in New York conducted a Phase III trial of modafinil, a nonamphetamine-based stimulant, in the management of fatigue for patients undergoing chemotherapy. Based on the data available for 631 patients, a benefit was seen for patients with severe fatigue, but not for those with mild or moderate fatigue. Modafinil-related side effects included allergic reaction, dyspnea (shortness of breath), and headache, which subsided upon treatment cessation.

Results Reported for Thalidomide and Rituximab Trial for WM – The Dana-Farber Cancer Institute released results of its Phase II study using thalidomide and rituximab in WM patients naïve to either agent. Twenty-three patients were evaluated, with an overall response rate of 78% and a major response rate of 70%. Median serum IgM decreased from 3,670 mg/dL to 1,590 mg/dL, while median hematocrit rose from 33.3% to 37.6%. Toxicities included neuropathy, sleepiness, confusion, rash, tremors, bradycardia (slow heart rate) and palpitations. With a median follow-up of 42+ months, the median time to progression was 35 months. Dose reductions of thalidomide occurred in all patients and 11 patients required treatment cessation.

New Anti-Kappa Monoclonal Antibody Tested in Multiple Myeloma – Researchers from Alfred Hospital in Australia, Immune System Therapeutics Ltd., Janssen-Cilag Australia Pty Ltd., Medarex Inc., and Bristol-Myers Squibb discussed a new anti-kappa light chain chimeric antibody, MDX-1097, that recognizes a cell surface antigen expressed on multiple myeloma and WM cells. Based on promising pre-clinical data, a Phase I dose study was conducted on multiple myeloma patients. No serious adverse events and no dose limiting toxicities were reported for the twelve patients who participated, although a transient increase in serum kappa light chain levels was seen immediately following infusion. One patient with bone pain and areas of disease demonstrated on PET scanning had resolution of bone pain and normalization of the PET scan following treatment. Based on this study, a Phase II study at a dose of 10 mg/kg will begin soon.

IMMU-114 Monoclonal Antibody Targets Cell Signaling Pathways – Garden State Cancer Center in New Jersey, Immunomedics Inc., and Weill Cornell Medical College tested a humanized monoclonal antibody called IMMU-114 in cell lines and mouse models. The antibody targets the ERK and JNK MAP kinase signaling pathways. These researchers found that IMMU-114 was toxic to mantle cell lymphoma, chronic lymphocytic leukemia, hairy cell leukemia, follicular

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lymphoma, and multiple myeloma cells, even those cells that were relatively resistant to anti-CD20 monoclonal antibodies.

T*he author gratefully acknowledges the efforts of Arlene Carsten, Peter DeNardis, Mike Dewhirst, Gareth Evans, Daniel Hachigian, John Paasch, Colin Perrott, Howard Prestwich, and Bert Visheau in disseminating news of interest to the IWMF-TALK community.*

IWMF AND LLS: A GREAT PARTNERSHIP HELPING WM PATIENTS

BY CINDY FURST AND JOAN BERGLUND

IWMF Trustee Cindy Furst is also co-chair of the support group committee and a support group leader for Colorado (as well as regional contact for Montana, North Dakota, South Dakota, and Wyoming). Cindy here teams up with Oregon support group leader Joan Berglund to describe the partnership their support groups enjoy with the Leukemia and Lymphoma Society in Denver and Portland.

In several locations across the US, local IWMF Support Group Leaders partner with their local LLS Patient Services Manager to provide combined benefits for WM patients and caregivers. In Portland, for example, we are very fortunate to have Sue Sumpter, RN, MS, and LLS Patient Services Manager working very closely with our IWMF support group leader, Joan Berglund, RN, MSN. Sue's link with the Portland support group goes back to the very first IWMF support group meeting held in Portland in September 2006 – when Sue was the speaker! For the next several meetings the IWMF-LLS support group used the LLS conference room in Portland but soon outgrew the space. In her role as Patient Services Manager, Sue Sumpter facilitates many different types of blood cancer support groups in addition to the WM support group. Sue has a network of local doctors, insurance specialists, nutritionists, an exercise physiologist, and others who are glad to come and speak at a meeting. The LLS (Sue again handles the details) provides lunch and rents a hotel conference room located near Interstate 5, for easy access from all directions in Oregon and southwest Washington.

Discussing our LLS-IWMF cooperative leadership in Portland, Sue Sumpter writes, "It always makes me feel good to see everyone reconnect or establish new bonds and leave feeling supported and encouraged by what they've learned during the meeting. We can collaborate successfully to reduce the workload and cost when two organizations work together with mutual respect. The winners are the patients who get access to more information, services, and speakers. It does not in any way diminish the patients' ability to continue to support IWMF and its goals; it is in no way a "competition" between the two organizations. We are both working for the mission, to find a cure and support our patients. The IWMF is jointly funding clinical research with the LLS on a current major WM research project. Both organizations realize that working together can produce greater results."

In Denver, Lynn Callaway, the Colorado LLS Patient Services Manager, has coordinated rooms for WM meetings, provided the refreshments, produced great speakers, and usually finds 2-3 new patients for each meeting. Typically, these new WM patients have only heard of the LLS, not the IWMF. When the LLS is called for information about WM or finds a WM patient by some other way, they direct them to the IWMF support group. Lynn works closely with all the Colorado IWMF leaders – Cindy Furst, Roy Parker, and Bill Bass. It is a "win-win" for both organizations, says Lynn, as the LLS charter is to cover all blood cancers and WM is such a unique rare blood cancer that the LLS cannot focus directly on it. At every meeting both the LLS and the IWMF leaders review their respective services that will help those patients and caregivers present.

Lynn also notes that in Kansas City, in addition to the benefits noted above, the LLS also provides a group facilitator to help with the meetings.

Another big benefit provided by the LLS is financial assistance offered to patients needing help. Qualifications are reviewed at every joint meeting to make sure WMers in Denver are taking advantage of these programs. A WM patient currently in treatment or actively followed by their physician is eligible for a Patient Aid Stipend of $150 per fiscal year. The LLS also provides a Co-Pay Assistance Program to patients to assist with treatment expenses. There is no income limitation on the Patient Aid Stipend, and the income limit on the Co-Pay Assistance Program is a very liberal 5 times the national poverty level. Co-Pay Assistance can be as high as $10,000. See the LLS website *www.lls.org* to get more details on both financial aid programs.

The LLS and IWMF have also teamed up with their research dollars. As Sue Sumpter states above, we have together provided funding to selected WM research efforts. The IWMF and the LLS jointly convened a forum in Washington, DC, in order to identify research areas most essential to further understanding of WM. As an outgrowth of that effort the two organizations have together awarded grants to four researchers tasked with developing new WM cell lines, a critical link in discovering new and more effective treatments for the currently incurable WM disease.

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IWMF and LLS, cont. from page 23

Cell lines are invaluable in understanding the genetics and biology of cancerous cells, as you can read on page 8 of this issue where the importance of this research is discussed and the recipients of LLS-IWMF support are listed.

Our partnership with the LLS will continue to grow and benefit WM patients worldwide. Moreover, our joint efforts show the larger cancer community how collaboration between organizations is more beneficial to patients than when such organizations act independently. We thank the LLS for being such great partners and hope that more collaboration occurs in more cities in the future!

SUPPORT GROUP NEWS

EDITED BY PENNI WISNER

Please note: contact information for all support groups is printed on pages 28-29.

IWMF CHAPTERS – USA

CALIFORNIA

Orange County

Get ready for an exciting meeting on Saturday 30 October, from 2 to 5 pm at Hoag Hospital's conference room in the Cancer Center, when Dr. Herbert Eradat, Assistant Clinical Professor of Medicine at UCLA's division of Hematology/Oncology, will update attendees on news from the very recent (6 to 10 October 2010) International WM Workshop in Venice, Italy. He will also cover new therapies and clinical trials in WM (including those available at UCLA) and field patient questions.

Sacramento and Bay Area

A rare and much appreciated opportunity provided the focus for the fall meeting, held in late September in San Francisco in conjunction with the Lymphoma Research Foundation (LRF). Two special sessions on Waldenstrom's macroglobulinemia, organized as part of the LRF North American Educational Forum on Lymphoma, were led by Dr. Steven Treon of the Dana-Farber Cancer Institute and Dr. Christine Chen of the Princess Margaret Hospital, University Health Network. These two back-to-back talks covered both the past and future of WM diagnosis, treatment, and research. A private lunch was provided so that Drs. Treon and Chen could answer questions both during and after the meal.

COLORADO & WYOMING

After two wonderful big-name-speaker meetings this past year, the group enjoyed a casual potluck brunch meeting in June at the home of **Roy** and **Eileen Parker** in Highlands Ranch, Colorado. Continuous rain obscured the gorgeous view from their deck of the Front Range of the Rocky Mountains, an unusual occurrence there in the dry, high desert. Instead, every chair in the house provided seating for all 28 participants including one newly diagnosed patient and several who received their diagnoses less than a year ago. Individual conversations centered on symptoms, doctors, treatments, side effects, new clinical trials available to us in Denver through Dr. Matous of the Rocky Mountain Cancer Center and his connection with Dana-Farber, as well as how some participating members in those trials are faring. General discussions included identifying future speakers, the recent Ed Forum in Las Vegas, and the upcoming DVDs from the forum which are routed through the mail from home to home each year. WM plastic bracelets and IWMF pins sent by IWMF office manager **Sara McKinnie**, as well as new literature, were passed out. The positive feedback on the opportunity for casual connections provided by this meeting encouraged the group to try and schedule two share-and-discuss meetings each year as well as two meetings with speakers. Over the next 6 months, the group may also try the new WebEx technology and invite another support group location to share the event.

A rainy day did not dampen spirits at the potluck brunch of the Colorado support group.

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Members of the Chicago area support group turned out for good food and a good time at their second annual picnic.

FLORIDA

West Coast

Dr. Steven Treon of Dana-Farber Cancer Institute will host the 4th International Patient & Physician Summit, 11 to 13 March 2011 in Orlando. Details are posted at the IWMF website, *www.iwmf.com*, on the Events Calendar page. **Herb Kallman**, support group leader for Florida's southwest coast, will be working with other Florida support group leaders to organize a state-wide – or wider, any WMer who attends the summit is invited – support group meeting to coincide with the Summit.

ILLINOIS

The Chicago area/SE Wisconsin support group had its second annual picnic on Saturday 14 August, with 11 WM families represented for a total of 22 people at **Hugh** and **Jackie Edfors'** home in Naperville. The weather was warm but not too hot for a game of beanbag toss in the backyard lined with beautiful roses. Between **Don Brown's** beer-simmered brats and the Edfors' great burgers there was plenty of food supplied by our gracious host and hostess. We were all thankful for the 67 degree F air conditioning which enabled us to avoid Chicago humidity and a big outbreak of mosquitoes. Future plans include a meeting in late October with a guest speaker and a spring 2011 day-long workshop.

MICHIGAN

In June about ten members enjoyed a delicious potluck at the Sparrow Cancer Center in Lansing. The group shared discussions of their symptoms and treatment options and was particularly interested to hear the experiences of one attendee with the new drug Treanda. The next meeting is planned for late fall.

NEW YORK

Eastern NY/Western New England

In late August a small but enthusiastic group gathered at Gilda's Club in Latham for the annual summer picnic where members enjoyed each other's company and ample great food. The fall meeting was also held at Gilda's Club on Saturday 25 September. Among other topics, the group set a tentative meeting schedule for 2011. Our final 2010 meeting will be held on Saturday 13 November, at Gilda's Club.

Rochester, Western and Central NY

In the spirit of late-summer outdoor gatherings, the group picnicked on the shore of Lake Ontario at the home of a group member in Webster. This provided a beautiful place to relax; it was a little like having a picnic on the sea shore but with fresh water. A new member arrived with his wife. They had attended a Leukemia and Lymphoma Society support group meeting at the Rochester Gilda's Club.

The eastern New York and western New England gang at Gilda's.

Support Group News, cont. on page 26

Support Group News, cont. from page 25

PENNSYLVANIA

Central and Southeast PA and Northern MD

Don and **Kate Wolgemuth** hosted this year's potluck picnic at their home. This is always a very informal gathering with great food and even better fellowship and conversation. This year a newly diagnosed patient attended and learned much from the "veterans" in attendance. The next meeting will be at Messiah Village on 14 November.

Philadelphia

This busy group held two meetings this summer, one in June and one in August. Sixteen people met in June to hear a report on the highlights of the 2010 Ed Forum and then shared personal WM experiences. Heidi, the group's four-footed unofficial mascot, spent most of the June meeting very close to one person or another, preferably in their lap, due to the thunderstorm outside. In August ten of us met and discussed research funding and the idea of putting instructions in one's will to leave a donation to IWMF after the second spouse has passed away, either a percentage of assets or a set amount. Everyone thought it was a good idea and that they probably wouldn't have thought of doing this if it hadn't been suggested. Other topics covered at the meetings were cholesterol, peripheral neuropathy, vitamin D's fat solubility and the possible dangers of overdose, flu shots, Rituxan, eye problems, alternative treatments (vitamins, juice drinks, and herbs), and low hemoglobin counts and use of Aranesp. Wonderful refreshments brought by a different member each time fuels the enthusiastic conversations.

SOUTH CAROLINA

Sue Herms, IWMF Trustee and *Torch* medical news editor, updated the group at their fun and informative summer meeting in Charleston. About 20 attendees, including three newly diagnosed WMers, shared their respective experiences. That evening, a number of members got together to explore low-country fare at one of the historic downtown Charleston restaurants. The next meeting of the support group will be held in early December.

INTERNATIONAL WM SUPPORT GROUPS

CANADA

The WMFC (Waldenstrom's Macroglobulinemia Foundation of Canada) held its second fundraiser this June in support of research for Waldenstrom's macroglobulinemia. The event, "Cruising for a Cure," took place on 12 June with a boat cruise around the Toronto harbor, lunch, and a silent auction. In spite of poor weather, a good time was had by all. The auction, which enjoyed great support by local businesses, brought on many bidding wars and all 26 items were enthusiastically carried off the boat by the highest bidders. Auction lots ranged from The Food Network cookbooks to a week's vacation on the beautiful Turks & Caicos Islands. Fine wines, cameras, watches, pictures, a handmade quilt, a golf weekend, and much more helped round out the items offered. There was something for everyone. The 120 attendees raised over $33,000. Everyone who came out and supported this event deserves many, many thanks.

FRANCE

Nicole Bastin sent news of an exciting development for French WM patients. After the patients' meeting in Vienne, September 2009, it was decided to create a French WM Patients' Association. This is now done. The statutes

SUPPORT GROUP LEADERS TALK LIST

This list is only for support group leaders to use in communicating with each other about support group issues. It is designed for the leaders to share their experiences and ideas for facilitating our IWMF support groups. Contact Cindy Furst at *cindyfurst@msn.com* if you would like to participate.

The Bogeymen of St. Augustine's Golf Club, a golf society in Ramsgate, held a fundraiser to honor WM patient and fellow Bogeyman Kevin Ahmed (the chap with no hair in the front row).

Support Group News, cont. on page 27

of "Waldenström France" were filed in January 2010. **Michel Houche** was elected President of the Board.

Waldenström France is located at:
2 rue Hernandez de Heredia,
F- 84000 Avignon, France

The French talklist link is: *http://sympa.medicalistes.org/wws/info/waldenstrom*

A patient/doctor meeting took place mid-September in Vienne.

IRELAND

Sheila Thompson will be taking over the group in September 2010. **Anne Staples** and her husband will be preoccupied packing up and selling the home that has held Anne's husband's family since 1875. She says it is time to build a new house; the much-loved old house is too big now that their two children have grown and moved away.

UNITED KINGDOM

Two generous contributions made to WM research in 2009 were reported by **Cheryl Luckie** for the UK WM support group. The first was made through the estate of Denis Donovan, a support group member and former lecturer at the University of East London. The second contribution was the result of a special fundraising event by the Bogeymen of St. Augustine's Golf Club in honor of their fellow Bogeyman, Kevin Ahmed, a WM patient. The support group donated these contributions to fund the ongoing WM research of Dr. Roger Owen at Leeds University and Dr. Surinder Sahota at Southampton University. Cheryl reports further that the WM support group has initiated contact with the Lymphoma Association in the UK in order to negotiate charity status for the support group to cover future charitable events and legacy donations. "Lastly," writes Cheryl, "we joined the European WM Network in 2009, which we hope will give WM support groups all over Europe a collective say in shaping legislation which directly affects patient care and treatment as well as helping to attract grants given by the EU."

IWMF SUPPORT GROUP CHAPTER LISTINGS

ALABAMA
Mal Roseman
770-392-1255
malroseman@comcast.net

ARIZONA
Phoenix
John Dethloff
623-388-7152
jdethloff1@cox.net

Ed Nadel
480-502-5045
enadeL63@aol.com

ARKANSAS
Eastern
Bill Paul
901-767-6630
Billpaul1@juno.com

CALIFORNIA
Los Angeles
Kathie Coen
310-454-7127
kdcoen@roadrunner.com

Monterey
(May – Oct.)
Sandy Skillicorn
831-277-5274
jLsLs@aol.com

Orange County
Emil Parente
949-388-9666
pnepar@cox.net

Marty Glassman
949-458-7147
mglassman@cox.net

Sacramento/
San Francisco Bay Area
Alyce & Terry Rossow
925-447-8881
Rossow@ieee.org

COLORADO
Bill Bass
303-753-0070
303-808-5734 cell
basswilliam9@gmail.com

Cindy Furst
970-667-5343
970-227-4686 cell
cindyfurst@gmail.com

Roy Parker
303-470-6699
roypar@gmail.com

CONNECTICUT
Francoise Lampe
203-431-1455
wmfgL@sbcglobal.net

Bob Hammond
203-426-2772
Rhamm17@aol.com

Linda McIntosh
860-460-6445
lynmac47@aol.com

DELAWARE
Karen Pindzola
717-845-5937
karenpindzola@yahoo.com

FLORIDA
Ft. Lauderdale Area
Charlie Koch
954-476-8726
bonnie143@bellsouth.net

Theo Vagionis
954-564-9262
wesport2@msn.com

West Coast
Herb Kallman
239-466-6911
margerina@aol.com

Tampa
Rita & John O'Brien
813-654-4986
promo1rita@verizon.net

Linda Rothenberg
352-688-0316
A1pets@tampabay.rr.com

GEORGIA
Atlanta
Mal & Judy Roseman
770-392-1255
malroseman@comcast.net

HAWAII
(Nov. – Apr.)
Sandy Skillicorn
808-891-2882
jLsLs@aol.com

IDAHO
Eastern
Barbara Britschgi
208-522-2130
cbrits@cableone.net

Western
Judy Clark
208-888-0346
jzclark@cableone.net

ILLINOIS
Chicago
Don Brown
630-323-5894
Ldonbrown@msn.com

INDIANA
Gayle Backmeyer
divagayle@comcast.net
765-962-3746

KANSAS
Eastern
Karen & Joe Davis
785-266-0121
karenjdavis@gmail.com

KENTUCKY
Marion Petry
mLpetry123@earthlink.net
937-438-8850

MARYLAND
Catherine Naylor
301-229-0319
catherinenaylor@verizon.net

MASSACHUSETTS
Boston
Lynne & Joe Mara
781-749-0204
jmara@nordicgroupusa.com

Judy Christensen
781-335-5698

MICHIGAN
Peter & Barbra Boyse
989-415-9936
peterdboyse45@charter.net

MINNESOTA
Minneapolis/St. Paul
Michelle Blazek
651-730-0061
mandsblazek@aol.com

MISSISSIPPI
Bill Paul
901-767-6630
billpaul1@juno.com

MISSOURI
Northwestern (KC Area)
Karen & Joe Davis
785-266-0121
karenjdavis@gmail.com

MONTANA
Barbara Britschgi
208-522-2130
cbrits@cableone.net

Regional Contact:
Cindy Furst
970-667-5343
970-227-4686 cell
cindyfurst@gmail.com

NEVADA
Eastern
Gerri McDonald
801-484-0360
gerri-sLc@comcast.net

Las Vegas
Robin Grenz
702-657-3860
Rgrenz1@cox.net

NEW ENGLAND
Boston
Lynne & Joe Mara
781-749-0204
jmara@nordicgroupusa.com

Judy Christensen
781-335-5698

Western MA, VT & CT
Mel Horowitz
518-449-8817
wmcure@yahoo.com

NEW MEXICO
Regional Contact:
Bill Bilbro
575-642-4987
wbilbro@gmail.com

NEW YORK
Albany
Mel Horowitz
518-449-8817
wmcure@yahoo.com

New York City
Neil Massoth
201-444-6253
nmassoth@aol.com

Rochester
Stephen E. French, Sr.
585-621-3317
sfrench@rochester.rr.com

NORTH CAROLINA
Bob Zehner
804-796-3571
bobnbetsz@comcast.net

Don Nolan
828-692-1114
nondolan@aol.com

NORTH DAKOTA
Regional Contact:
Cindy Furst
970-667-5343
970-227-4686 cell
cindyfurst@gmail.com

EASTERN OHIO
Shariann Hall
330-533-4921
shari19@juno.com

Marcia Klepac
412-421-2437
marciaklep@hotmail.com

WESTERN OHIO
Marion Petry
mLpetry123@earthlink.net
937-438-8850

OKLAHOMA
Western
Regional Contact:
Bill Bilbro
575-642-4987
wbilbro@gmail.com

OREGON
Joan Berglund
503-668-5037
rjbergie@verizon.net

Jules Auger
503-746-7990
j.auger@comcast.net

PENNSYLVANIA
Philadelphia
Karen Pindzola
717-845-5937
karenpindzola@yahoo.com

IWMF SUPPORT GROUP CHAPTER LISTINGS

PENNSYLVANIA (cont.)
Harrisburg
Terrie Eshleman
717-665-7393
tmesh74@ptd.net

W. PENN, E. OH, WV
Shariann Hall
330-533-4921
shari19@juno.com

Marcia Klepac
412-421-2437
marciaklep@hotmail.com

RHODE ISLAND
Linda McIntosh
860-460-6445
lynmac47@aol.com

SOUTH CAROLINA
John & Paula Austin
803-644-6002
jhaustin@bellsouth.net

SOUTH DAKOTA
Regional Contact:
Cindy Furst
970-667-5343
970-227-4686 cell
cindyfurst@gmail.com

TENNESSEE
Central & Western
Bill Paul
901-767-6630
Billpaul1@juno.com

Eastern
Regional Contact:
Myrna Daniel
706-539-2866
mdmermer@yahoo.com

TEXAS
Dallas
John Knutson
972-726-7790
johnknutson@tx.rr.com

Steve Pine
214-244-5515
iwmf4steve@verizon.net

Houston
Barbara & John Manousso
713-840-0828
wm@manousso.us

Western
Regional Contact:
Bill Bilbro
575-642-4987
wbilbro@gmail.com

UTAH
Gerri McDonald
801-484-0360
or 801-232-5811
gerri-sLc@comcast.net

VIRGINIA
Bob Zehner
804-796-3571
bobnbetsz@comcast.net

WASHINGTON
Malcolm Brewer
206-772-7430
clanbrewer@gmail.com

Kristen Jenson
425-483-6605
Kristen@jensonfamily.org

WASHINGTON D.C., NORTHERN VA
Catherine Naylor
301-229-0319
catherinenaylor@verizon.net

WISCONSIN
Northwest WI
Michelle Blazek
651-730-0061
mandsblazek@aol.com

Southeast WI
Don Brown
630-323-5894
ldonbrown@msn.com

WYOMING
Bill Bass
303-753-0070
303-808-5734 cell
basswilliam9@gmail.com

Regional Contact:
Cindy Furst
970-667-5343
970-227-4686 cell
cindyfurst@gmail.com

INTERNATIONAL SUPPORT GROUPS AND CONTACTS

AUSTRALIA
Gareth Evans
WMozzies-owner@yahoogroups.com

BELGIUM
Joanna Van Reyn
+32 9 335 46 60
joanna.vanreyn@cmp-vlaanderen.be

CANADA
Alberta
Cam Fraser
403-281-8278
cmfraser@shaw.ca

Stu Boland
403-281-0271
stu_boland@hotmail.com

Montreal
Regional Contact:
Sandra Proctor
450-672-4336
sandra.proctor@sympatico.ca

Nova Scotia
Susan Gagnon
902-446-9533
suemarge3x3@hotmail.com

Ottawa
Jan Jones
613-722-2385
janellejones@rogers.com

CANADA (cont.)
Janet Cherry
613-596-1413
janet.parcher.cherry@sympatico.ca

Toronto
Arlene Hinchcliffe
905-337-2450
wmfc@noco.ca

Vancouver
Charlene Kornaga
250-474-7011
dennischarlene.kornaga@shaw.ca

DENMARK
Steffen Stello
+45 3582 7707
Mobile: +45 2123 7707
snejka@mail.dk

FINLAND
Veikko Hoikkala
+35 8500 48 4864
veikko.hoikkala@dnainternet.net

FRANCE
Nicole Bastin
+02.54.37.89.52
nicbastin@aol.com

GERMANY
Regional Contact:
Dr. Rolf Pelzing
rolf.pelzing@t-online.de

GREECE
Alexia Kapralou
+30 210 6858574
kapralou_alexia@hotmail.com

INDIA
Regional Contact:
Anil and Vasundhara Somani
+91 98300 49300
asomani@vsnl.com

Mumbai & Western India
Sanjeev Kharwadkar
91-98210-69769
92-22-6691-9957
swkharwadkar@yahoo.co.in

IRELAND
Sheila Thomson
+35312822481
sheliathomsonmail@gmail.com

ISRAEL
Moshe Kwart
+97 254 2270527
m.kwart@tehilot.com

JAPAN
Regional Contact:
Sanjeev Kharwadkar
+81 03-6712-1887
+81 090-9971-4541 mobile
swkharwadkar@yahoo.co.in

NEW ZEALAND
Michael Goldschmidt
+03 384 5399
goldschm@paradise.net.nz

THE NETHERLANDS
Regional Contact:
Marlies Oom
+31 (0) 73.52.17.643
moom@planet.nl

UNITED KINGDOM
Nigel Pardoe & Cheryl Luckie
+44 020 8579 8120
info@septemberservices.com
cheryl.luckie@
septemberservices.com

Sussex
Mike Dewhirst
mkdewhirst@yahoo.co.uk

Birmingham & West Midlands
Geoffrey Willsher
+44 0121429 1038
willsher.s@btinternet.com

THE LIFELINE

If you can't get to a local support group meeting, use our IWMF Telephone and Email Lifeline to call a WM veteran. The Lifeline provides telephone numbers and email addresses of IWMF volunteers who will answer questions about their first-hand experience with specific treatments for WM.

**The Lifeline is seeking volunteers who speak a language other than English. If you would like to volunteer, please contact the IWMF business office at 941-927-4963 or info@iwmf.com.*

TREATMENTS

ALLOGENEIC STEM CELL TRANSPLANTS
Eileen Sullivan 617-625-6957
ebsullivan27@comcast.net

2-CdA (CLADRIBINE) WITH RITUXAN
Bernard Swichkow 305-670-1984
theswichkows@aol.com
Brent Wingett 805-466-2345
bwingett@charter.net

BORTEZOMIB DEXAMETHASONE & RITUXIMAB (BDR)
Joe Gallo 941-493-1809
galljocon@verizon.net
Ron Linford 865-657-9895
rongl@aol.com

CHLORAMBUCIL
Janice Stein 415-346-6620
janicemstein@aol.com

CRYOGLOBULINEMIA
Fay Langer 904-625-3135
fhlanger@gmail.com

FLUDARABINE with cyclophosphamide (Cytoxan)
Penni Wisner 415-552-6579
penniw@pacbell.net

FLUDARABINE with Rituxan
Marty Kopin 310-390-1546
mkopin@yahoo.com
Jerry Block 301-460-9799
Jblock35@comcast.net
Eileen Sullivan 617-625-6957
ebsullivan27@comcast.net

ORAL CYTOXAN
Lou Birenbaum 314-961-5591
lbirenbaum@aol.com

PLASMAPHERESIS
Fred Bickle 805-492-4927
Flb134@msn.com

RAD 001
Tom Howenstine 419-542-8921
Howen978@verizon.net

(revlimed) LENALIDOMIDE
Christopher Patterson 617-632-6285
christopher_patterson@dfci.harvard.edu

RITUXAN
Charles Vassallo 201-947-6977
cvassallo@nj.rr.com
James Townsend 352-376-3664
Allen Weinert 603-863-5347
anweinert@gmail.com 760-568-2918

SPLENECTOMY
Kathleen Ugenti 631-470-0971
Patricia McCue .....239-348-3456 winter
802-468-5779 summer

STEM CELL TRANSPLANT
Howard Donley 307-587-3397
donleyh@tctwest.net

THALIDOMIDE
Mel Horowitz 518-449-8817
wmcure@yahoo.com

VELCADE
Jeff Atlin 905-707-5640
jeffatlin@hotmail.com

SPECIALTY TOPICS

CAREGIVING
Lynn Bickle 805-492-4927
Flb134@msn.com
Brad Alexander 972-529-2002

CLINICAL TRIALS
Tom Hoffmann 501-868-8305
Thh97@msn.com
Guy Sherwood 765-282-4377
guysherwood@comcast.net

HEARING IMPAIRED TTY FACILITY
Betty McPhee 647-348-7440
bjmcphee@hotmail.com

LATEST RESEARCH
Bert Visheau 905-528-1789
visheau@mcmaster.ca

NEWLY DIAGNOSED
Guy Sherwood 765-282-4377
guysherwood@comcast.net
Sallie Moore 16-795-3746
Smoore6042@aol.com

SOCIAL SECURITY DISABILITY
Howard Prestwich 815-233-0915
prestwic@mwci.net

WATCH AND WAIT
Mel Horowitz 518-449-8817
wmcure@yahoo.com
Renee Paley-Bain 203-744-7851
paleybain@aol.com

YOUNG WM
Nobby Riedy 650-879-9104
knobby@wildspaces.net
Bob Bailey 770-664-8213
Laurabailey64@gmail.com

REQUEST FOR TELEPHONE AND E-MAIL LIFELINE VOLUNTEERS

Recently, the office has heard from patients who have questions about perifosine and ofatumumab. If you have experience with perifosine and/or ofatumumab and would be willing to answer questions and share experiences about these treatments, we would appreciate hearing from you. As a Lifeline volunteer your contact information will be published in the Lifeline that appears in each issue of the *Torch* and at the IWMF website. The Telephone and E-mail Lifeline is a valuable resource for putting patients in touch with each other so that they may discuss WM disease-specific issues.

THE LIFELINE

INTERNATIONAL

BELGIUM
Joanna Van Reyn ..... +32 9 335 46 60
joanna.vanreyn@cmp-vlaanderen.be

DUTCH SPEAKER
Lia van Ginneken-Noordman ..... 00-31-(0)70-3475520
Ginneken.noordman@wxs.nl

FINNISH SPEAKER
Veikko Hoikkala
veikko.hoikkala@dnainternet.net

FRENCH SPEAKER
Guy Sherwood 765-282-4377
guysherwood@comcast.net
Sybil Whitman 506-450-3970
hcouture@nbnet.nb.ca

FRENCH LANGUAGE TALK LIST
http://sympa.medicalistes.org/wws/info/waldenstrom

GERMAN SPEAKER
Roy Parker (Colorado, USA) 303-470-6699
roypar@gmail.com
Sybil Whitman (New Brunswick, CANADA) 506-450-3970
hcouture@nbnet.nb.ca

GERMAN LANGUAGE TALK LIST
Http://www.leukaemie-hilfe.de/foren.html?&tx_mmforum_pi1(action)=list_topic&tx_mmforum_pi1(fid)=14

SPANISH SPEAKER
Peter Mitro 440-247-3460
stonehill@earthlink.net
Betsy Beazley 510-527-5827
betsybeazley@gmail.com
Gladys Mendieta 215-860-9216
Gladysmendieta@aol.com
Leon Maya 865-694-9581
veraleon@comcast.net

SPANISH LANGUAGE TALK LIST
iwmf-talk-espanol-subscribe-request@lists.psu.edu

SWEDEN/NORWAY
Anne Odmark ..... +46 18-14 05 13
ag.odmark@gmail.com

NORDIC COUNTRIES TALK LIST
iwmf-talk-nordic-subscribe-rquest@lists.psu.edu

UNITED KINGDOM LIFELINE

2Cda (CLADRIBINE)
Roger Brown ..... +44 01285 650107
Rogerbrown961@btinternet.com

FLUDARABINE
Ken Rideout ..... +44 1278 782108
ken@4rosetree.fs.co.uk

FLUDARABINE AND RITUXIMAB
Mike Dewhirst
dewhirst_6@hotmail.com

OPTHALMOLOGY
Terry Betts ..... +44 01992 583643
tjb-planning@freeuk.com

PLASMAPHERESIS
Roger Brown ..... +44 1285 650107
Rogerbrown961@btinternet.com

RITUXAN
Nigel Pardoe ..... +44 0208 326 3270
pardoe@aol.com

UK SUPPORT GROUP ONLINE FORUM
Raphael Altman
raltman@btinternet.com

CANADA LIFELINE

CLINICAL TRIALS
Jan Jones (Ottawa, ON) 613-722-2385
janellejones@rogers.com
Rod Anderson (Cobourg, ON) 905-372-2410
rod@rodmer.com

TTY- HEARING IMPAIRED
Betty McPhee (Toronto, ON)
bjmcphee@hotmail.com
Fluent in American Sign Language

NEWLY DIAGNOSED
Jeff Atlin (Toronto, ON) 905-707-5640
jeffatlin@hotmail.com
Rod Anderson (Cobourg, ON) 905-372-2410
rod@rodmer.com

WAIT & WATCH
Jim Bunton (Toronto, ON) 416-621-7864
jbunton@sympatico.ca
Debbie Irwin (Toronto, ON)
Debbie.Irwin@Mecglobal.com

CVP/RITUXAN
Betty Mcphee (Toronto, ON) 647-348-7440
bjmcphee@hotmail.com
Ritwik Ray (Toronto, ON) 416-693-0910
ritwik@rogers.com
Rod Anderson (Cobourg, ON) 905-372-2410
rod@rodmer.com
Debbie Irwin (Toronto, ON)
Debbie.Irwin@Mecglobal.com

FLUDARABINE
Jeff Atlin (Toronto, ON) 905-707-5640
jeffatlin@hotmail.com
Gary Dvorkin (Mississauga, ON)
annawill@sympatico.ca
Bert Visheau (Hamilton, ON)
visheau@mcmaster.ca

RITUXAN
Rod Anderson (Cobourg, ON) 905-372-2410
rod@rodmer.com
Gary Dvorkin (Mississauga, ON)
annawill@sympatico.ca
Susan Gagnon (Halifax, NS)
suemarge3x3@hotmail.com
Bert Visheau (Hamilton, ON
visheau@mcmaster.ca

STEM CELL TRANSPLANT
Sybil Whitman 506-450-3970
hcouture@nbnet.nb.ca

VELCADE
Jeff Atlin (Toronto, ON) 905-707-5640
jeffatlin@hotmail.com
Rod Anderson (Cobourg, ON) 905-372-2410
rod@rodmer.com

VETERANS
Jan Jones (Ottawa, ON) 613-722-2385
janellejones@rogers.com
Bert Visheau (Hamilton, ON)
visheau@mcmaster.ca

SINCE JUNE 2010, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE IN MEMORY OF:

In memory of Olga Anderson:
Susanne Anderson
Basil Gooldridge
Deirdre Oconner
Norman & Ted Raspin
Aubrey Yearwood

In memory of Richard Anderson:
Jan Izzo
Steven Wunderle

In memory of Herbert Bisol:
Soon Hee Bisol

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In memory of Michael Vosburg:
Marilyn Canon

SINCE JUNE 2010, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE IN HONOR OF:

In honor of Aldes Boudreaux, Jr.:
Leslie Romero

In honor of Johannes & Holly Grent's 1st Wedding Anniversary:
Gilbert & Patricia Glass

In honor of Jeremy & Arlene Hinchcliffe:
Peggy Bryant
Thomas Long

In honor of Elinor Howenstine:
Marisa Howenstine

In honor of Joy Kramer:
Debbie Trujillo at Kimo Kards

In honor of Don Lindemann – For your support of the WM Community:
John Paasch
The *Torch* Team

In honor of Mike Pennington:
Karen Blocksom

In honor of the Ellen & Arthur Pincus' Wedding Anniversary:
Edi & Rich Vogel

In honor of Anna Mae Quitter:
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In honor of Elaine Van Bloom:
Fred & Dolores Pernerstorfer

In honor of Ubaldo Vitali:
Kate & Darla Hollitscher
Val Iacovantuno
Nicole Wagner

antibody sequences which may further decrease the risk of immune reactions.

How active is rituximab as a single agent in WM patients?
WM is a malignancy of the B-lymphocyte and typically expresses high levels of the CD20 antigen. This led to clinical trials in WM using the standard dosing approved for low grade lymphoma (one dose each week x 4 weeks). Several studies in previously untreated patients and in patients previously treated with chemotherapy have demonstrated that about 30-40% of patients have at least a partial remission (more than 50% reduction in IgM protein) from the treatment. An additional 15-20% of patients have a minor response (25-50% reduction). Recent studies suggest that patients who have a minor response also benefit from the treatment with improvement in bone marrow function and symptoms.

What about repeat courses of rituximab?
Treatment with two, four-week courses of rituximab separated by 2-3 months has been well tolerated and appears to improve the response rate and may improve the response duration. It is reasonable to consider repeated courses of rituximab in patients who appear to be responding to the initial course (or to consider "maintenance therapy" as discussed below).

What about "maintenance" therapy with rituximab?
Several large, recent clinical trials in patients with other low-grade lymphomas have demonstrated that treatment with extended doses of rituximab has been associated with a decrease in the risk of tumor progression and an extension of the duration of remission. Two different schedules have been used. The first, and most common, is treatment with one dose of rituximab given every 2-3 months for 2 years following the initial treatment with rituximab or rituximab/chemotherapy combination. The other common schedule is treatment with a 4-week course of rituximab, repeated every 6 months for up to 2 years. Direct comparison of these different schedules has not been done. Studies evaluating courses longer than 2 years are ongoing. Thus far, there have not been any reported randomized trials of maintenance rituximab in patients with WM. However, patients with WM who respond to initial rituximab and then go on to receive maintenance rituximab appear to have had prolonged remissions. Based on the data in indolent lymphoma, maintenance rituximab should be considered for patients with WM. In my clinical practice, in the case of patients not on a clinical trial, I discuss the risks and benefits of maintenance treatment (one dose every 2-3 months for up to 2 years) for all patients who respond to therapy with rituximab or rituximab/chemotherapy combination.

Are there risks associated with "maintenance" rituximab?
Although this has not yet been studied in detail in WM patients, maintenance therapy with rituximab has been fairly well tolerated in other indolent lymphoma patients. The risk of infusion-related symptoms usually decreases over time. There has been a small increased risk of suppression of the immune system and thus an increased risk in minor (upper respiratory or sinus) infections. In some patients this is associated with a decrease in the normal immunoglobulin levels (IgG). In addition, some patients may have drops in their white blood cell counts. Patients on maintenance need to be closely monitored. As discussed below rare patients may have serious complications following rituximab therapy.

Can there be severe reactions during or following rituximab therapy?
There can be rare severe reactions to rituximab-based treatments. These include severe infusion reactions as well as the risk of reactivation of serious viral infections such as hepatitis B or other viruses. Progressive multifocal leukoencephalopathy (PML) is an extremely rare and usually fatal brain condition that has been rarely observed in patients treated with rituximab. It is also seen in patients with cancer treated with other agents. It is not clear what the impact of maintenance rituximab will be on this devastating but, fortunately, at this time rare toxicity. All of these issues impact the risk versus benefit of rituximab therapy and need to be carefully considered with your oncologist.

Are there any factors that may predict how well rituximab will work in WM?
The clinical trials with single agent rituximab in WM have led to the observation that patients with IgM levels less than 4-6,000 have had higher response rates, as have patients with higher normal serum albumin levels. In addition, patients with immune systems with the higher affinity FC receptor variants have had higher response rates. These factors are most important when using rituximab as a single treatment. Combination of rituximab with other agents, such as chemotherapy, appears to overcome some of these limitations.

Why does the IgM level effect the response to rituximab?
This is an area that needs more attention. It is possible that the high levels of IgM either impact the interaction of rituximab with the immune system or possibly alter the levels and persistence of rituximab in the circulation. Additional studies that explore different doses and schedules of rituximab are needed.

What is the IgM "flare" seen in WM patients treated with rituximab?
Early studies using rituximab in WM patients detected the interesting finding that about 50-60% of patients actually had an increase in IgM levels in the first weeks following rituximab treatment. In some patients with high IgM levels (generally greater than 5,000 mg/dl), or in patients with high viscosity, this increase in IgM levels may be associated with severe worsening of symptoms. In most patients, this is a transient rise, with resolution in 2-6 months. There does not appear to be a correlation with the ultimate anti-tumor effect. Patients with high IgM levels or hyperviscosity may require plasmaphereses to decrease the IgM levels or combination

Doctor on Call, cont. on page 35

therapy with chemotherapy to prevent toxicity associated with the IgM flare. The cause of the IgM flare is unknown, but it is not simply the destruction of tumor cells and the dumping of IgM into the blood. It may be a result of alterations in the tumor cell or the effect of substances (cytokines) released from other cells in the blood and bone marrow, or due to changes in the kinetics of the antibody in the blood.

Why do some patients not respond to rituximab, and why does it stop working in others?

Resistance to rituximab treatment has been observed in two situations. Patients who do not respond to the initial treatment with rituximab have primary resistance. The mechanism of this is poorly understood, but this may be associated with high IgM levels or low affinity FC receptors. Other patients, in whom rituximab works initially, are found to be resistant to a repeat course of treatment. This "acquired" resistance is also poorly understood but may be due to changes in the tumor cells making them less susceptible to antibody-based killing. In low grade lymphoma, approximately 50% of patients who initially respond to rituximab are resistant to the next treatment. Combinations with chemotherapy or other novel agents such as thalidomide may be able to reverse this resistance.

What are the best chemotherapy and rituximab combinations for WM?

Unfortunately this is an area that remains controversial and suffers from a lack of randomized clinical trials. Encouraging activity has been associated with conventional chemotherapy regimens such as rituximab combined with CVP or CHOP chemotherapy or with fludarabine or pentostatin based treatments. Recent trials have incorporated rituximab with newer combinations of agents such as bortezomib or thalidomide along with other agents such as dexamethasone and Cytoxan. The decision of which rituximab and chemotherapy combination to use needs to be individualized for each patient based on many factors such as the presence of neuropathy or other comorbidities.

What about the newer anti-CD20 antibodies?

The success of rituximab has prompted an explosion of next generation anti-CD20 antibodies hoping to improve response rates and outcome in lymphoma patients. Most of these have failed to demonstrate increased activity over what would be anticipated with rituximab alone. The FDA has recently approved ofatumumab (Arzerra), a human antibody for treatment of patients with relapsed chronic lymphocytic leukemia. Direct comparisons with rituximab have not yet been reported. Several other promising anti-CD20 antibodies are currently in clinical trials.

Can rituximab responses be increased by immune stimulants?

This is an area of very active investigation, but as yet firm conclusions are few. Because rituximab is thought to work in part through interaction with the immune system, it stands to reason that agents that make the immune system better may improve the activity of rituximab. Many agents have been tried, including Neupogen, cytokines such as interleukin-2, or interferon, with no proven benefit. Other agents, such as thalidomide or lenolidomide have had mixed results in the clinic. Randomized trials in patients with WM and other lymphomas are required.

Dr. Maloney received his M.D. and Ph.D. in cancer biology from Stanford University, followed by an internship and residency in internal medicine at Brigham and Woman's Hospital and a fellowship in oncology at Stanford. While at Stanford, Dr. Maloney worked with Dr. Ronald Levy to develop monoclonal antibody treatments for lymphoma and has since participated in several clinical trials studying these agents. His current research focuses on the mechanisms of action of monoclonal antibodies and the use of non-myeloablative allogeneic transplantation for the treatment of hematologic malignancies.

Currently a member of the American Society of Hematology, American Society of Clinical Oncology, American Society of Blood and Marrow Transplantation, the Southwest Oncology Group Lymphoma Committee, and the National Comprehensive Cancer Network (NCCN) Committee on Hodgkin's Disease, Dr. Maloney is also Co-Chair of the Lymphoma Working Committee for the Center for International Blood and Marrow Transplant Research. Throughout his career, Dr. Maloney has authored and co-authored many articles focusing on antibody therapy, lymphoma, myeloma and transplantation that have appeared in publications such as the Journal of Immunology, *the* New England Journal of Medicine, *and* Blood.

International Waldenstrom's
Macroglobulinemia Foundation
3932D Swift Road
Sarasota, FL 34231-6541

Telephone 941-927-4963 • Fax 941-927-4467
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