

RESEARCH REPORT

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A Report from the Lymphoma Research Foundation

Introduction

Research makes advances in lymphoma treatment possible. Through research, clinicians and scientists are constantly learning more about cancer and its development. For this reason, the Lymphoma Research Foundation (LRF) continually strives to find the world's best scientific talent and fund the most cutting-edge research.

In March 2009, LRF held its sixth annual Mantle Cell Lymphoma (MCL) Consortium Scientific Workshop. The aim of this annual workshop is to accelerate advances made in the field of MCL by creating a forum in which to share data, exchange ideas, foster collaboration within the MCL research community and identify and prioritize areas of clinical and translational research that will have the largest impact.

Workshop attendees, comprised of LRF MCL Consortium members, LRF MCL grantees and other investigators conducting cutting-edge MCL research, heard 17 oral presentations and viewed 9 poster presentations covering the following subjects: biology of MCL; prognostic markers; new molecular targets; chemoimmunotherapy, transplantation and cellular therapy; and novel therapeutic approaches.

This *Research Report* provides detailed summaries of each oral and poster presentation that occurred at the meeting and highlights some of the most significant MCL research findings.

2009 MANTLE CELL LYMPHOMA SCIENTIFIC WORKSHOP

Spring 2009 saw more than 70 lymphoma researchers from around the world gather together for the sixth Mantle Cell Lymphoma Consortium (MCLC) Scientific Workshop. The meeting, held on March 30-31, 2009 in Atlanta, GA, provided a unique opportunity for these experts to report on their research findings and exchange ideas on how to best improve treatment options for individuals living with MCL.

The MCLC was formed in 2005 by the Lymphoma Research Foundation (LRF) and is made up of LRF MCL grant recipients as well as other scientific investigators conducting MCL research. This diverse group of researchers approaches the challenge of MCL research from many different angles, with the common goal of improving outcomes for patients with MCL.

LRF President Suzanne Bliss took the opportunity to express her gratitude to the MCLC researchers for their continued hard work. "I am so appreciative, as is the en-

tire organization, for all the time and effort that the group in this room has given to LRF on behalf of MCL patients," she said. Richard Fisher, MD, Chairman of LRF's Scientific Advisory Board, called the MCLC, "the most successful attempt to bring together investigators to generate a focus on science in an uncommon disease."

The workshop addressed several key questions, including:

- How do genes and proteins interact to cause the development of MCL and the survival of MCL cells despite chemotherapy?
- How can the latest research techniques be used to better diagnose, treat and monitor MCL patients?
- How can existing therapies be optimized to improve survival?
- How can our growing understanding of MCL biology be applied to the development of new therapies?
- What factors can clinicians use to predict how patients might respond to different therapies?

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LYMPHOMA RESEARCH FOUNDATION

The Lymphoma Research Foundation (LRF) is the nation's largest lymphoma-focused voluntary health organization devoted exclusively to funding lymphoma research and providing patients and health care professionals with critical information on the disease. LRF's mission is to eradicate lymphoma and serve those touched by this disease.

The Lymphoma Research Foundation is the world's largest private funder of MCL research, having raised more than \$22.3 million.

SCIENTIFIC HIGHLIGHTS

One focus of the meeting was systems biology, a new, integrated way of approaching research questions. Rather than the traditional method of studying individual genes or proteins, systems biology is the study of how the various parts of a biological system interact. "These sorts of approaches will hopefully move research forward at a faster rate," explained MCLC Chairman Michael E. Williams, MD (University of Virginia School of Medicine).

Researchers are also using other techniques to study the biology of MCL. Overall, these scientific investigations increase our understanding of the disease and may someday lead to better ways of diagnosing and treating MCL. Findings presented at the workshop include:

- Characteristics of some genes vary in MCL versus other types of lymphoma.
- Small pieces of genetic material called microRNAs can be used to distinguish between different types of lymphomas.
- One microRNA, called miR17-92, may be associated with resistance to chemotherapy in MCL.
- Certain genes seem to be associated with longer survival in patients with MCL.

The study of epigenetics—the regulation of gene expression—has gained increasing attention in cancer research. One important type of epigenetic change is methylation, a process that modifies genes in a way that affects their function. Several findings related to epigenetics were presented at the Workshop. For instance, the chromosomal abnormality characteristic of MCL, called t(11;14), seems to affect the function of the cyclin D1 gene through a long-distance process never seen before in human cancer. Another discovery was that global patterns of methylation differ between MCL cells and normal cells.

Several researchers presented results from clinical trials investigating new therapies for MCL. The following treatment approaches are currently being evaluated:

- Different strategies of chemotherapy and transplantation.
- A new chemotherapy drug that is only activated once inside a cancer cell.
- Combination therapy using different types of targeted drugs.
- New ways of causing cancer cells to undergo programmed cell death.

Researchers are also investigating possible new targets for MCL therapy. Although these are in a more pre-

liminary stage of development, they may translate into promising future therapies. These are:

- Cyclin-dependent kinase 4/6, a protein related to cell division.
- MCL cell's protein quality-control system, causing cell death.
- Pim-1, a gene important in cancer cell biology.
- Oxidoreduction, a process important for a cell's functioning.

PRESENTATIONS

Oral presentations at the Workshop were divided into five topic-specific sessions focused on different aspects of MCL research. The sessions gave scientists the opportunity to present their research findings, exchange ideas and share their unique perspectives on this disease.

SESSION 1: Biology of MCL

Chair: John P. Leonard, MD (Weill Medical College of Cornell University)

Researchers are using new techniques to study which genes are important in MCL and how these genes may influence each other. A better understanding of these interactions may lead to more effective therapies.

Sandeep Davé, MD (Duke University) discussed the nature of microRNAs in normal and malignant B-cells. MicroRNAs are small pieces of genetic material that regulate gene expression. Researchers have been investigating whether the presence or absence of different microRNAs could be used to distinguish different



Dr. Sandeep Davé (Duke University)

cancers. Dr. Davé and his associates evaluated the presence of microRNAs in healthy B-cells and in lymphomas and discovered that it was possible to distinguish different lymphoma types based on the presence of different microRNAs. They also found that certain microRNAs were reduced in malignant B-cells. This new way of characterizing cells might lead to new diagnostic tools and new targets for lymphoma therapy.

In another report on microRNAs, Kai Fu, MD, PhD (University of Nebraska Medical Center) reviewed how a certain group of microRNAs called miR-17~92 may reduce the effectiveness of chemotherapy. Previous studies have shown that levels of miR-17~92 are higher in B-cell lymphomas compared with healthy tissues. Also, patients with MCL who have high levels of miR-17~92 appear to have worse clinical outcomes than patients with lower levels. Dr. Fu exposed MCL cells that had been forced to produce high levels of miR-17~92 to a chemotherapy drug called topotecan and discovered that these cells survived despite the exposure to chemotherapy. Studies such as these, which increase our understanding of chemotherapy resistance, could help researchers develop ways of overcoming this resistance, making treatments more effective.

Elena M. Hartmann, MD (University of Wuerzburg) presented her group's efforts to analyze chromosomal copy number changes in MCL using single-nucleotide polymorphism (SNP) arrays. SNPs are variations of only a single molecule in a DNA sequence. The researchers analyzed tumors from 78 patients with MCL and found that these tumors had, on average, about 15 copy number alterations. They also found that nearly 40% of tumors had large regions of variation called copy number-neutral loss of heterozygosity (CNN-LOH). The investigators will correlate these chromosomal alterations with changes in gene expression to try to identify genes that could be used as targets for MCL therapy.

Elliot Epner, MD, PhD (Penn State Hershey Cancer Institute) discussed his laboratory's investigations into how cyclin D1, a protein critical for cell division, is turned on in MCL. The researchers focused on the effects of t(11;14), a chromosomal abnormality characteristic of MCL. Their experiments showed that translocated cyclin D1 can cause long-distant effects on the normal cyclin D1 gene. In this "trans-allelic" effect, the translocated cyclin D1 changes the structure of the normal cyclin D1 gene. This is the first demonstration of such a trans-allelic effect in human cancer.

Executive Committee Members

Mantle Cell Lymphoma Consortium:

- Michael Williams, MD - Chair (University of Virginia)
- Leo I. Gordon, MD (Northwestern University Medical Center)
- Brad Kahl, MD (University of Wisconsin)
- Martin Dreyling, MD, PD (University of Munich)
- John Leonard, MD (Weill Medical College of Cornell University)
- Thomas Witzig, MD (Mayo Clinic College of Medicine)

SESSION 2: Prognostic Markers

Chair: Wyndham Wilson, MD, PhD (National Cancer Institute)

Prognostic markers in MCL could predict a patient's outcome following an MCL diagnosis.

Thomas Habermann, MD (Mayo College of Medicine, Mayo Clinic) provided an update on whether certain genetic variations could provide information on a patient's prognosis following an MCL diagnosis. The researchers focused on genes involved in two important cellular processes: the cell cycle, which is the series of events leading to cell division and replication, and the nuclear factor- κ B (NF- κ B) signaling pathway, which allows cells to respond to various stimuli. The investigators followed 39 patients with MCL for an average of 7.5 years and evaluated whether levels of different genes correlated with these patients' outcomes. They found



Dr. Elena Hartmann (University of Wuerzburg)



Dr. Thomas Habermann (Mayo Clinic)

that eleven NF- κ B genes and three cell cycle genes were associated with longer survival in these patients. Future studies will investigate the role of clinical factors and lifestyle factors, such as smoking, obesity and physical activity, with outcomes in non-Hodgkin lymphoma (NHL) patients.

Many researchers are working to identify molecular biomarkers—a molecule or compound, such as a gene or protein, that can be used to indicate the presence of disease or response to therapy. However, current methods of measuring biomarkers have some limitations. Brad Kahl, MD (University of Wisconsin School of Medicine) discussed new methods of identifying biomarkers. Not only can these methods test the presence of many different biomarkers at once, but they also allow clinicians to use tissue samples that have been formalin-fixed and paraffin-embedded. Tissues prepared in this manner are more convenient to use than other methods and can be readily stored and evaluated at a later time. The researchers hope to apply their new methods to a large collection of MCL tissue samples in hopes of identifying relevant biomarkers.

SESSION 3: New Molecular Targets

Chair: Oliver Press, MD, PhD (University of Washington, Fred Hutchinson Cancer Research Center)

In their search for effective therapies for MCL, scientists are evaluating compounds that interfere with cancer cell functioning and survival in new and different ways.

Geoffrey Shapiro, MD, PhD (Dana-Farber Cancer Insti-

tute) presented preclinical and clinical studies of the investigational compound PD0332991, which prevents cell division of MCL cells. Dr. Shapiro and his associates conducted a preliminary study of the safety and activity of PD0332991 in 17 patients with previously treated MCL. PD0332991 was associated with low neutrophil counts, low platelet counts, diarrhea, fatigue and headache. However, 15 of 17 patients had reductions in MCL cell growth after taking the drug. Two patients had partial responses and six patients had stable disease for at least 16 weeks.

Sven de Vos, MD, PhD (University of California Medical Center) discussed the role of the gene PIM-1 in the growth and development of MCL. PIM-1 normally functions in cell survival and division and contributes to the development of resistance to cancer drugs. Dr. de Vos and his colleagues investigated the interaction of PIM-1 and T-cell leukemia/lymphoma 1 (TCL1), another gene involved in cancer growth and development. Using genetically altered mice, the researchers found that PIM-1 speeds up the development of lymphoma caused by TCL1. The researchers will continue to investigate how these molecules interact and cause lymphomas. An ongoing phase I/II trial will evaluate the PIM inhibitor SGI-1776 in patients with relapsed B-cell NHL.

Steven H. Bernstein, MD (University of Rochester Medical Center, James P. Wilmot Cancer Center) reported on a new approach to lymphoma therapy. Whereas many targeted therapies inhibit specific proteins in



Dr. Brad Kahl (University of Wisconsin)

the cell, this approach interferes with a chemical reaction which occurs outside the cell. Dr. Bernstein and his colleagues found that parthenolide, a component of the feverfew plant, reduces the survival of NHL cells in the laboratory. Parthenolide appears to act at the cell surface of cancer cells and inhibits a type of chemical reaction called oxidoreduction. The location of this effect is important, as the immediate area around cancer cells differs compared with normal cells. Such a therapy therefore might affect malignant but not healthy cells.

Adrian Wiestner, MD, PhD (National Institutes of Health) discussed a potential new treatment approach that targets another important cellular process. When proteins are manufactured in the cell, those that do not pass quality control are degraded. The investigational drug eeyarestatin I (Eerl) interferes with this essential process, causing cell death. Recent laboratory studies conducted by Dr. Wiestner suggest that Eerl and bortezomib may work well in combination. In these studies, Eerl has shown activity against MCL cells that are resistant to bortezomib.

SESSION 4: Chemoimmunotherapy, Transplantation and Cellular Therapy

Chair: Brad S. Kahl, MD (University of Wisconsin)

Researchers are evaluating different treatment modalities, including combinations of chemotherapy, immunotherapy, radiotherapy and transplantation, in hopes of improving outcomes in MCL patients.

Mitchell R. Smith, MD, PhD (Fox Chase Cancer Center) discussed results of a phase II trial studying a new regimen involving chemotherapy followed by treatment with a radioactive antibody (radioimmunotherapy) in patients with previously untreated MCL. A total of 52 patients received chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) followed by radioimmunotherapy with 90Y-ibritumomab tiuxetan. Of the patients who received the full regimen, 55 percent of patients had a complete response and 33 percent had a partial response. The addition of radioimmunotherapy improved responses over chemotherapy alone in 55 percent of patients. Seventy-eight percent of patients were alive after 3 years. Dr. Smith said that a longer follow-up was needed to fully assess the efficacy of the regimen.

Martin Dreyling, MD, PD (University of Munich) reviewed the long-term follow-up results from several MCL clinical trials conducted in Europe. One trial showed that

compared with CHOP, R-CHOP is associated with a longer time to treatment failure with a trend towards survival-benefit. Another trial compared early consolidation therapy (therapy used to eliminate any residual disease after initial therapy) with myeloablative radiotherapy (treatment given prior to a transplant to help eradicate the patient's disease) followed by autologous stem cell transplant (ASCT) versus conventional interferon- α maintenance therapy. Patients receiving early consolidation therapy remained progression-free for a longer period, and for the overall group again, there was a significant lengthening of survival. Another treatment approach that has been evaluated in patients with previously untreated MCL is intensive immunochemotherapy with CHOP, alternating between the addition of rituximab or high-dose cytarabine (Ara-C), followed by ASCT. After inclusion of just under 450 patients, it is not yet clear whether this alternating therapy approach achieves better outcomes.



Dr. Ajay Gopal (Fred Hutchinson Cancer Research Center)

Ajay Gopal, MD (University of Washington, Fred Hutchinson Cancer Research Center) reviewed radioimmunotherapy-based transplant conditioning regimens for patients with MCL. The researchers studied outcomes in 61 patients who received high-dose radioimmunotherapy with anti-CD20 followed by autologous stem cell transplant (ASCT). Thirty-three patients in the study were younger than age 60. Of these patients, after an average of 3 years post-treatment, 60% remained progression-free. The remaining 28 patients were older than age 60; these patients had only been followed-up for an average of 6 months. Among the older patients, 64% remained progression-free.



Dr. Michael Williams - MCLC Chairman (University of Virginia School of Medicine)

MCL Scientific Workshop

The Workshop brings together scientists working to find a cure for mantle cell lymphoma. These dedicated researchers find the workshop to be an opportunity to share their findings and build relationships that bloom into active collaborations.



2009 MCL Consortium Scientific Workshop Attendees



Panel of Discussants



Dr. Richard Fisher - SAB Chairman (University of Rochester)



Poster Session



Mingling between sessions



Dr. Samir Parekh (Albert Einstein College of Medicine)



Drs. Owen O'Connor (Columbia University) and Morton Coleman (Weill Medical College at Cornell University)



Presenting to the MCL Consortium

SESSION 5: Novel Therapeutic Approaches

Chair: Owen O'Connor, MD, PhD (Columbia University, College of Physicians and Surgeons)

Scientists are evaluating new ways to target MCL cells and studying the mechanisms of drug resistance in order to develop more effective therapies.

Samir Parekh, MD (Albert Einstein College of Medicine) presented studies investigating mechanisms of resistance to proteasome inhibition in MCL. The investigators first identified differences in gene methylation between MCL cells and normal B-cells. Methylation is a biological process involved in the regulation of genes and proteins. The scientists found that genes relating to two essential molecules, NF- κ B1 and HDAC1, were under-methylated (“hypomethylated”) in MCL cells. On the other hand, certain genes involved in tumor suppression were highly methylated (“hypermethylated”) in MCL. The researchers are trying to use this information to develop more effective therapies and to predict whether patients will respond to existing therapies.

Marc A. Weniger, PhD (National Institutes of Health) discussed his group's studies of changes in gene expression that occur in MCL cells following exposure to the drug bortezomib. In studies such as these, scientists measure which genes are turned on or off, and which genes are present at increased or decreased levels, under different circumstances. Dr. Weniger's studies showed that following bortezomib treatment, borte-

zomib-sensitive cells show changes in several genes, including those related to protein production, the cellular stress response and cell division. These changes were not seen in bortezomib-resistant cells. Dr. Weniger explained that understanding these drug-related changes in gene expression could help identify pathways related to drug sensitivity or resistance. In turn, scientists may be able to develop ways of overcoming drug resistance.

Thomas E. Witzig, MD (Mayo Clinic) discussed a new potential combination therapy for MCL that involves two different types of drugs: a mammalian target of rapamycin (mTOR) inhibitor plus a histone deacetylase (HDAC) inhibitor. The mTOR inhibitor temsirolimus has shown activity in patients with relapsed MCL, although most patients develop resistance or relapse. Dr. Witzig and colleagues investigated why this might be. They discovered that although temsirolimus interferes with one signaling pathway important for cell division, it simultaneously has a positive effect on another part of that pathway. Laboratory studies showed that a type of drug called an HDAC inhibitor can block activation of the second part of that pathway. A combination of an mTOR inhibitor and an HDAC inhibitor might therefore be more effective than the mTOR inhibitor alone. A phase I/II trial will evaluate the HDAC inhibitor LBH589 plus the mTOR inhibitor everolimus in patients with relapsed myeloma or lymphoma, including MCL.

Daniel J. Medina, PhD (The Cancer Institute of New Jersey UMDNJ/Robert Wood Johnson Medical School) described the preclinical evaluation of TLK286 (canfosamide HCl), a chemotherapeutic agent that is activated by tumor cells. Dr. Medina and his colleagues showed that TLK286 prevented MCL cells from undergoing cell division, resulting in cell death. The drug also appeared to restore the sensitivity of MCL cells to the chemotherapy agent doxorubicin.

POSTER SESSION

Tulin Budak-Alpdogan, MD (Cancer Institute of New Jersey, UMDNJ/Robert Wood Johnson Medical School), on behalf of Joseph R. Bertino, MD, reported on a potential advancement for using umbilical cord blood (UCB) as a source of stem cells for transplantation. She explained that while cord blood is a good potential source of stem cells for patients requiring stem cell transplantation, the small number of cord blood cells available limits their use. Experiments in mice showed that supplementing

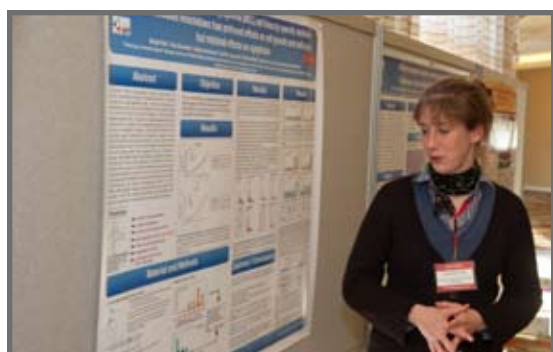


Dr. Thomas E. Witzig (Mayo Clinic)

the cord blood cells with radiation-treated blood cells from an unrelated donor increases the success of the cord blood stem cell transplant.

Pedro Jares, PhD (IDIBAPS, University of Barcelona) discussed his group's efforts to identify genes that are turned off, or silenced, in MCL. To identify these silenced genes, the researchers treated MCL cells with drugs at doses high enough to turn the genes back on, but not high enough to cause significant cell death. The researchers have identified 377 genes that may be silenced in MCL. They are now studying the relevance of these silenced genes.

Shantaram S. Joshi, PhD (University of Nebraska Medical Center) presented results from preclinical animal model studies designed to better understand the development of drug resistance in MCL. Compared with chemotherapy-sensitive cells, those resistant to chemotherapy exhibited more cell growth and division both on their own and after being transplanted into mice. The researchers also found that a certain protein, known as GLI transcription factor, was present at higher levels in the resistant cells. By inhibiting that protein, mice that normally had chemotherapy-resistant MCL responded better to chemotherapy and survived longer.



Dr. Margit Klier (University of Tubingen)

Margit Klier, PhD (Institute of Pathology, University of Tubingen) and her colleagues have been investigating the role of a specific protein called cyclin-dependent kinase 4 (Cdk4) in the development of MCL. The scientists studied the effects of experimentally eliminating Cdk4 from MCL cells. In MCL cells that normally make high levels of Cdk4, eliminating Cdk4 caused a reduction in cell growth and division, but caused only a small increase in MCL cell death. This result differs from the reported effects of the Cdk inhibitor flavopiridol, which causes significant cell death.



Researchers listen to poster presentation

Martin Dreyling, MD, PD (University of Munich), on behalf of Christiane Pott, MD, presented work on the development of a new, sensitive method for monitoring minimal residual disease (MRD), which is low-level disease that can remain after cancer treatment. MRD could be a valuable tool for predicting outcomes early after therapy. The researchers already evaluated the usefulness of MRD in patients with MCL enrolled in European clinical trials. Patients with no MRD after treatment remained in remission for a longer period of time than those with MRD.

Most MCL cells have elevated levels of a protein called cyclin D1 and a genetic abnormality at the cyclin D1 gene. Leticia Quintanilla-Fend, MD (Institute of Pathology, University of Tubingen) and her associates found that this is not always the case. The researchers reported on four patients with MCL who instead had high levels of cyclin D2 and a genetic abnormality at the cyclin D2 gene. Dr. Quintanilla-Fend used various diagnostic techniques to ensure that these patients did indeed have MCL and not other lymphomas.

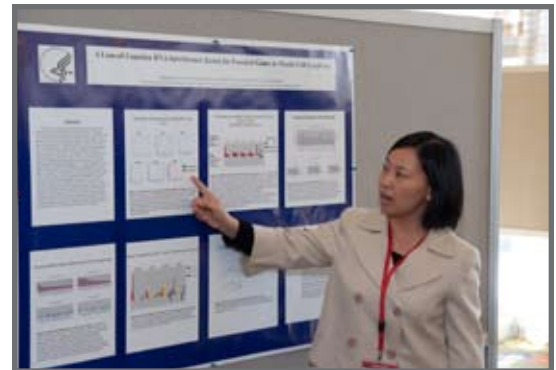
Amareshwar Singh, PhD (Northwestern University Feinberg School of Medicine, Northwestern Memorial Hospital) and colleagues have shown that a drug, called all-trans retinoic acid (ATRA), a Vitamin A metabolite, caused the production of reactive oxygen species (ROS), also called oxygen radicals, in MCL cells. It is possible that this generation of ROS may kill MCL cells. Dr. Singh and his group pursued a novel approach to deliver ATRA by a targeted drug payload to MCL cells. They used a novel delivery vehicle wherein ATRA is solubilized in nanoscale, protein stabilized lipid particles, termed nanodisks (ND). It is hypothesized that following cellular uptake/liberation of ATRA from ND, the bioactive lipid will interact with proteins inside cells leading to cell growth arrest or cell death. The data show

that, compared to free ATRA, ATRA-ND elicit a dramatic stimulation of ROS production, cell death and growth arrest in mantle cells. The researchers plan on investigating the potential for ATRA nanodisks as a therapy for MCL.

Wendy Stock, MD (The University of Chicago) reviewed several new potential treatment strategies for MCL patients. One study, being performed in the cooperative group Cancer and Leukemia Group B, is evaluating whether the addition of bortezomib maintenance therapy after chemotherapy and autologous stem cell transplantation (ASCT) can improve treatment outcome. The researchers are focusing on whether this treatment could eliminate minimal residual disease (MRD) and whether this correlates with improved response to treatment. Minimal residual disease detection is done using a quantitative method that allows for detection of one lymphoma cell in a background of approximately 50,000 normal blood cells. Of 6 patients who have completed the treatment protocol and have undergone MRD monitoring, 4 patients had no MRD after chemotherapy, and the other 2 still had MRD after chemotherapy, but not after bortezomib. Dr. Stock and her colleagues are also conducting preliminary studies using small proteins called peptides that block cell cycle progression and inhibit growth of MCL cells. In the laboratory, treatment of MCL cells with these peptides was toxic to MCL cells, but not to normal cells. Her goal is to test these peptides in autologous stem cell collections to try to purge any residual disease that may exist prior to the patient's autologous stem cell transplant.

Yandan Yang, PhD (National Cancer Institute) reported on her group's efforts to identify new potential gene targets for MCL treatment. Out of 1427 genes evaluated, the scientists identified 22 genes that appeared to be toxic to MCL cells, but not to other lymphoma

cells. More detailed analyses identified five genes that were toxic only to MCL cells. These included the genes CCND1, Homer2, PUF60, RPS6KAS and TCF3. The scientists have also repeated their initial screening experiments using a more sensitive technique, and found several additional genes (TCF3 and C/EBP β) that are important for growth and survival of MCL cells.



Dr. Yandan Yang (National Cancer Institute)

ROUNDTABLE DISCUSSIONS: Future Directions in MCL Research

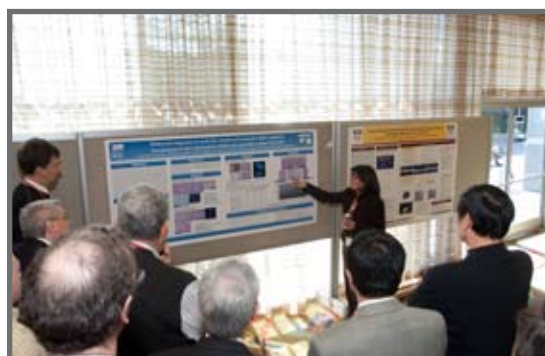
Participants gathered over dinner to discuss the most important ongoing questions in MCL research. Each table focused on a different pressing issue and reported back to the group with their conclusions, as follows:

Issue #1: Clinical Trial Questions for Older Patients

As older patients are not ideal candidates for intensive therapy, clinical trials for these patients should focus on identifying the most effective non-intensive strategies. Also, although many patients with MCL initially attain remission, the disease often relapses. Thus, clinical trials should investigate strategies for maintaining remission. Monitoring of minimal residual disease is also an important topic of research. The group suggested that randomized phase II trials should be used to optimally investigate these issues.

Issue #2: Clinical Trial Questions for Younger Patients

Younger patients are better candidates for more intensive therapies. Clinical trials should therefore focus on improving survival using all therapies available. Phase III trials should compare transplantation strategies against non-transplantation strategies as induction therapy. The optimal role of biologic therapies should also be evaluated.



Dr. Leticia Quintanilla-Fend (University of Tubingen)

Issue #3: Role of Biomarkers in MCL

The usefulness of the biomarker Ki-67 was a hot topic at this year's meeting. Although Ki-67 may be the biomarker furthest along in development, studies of Ki-67 have given mixed results. The group suggested possible ways of improving the usefulness of Ki-67 and working towards standardizing its use. The experts debated on how to best use biomarkers in clinical trials. They also discussed the role of minimal residual disease (MRD) as a marker of response to therapy, and suggested that trials should look at how MRD changes over time, rather than looking at a single point in time.



Dr. Geoffrey Shapiro (Dana-Farber Cancer Institute)

Issue #4: Epigenetic Studies in MCL

Epigenetic refers to a change in appearance or gene expression that affects a cell, organ or individual without changing its DNA. One important issue in epigenetic studies is what types of cells are being used for these experiments. Tumor samples directly from patients with MCL may have different properties than the often-studied cell lines which are grown in the laboratory. Another issue will be how to best incorporate epigenetic therapies into MCL. The group also said that studies should investigate the epigenetic changes that occur with chemotherapy and the role of interactions between tumor cells and other cells.

Issue #5: Cell Cycle Targets for MCL

Given the importance of the cell cycle in MCL biology, experts discussed how to best target this process to combat the disease. Resistance to currently available

cell cycle inhibitors is an issue, though new small-molecule therapies may help overcome that resistance. New cell cycle targets should also be investigated. Moreover, combination strategies that target the cell cycle plus another aspect of MCL biology might also be more effective than targeting the cell cycle alone.

Issue #6: Signal Transduction Questions

The group that discussed the process of cell signaling in MCL cells also questioned the relevance of using laboratory cell lines instead of tumor cells. They commented that studies are showing that certain signaling pathways do appear to be important to the growth, survival and drug resistance of MCL cells. Ongoing research should continue to investigate these processes and determine how they might be targeted for MCL therapy.

SUMMARY

Outcomes continue to improve for patients with MCL. As Dr. Martin Dreyling pointed out, patients with MCL have more therapeutic options available now than were available just five years ago. These advancements have been made possible through the important work being done by Mantle Cell Lymphoma Consortium (MCLC) scientists. Dr. Michael Williams commented that the content and level of sophistication of the MCLC Scientific Workshop has grown over the past five years, reflecting the progress that has been made in the field.

Despite this progress, there is still headway to be made in the treatment of MCL. Laboratory scientists will continue to investigate the biology of MCL, the feasibility of new therapies and the use of biomarkers for predicting prognosis and responses to therapy. Meanwhile, clinical investigators will continue to conduct trials to evaluate the efficacy and safety of these new therapies, while optimizing the use of the therapies we have available today.

Throughout this whole process, the MCLC and the Lymphoma Research Foundation (LRF) will continue to play a crucial role in the eradication of MCL by funding the best science and most cutting-edge MCL research and by creating innovative ways for the MCLC researchers to share their knowledge, collaborate and move the field forward.

The Lymphoma Research Foundation is pleased to recognize our many generous and compassionate donors for their support of lymphoma research, patient services and advocacy programs.

Thank You!

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