

LYMPHOMA

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RESEARCH REPORT

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New Approaches to Basic Research and Therapeutics in Lymphoma Presented

The 47th Annual meeting of the American Society of Hematology, originally scheduled to meet in New Orleans, instead convened in Atlanta, Georgia from December 10 to 13, 2005. The Lymphoma Research Foundation was again well represented with 82% of Scientific Advisory Board (SAB) Members and 38% of all grant recipients (including Fellows, Career Development and MCL Awardees) since 1992 participating.

BRIEF OVERVIEW

Much effort is being devoted to understanding the basic biology of lymphoma so that this knowledge can be directed toward finding therapeutic targets. Researchers are gaining a clearer picture of the genetics of the different types of lymphoma, the different molecular markers, and the proteins that are inappropriately expressed. With this knowledge, physicians are getting closer to a way of determining the prognosis for each individual patient, and can then use that information to chart a treatment plan.

Although little data presented at the meeting is immediately applicable to offering broad new therapeutic options for lymphoma, several clinical trials are near completion and will lead to improvements in the treatments used as well as the timing and duration of therapy.

Many lymphoma patients are being treated, or will be treated, with rituximab at some point in their care. Rituximab (Trade name: Rituxan) is a monoclonal antibody that binds to a receptor on the surface of B-cells, including B-cell lymphoma cells, called CD20. When rituximab binds to cells, they are cleared from the body by the immune system. Rituximab continues to be extensively studied to determine how to best use the drug to get optimal results for patients. At ASH

there were 325 abstracts presented on rituximab. Standard chemotherapy regimens continue to be investigated, both to determine how to best administer them alone, and in combination with rituximab. The radioimmunotherapy drugs are showing some promising results in small studies, and work continues to discover new antibodies and new drugs.

Abstract numbers are noted for each of the studies summarized. The entire study abstract can be found online at www.hematology.org, the website of the American Society of Hematology.

RESEARCH AIMED AT OPTIMIZING THE USE OF CURRENT THERAPIES

Studies have shown that adding rituximab to CHOP chemotherapy (a combination of four drugs [cyclophosphamide, doxorubicin, vincristine, prednisone], considered the "standard of care" for many types of lymphoma) improves outcomes in patients with lymphoma. The "standard" regimen of four doses administered weekly leads to objective response rates of 48% in recurrent, indolent NHL and about 30% in patients with Diffuse Large B-cell Lymphoma (DLBCL) and Mantle Cell Lymphoma (MCL). However, many patients do not respond and many relapse. Research is

now being conducted to determine the best way to give this treatment (R-CHOP) to improve response rates and duration of response. Studies are looking at increasing the dose of rituximab given (by changing the dose, or how frequently it is given) and at extending the duration of therapy (maintenance dosing). In addition, work is ongoing to assess the best way to combine rituximab with chemotherapy or other biologic agents.

OPTIMAL DURATION OF TREATMENT – DIFFUSE LARGE B CELL LYMPHOMA

Dr. Michael Pfreundschuh (University Clinic, Saarland) and his colleagues in Germany evaluated whether six cycles of CHOP were better than eight cycles, and assessed the benefit of adding rituximab, in elderly patients with diffuse large B-cell lymphoma. The chemotherapy was given every two weeks. Over 1300 patients were enrolled in the study. Interim results on 800 patients were reported. The results were the best ever reported for elderly patients with DLBCL, providing the longest freedom from treatment failure for patients who received six cycles of R-CHOP. Importantly, adding rituximab to CHOP was associated with statistically significant differences in outcome. Freedom from treatment failure was similar whether patients received 6 or 8 cycles of R-CHOP, but projected 2.5 year survival was significantly better, for patients with a poor prognosis, on 6 cycles. Although this study may change treatment practices in Europe, it will likely not yet affect patients in the United States, since standard of care here is R-CHOP given every 3 weeks, not every 2 weeks, and there are currently no randomized data to support the change in the dosing interval. (*Abstract 13*)

INCREASING THE INTENSITY OF CHOP - INTERMEDIATE RISK AGGRESSIVE NHL

Dr. Leo Verdonck (University Hospital, Utrecht) and colleagues from the Netherlands evaluated six courses of intensified CHOP compared to standard CHOP in 513 patients. In the intensified arm, CHOP was given every 2 weeks for 6 courses, versus every 3 weeks for 8 courses in the standard arm. Also, in the intensified arm, the cyclophosphamide and doxorubicin doses were doubled, compared to the standard arm. Growth

factor support (G-CSF) was given to patients in the intensified arm. At 72 months of follow-up, there were no differences noted in overall survival, event free survival, or disease free survival when the treated population was analyzed as one group (low-intermediate risk disease as well as high-intermediate risk disease). However, there was a significant difference in disease free survival and event free survival for patients in the low-intermediate risk group. Toxicity was doubled with the intensified CHOP regimen. (*Abstract 14*)

CHEMORADIOTHERAPY VS CHEMOTHERAPY - LOW RISK AGGRESSIVE NHL

Dr. Georges Fillet (University Hospital of Liege) and his colleagues from Belgium studied the value of chemoradiotherapy versus chemotherapy alone in elderly patients with localized low risk aggressive lymphoma. A total of 576 patients over age 60 were treated with 4 cycles of CHOP every 3 weeks followed by radiotherapy (40 Gy) or 4 cycles of CHOP, without radiotherapy, every 3 weeks. Complete response was similar in both groups, as were overall survival and event free survival. Although chemoradiotherapy is currently the standard-of-care in this disease, Dr. Fillet conducted this study because previous studies did not specifically look at the value of this treatment approach in older patients. As a result of these findings, Dr. Fillet recommended that older patients should be treated with rituximab-CHOP, not chemoradiotherapy. Participants in the audience noted that more data needs to be collected before this approach replaces the current standard. (*Abstract 15*)

CHOP PLUS RITUXIMAB IN ELDERLY PATIENTS - INTERMEDIATE OR HIGH RISK NHL

Dr. Pieter Sonneveld (Daniel Den Hoed Cancer Center, Rotterdam) from the Netherlands presented an interim analysis of a Phase III trial in elderly patients being conducted by the Dutch and Nordic Lymphoma Study Groups. The study compared 8 cycles of CHOP given every 2 weeks with the same regimen of CHOP, given with 6 cycles of rituximab, in patients who had not received prior treatment for intermediate or high risk lymphoma and who were over 65 years of age. The interim analysis included data from 171 patients.

Highly significant differences in event free survival and overall survival were noted in favor of the CHOP plus rituximab treatment. There were no differences in toxicity. As a result of the interim analysis, all patients were switched to treatment with CHOP and rituximab. Data are still being collected, with final results to be reported in mid-2006. (*Abstract 16*)

TIMING OF RITUXIMAB PLUS CHEMOTHERAPY/RESISTANCE TO RITUXIMAB

Researchers are attempting to confirm the best way to give rituximab with chemotherapy. Since it is known that rituximab works better with a small disease burden, it has been suggested that it might be better to give chemotherapy first to reduce disease, then follow with rituximab. Since it works through the immune system, some believe that rituximab should be given first, to get the body ready for chemotherapy. Noting the data that there is a synergistic effect of rituximab plus chemotherapy, others conclude that they should be given together. It has already been confirmed clinically that rituximab following chemotherapy improves the quality of the chemotherapy response.

None of these questions is changing the current standard approach of giving rituximab after chemotherapy. Multiple studies are ongoing to ensure that rituximab and chemotherapy are being administered in the right way to achieve optimal clinical results for patients, including an ongoing study to assess rituximab, followed by CHOP chemotherapy, followed by radioimmunotherapy (Zevalin).

Resistance to rituximab and the radio-immunotherapy products, Zevalin and Bexxar, continues to be a problem. It is thought that mutations in the CD20 receptor may be the cause of resistance. Some researchers believe that enhancing immunologic activity may help to overcome resistance. Work is ongoing to add different biologic agents (G-CSF, IL-2, GM-CSF). Very small numbers of patients have been treated with this type of approach in clinical studies, but the early data is encouraging, with patients having a longer time to progression. Before this approach can be used on a broader basis, the problem of additional toxicity needs to be resolved. Also, new immunomodulators are in development and can also be studied.

RITUXIMAB MAINTENANCE - RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

Dr. Marinus Van Oers (U. of Amsterdam) and his colleagues in the Netherlands studied the benefit of using rituximab as maintenance therapy following initial treatment (induction) with R-CHOP. Patients with follicular lymphoma who either didn't respond to initial treatment (refractory) or whose disease returned after initial treatment (relapsed) were followed in this study. Patients were treated with 6 cycles of CHOP or R-CHOP. Those who responded to this regimen (either a partial or complete response) were divided into two groups. One group received rituximab maintenance therapy once every three months for a maximum of two years. The other group received no further treatment, but were observed closely. At the time the study was analyzed, data was available for 268 patients. A highly statistically significant advantage was observed in progression-free survival in patients who received rituximab maintenance (38 months for rituximab-treated patients versus 15 months for observation-only patients). With limited follow-up at this time, the overall survival is 85% for those treated with rituximab compared to 77% for those not. The rituximab maintenance was associated with minimal toxicity. (*Abstract 353*)

One thing is important to note from this trial. Patients enrolled in this study had been previously treated for their lymphoma, but not with CHOP or R-CHOP. This study is not able to confirm if rituximab maintenance will be as useful in patients who were already treated with rituximab. An ongoing study, the PRIMA study, is being conducted to answer that important question.

RITUXIMAB MAINTENANCE - AFTER CVP THERAPY FOR ADVANCED FOLLICULAR LYMPHOMA

Dr. Howard Hochster (NYU Cancer Center) reported on a trial conducted by the Eastern Cooperative Oncology Group. E1496 was a Phase III trial to evaluate the use of two years of maintenance rituximab to prolong progression-free survival after CVP (cyclophosphamide, vincristine, prednisone) chemotherapy in follicular lymphoma. Patients received 6-8 cycles of CVP. Those who responded or had stable disease received either rituximab weekly for 4 weeks every 6 months, or were observed carefully, but received no further therapy. With 3 years of follow-up,

patients given rituximab maintenance have a better progression-free survival and overall survival. Estimated 4-year survival is 88% for patients given rituximab and 72% for those who were only observed. (Abstract 349)

RITUXIMAB WITH OTHER CHEMOTHERAPY REGIMENS - CVP IN ADVANCED FOLLICULAR LYMPHOMA

Dr. Philippe Solal-Celigny (Centre Jean Bernard, Le Mans, France) reported final results on an international Phase III study evaluating the benefit of adding rituximab to each of 8 cycles of CVP in patients with advanced follicular lymphoma compared to CVP chemotherapy alone. A total of 342 patients were studied. Approximately half of the patients had high risk disease. The median time to progression was more than doubled for patients receiving R-CVP. Median time to new lymphoma treatment or death was 12.3 months in the CVP group but 46.3 months in the R-CVP group. Median disease free survival in complete responders was 44.8 months in the R-CVP arm and 20.5 months in patients receiving CVP alone. (Abstract 350)

NEW ANTIBODIES

New monoclonal antibodies are being developed that target the CD20 receptor on B-cells, as does rituximab. However, these antibodies are being altered in an attempt to improve their efficacy. Ongoing work is attempting to engineer antibodies that are better at utilizing the immune system (antibody-mediated cellular cytotoxicity or complement-dependent cytotoxicity). Additionally, changing the antibodies to make them more or completely human in structure by removing some of the mouse-based components present in rituximab, may make them work better. It is difficult to study these monoclonal antibodies in patients, since many patients receive rituximab as part of their standard care. (Note that all of this work is in its early stages.)

SGN-30 TARGETS THE CD30 ANTIGEN

Several scientists affiliated with LRF (**Dr. Ajay Gopal, Dr. John P. Leonard, Dr. Nancy L. Bartlett and**

Dr. Bruce D. Cheson¹) were among the authors of a poster (Abstract 3356) describing a phase II trial of a new monoclonal antibody, SGN-30, which targets the CD30 antigen expressed in hematologic malignancies, notably T-cell and anaplastic large cell lymphoma (ALCL). Preliminary results from this ongoing multi-center trial found SGN-30 to be active and well tolerated in patients with refractory or recurrent ALCL and the study is continuing.

GALIXIMAB TARGETS ANTI-CD80

A phase II study of another new monoclonal antibody, Galiximab (anti-CD80) was reported in a poster (Abstract 2435) which included LRF-affiliated scientists among its authors (**Dr. Jonathan W.**

MONOCLONAL ANTIBODIES CURRENTLY UNDER EVALUATION		
Antibody	Study	Company Developing
HuMax-CD20	Phase I trial in follicular lymphoma	Genmab
PRO70769	Studies in autoimmune disease may future use in lymphoma	Genentech
IMMU-706	Phase I/II lymphoma	Immunomedics

Friedberg, Dr. John P. Leonard, Dr. Bruce D. Cheson and Dr. Arturo Molina²) . Preliminary data from this study show that Galiximab plus Rituximab may be more effective than either antibody alone in treating relapsed or refractory follicular lymphoma.

RADIOIMMUNOTHERAPY

Radioimmunotherapy products have a radioisotope attached to a monoclonal antibody. The monoclonal

¹ Respectively of: Fred Hutchinson Cancer Research Center; Weill Medical College of Cornell University; Washington U., St. Louis; Georgetown U. Hospital Center)

² (J.P Wilmot Cancer Center, Weill Cornell; Georgetown; City of Hope Medical Center)

antibody finds and binds to specific types of cells, delivering the radiation in a more targeted way than other types of radiation therapy.

Two radioimmunotherapy products are currently available, Bexxar (Tositumomab and Iodine I 131 Tositumomab) and Zevalin (Ibritumomab Tiuxetan). Although these products are on the market, researchers are continuing to evaluate them to assess how they can best be used. While the radiolabeled antibodies seem to be more effective, the problem exists of radiation going not only to the tumor cells, but to neighboring tissues as well, often the bone marrow. This then creates problems with low numbers of white cells, red cells and platelets. Radioimmunotherapy has been shown to be effective in both chemotherapy-resistant patients and rituximab-resistant patients. Many physicians are still unsure about exactly how and when to use radioimmunotherapy.

RADIOIMMUNOTHERAPY IN FOLLICULAR LYMPHOMA



Dr. Oliver Press (Fred Hutchinson Cancer Research Center)

Better therapies are still needed for follicular lymphoma. Chemotherapy results in responses, but not cure, therefore, radioimmunotherapy may have a role in this disease. Data from a study with CHOP followed by Bexxar was reported at the meeting. **Dr. Oliver Press** (Fred Hutchinson Cancer Research Center; also the new Chairman of the LRF Scientific Advisory Board[SAB]) and his colleagues from around the US reported on a Phase II trial conducted by the Southwest Oncology Group. A total of 90 patients who had advanced follicular lymphoma and had not received any prior therapy, were treated with 6 cycles of CHOP every

21 days. Patients who had a response to the CHOP therapy received radioimmunotherapy with Bexxar. 69% of treated patients achieved a complete response, 22% had a partial response and 2% had stable disease. The 4-year progression free survival was 70%. This compares to other studies of CHOP in similar patients, where the 4-year progression free survival was 46%. The 4-year overall survival was 91% with combined therapy, compared to 69% seen with just CHOP alone. (*Abstract 352*). This was just a pilot study with a relatively small number of patients, but it demonstrated the potential value of radioimmunotherapy in follicular lymphoma. A Phase III trial is ongoing assessing CHOP followed by Bexxar versus CHOP followed by rituximab. A key question to answer regarding radioimmunotherapy is *when* to use it: initially, in relapsed patients or in patients resistant to rituximab?

RADIOIMMUNOTHERAPY AND TRANSPLANT FOR OLDER PATIENTS

Dr. Ajay Gopal and colleagues conducted a Phase II study that evaluated the use of radioimmunotherapy and autologous stem cell transplantation for adults over 60 years of age with high-risk relapsed or refractory B-cell lymphoma. His study was partially funded by the Lymphoma Research Foundation.

Dr. Gopal's research is important because there are few options for the treatment of older patients with lymphoma in cases where the disease comes back after initial treatment, or who do not respond to initial treatment. Younger patients receive high dose chemotherapy followed by a stem cell or bone marrow transplant, however, this treatment is too aggressive for older adults who may have other health issues, and for



Dr. Ajay Gopal (Fred Hutchinson Cancer Research Center)

whom the risk of the procedures outweighs the potential benefits.

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SETTINGS WHERE RADIOIMMUNOTHERAPY IS BEING EVALUATED

- Chemotherapy-refractory indolent and transformed NHL
- Rituximab-refractory indolent and transformed NHL
- Follicular NHL therapy
- Combination chemotherapy & RIT in indolent NHL, mantle cell lymphoma and DLBCL (initial therapy)

lymphoma in cases where the disease comes back after initial treatment, or who do not respond to initial treatment. Younger patients receive high dose chemotherapy followed by a stem cell or bone marrow transplant, however, this treatment is too aggressive for older adults who may have other health issues, and for whom the risk of the procedures outweighs the potential benefits.

Dr. Gopal studied 24 patients with an average age of 64. The oldest patient in his study was 76 years of age. Radioimmunotherapy was used to find and eliminate lymphoma cells in the body. Radio-immunotherapy uses a monoclonal antibody with radiation attached, to locate specific types of cells, in this case B-cells. The antibody attaches to a specific receptor on the cell, called CD20. The radiation is delivered when the antibody binds to the cell. While some radiation affects other parts of the body, twice as much is delivered to tumor cells, so more radiation can be given with fewer serious side effects. This treatment kills both the lymphoma B-cells and normal blood cells. Therefore, after the radioimmunotherapy, an autologous stem cell transplant was performed so that patients could recover their ability to make normal blood cells.

This was a preliminary (Phase II) study with a small number of patients. However, the results are encouraging, with 55% of patients alive at 4 years post-transplant. The study demonstrated the feasibility

of this approach, and confirmed that radioimmunotherapy would be less toxic in older adults than the conventional treatment. There were acceptable levels of side effects and no deaths related to the therapy in the study. This compares with a 5% risk of death from therapy that is observed with the standard high dose chemotherapy and transplant approach. (*Abstract 487*)

Dr. Gopal will be continuing this research with a larger study done at several different locations to confirm these results. Not enough patients have been studied to make this approach appropriate for patients not participating in a clinical trial.

HIGH DOSE ZEVALIN TREATMENT WITH TRANSPLANT

Dr. Anna Vanazzi (European Oncology Institute, Milan, Italy) reported on a Phase I trial using high dose Zevalin in patients with aggressive disease that have relapsed or not responded to prior therapies, and who are not appropriate candidates for high dose chemotherapy. She enrolled 12 patients in this small trial done to test the feasibility and toxicity of using higher than standard doses of Zevalin (up to 4 times the standard dose). All of the treated patients had received rituximab previously, and 7 of the 12 had previously received more than three chemotherapy regimens. Prior to the Zevalin treatment, peripheral blood stem cells were taken from the patients which were re-infused following the treatment so that white cells, red cells and platelets could again be made. Although only 12 patients were treated, the results were encouraging. Five patients experienced a complete response, and 4 of these have maintained the response at 12, 11, 9 and 8 months after treatment.

The drug was safely administered at the higher doses with no pulmonary, renal or cardiac toxicity. More data will be needed, in larger numbers of patients, to confirm these results and determine the value of high dose Zevalin, but it appears from this study that there may be another option for elderly, pretreated patients who cannot tolerate high dose chemotherapy. (*Abstract 488*)

PERIPHERAL T-CELL LYMPHOMAS

Peripheral T-cell lymphomas make up 12% of NHL. The therapy for this type of lymphoma is very unsatisfying. The five year failure-free survival is 23% and 5 year overall survival is 36%, based on a review of 1162 patients with PTCL. Anthracycline based therapy is not particularly effective in this type of lymphoma (*Abstract 811*). Chemotherapy resistance is a major issue for these patients. The role of high dose therapy with stem cell transplantation is undefined. Several reported studies showed some promising results, with at least some patients able to obtain a significant remission (*Abstracts 2074, 2077, 2079*), however many patients relapsed and died of their disease. This being the case, novel agents are needed to improve the clinical outcome of these patients. Several new drugs are being studied, including nelarabine and pralatrexate, but these drugs are in early clinical trials and require more study to determine their value in this disease. (*Abstracts 2678 and 2681*) Also being studied is the drug alemtuzumab (Campath 1-H), which is currently used to treat B-cell chronic lymphocytic leukemia. Nine studies are ongoing to test alemtuzumab in combination with chemotherapy in relapsed peripheral T-cell lymphoma. **Dr. Owen O'Connor**, (Memorial Sloan-Kettering Center; MCL awardee) was the lead author of a poster (*Abstract 2678*) describing a phase I study of pralatrexate for the treatment of drug-resistant T-cell lymphomas. Early results have shown that this new anti-folate drug achieves a high complete remission rate with minimal toxicity.

A different approach to the study of peripheral T-cell lymphomas (PTCL) was described in a poster (*Abstract 3012*) which included **Dr. Elaine S. Jaffe**, (George Washington University School of Medicine; SAB member) and **Dr. Louis Staudt** (National Cancer Institute; MCL awardee) among its authors. Since PTCLs constitute a heterogeneous and aggressive group of tumors whose pathogenic changes remain largely unknown, these scientists are using DNA microarrays to look for the molecular changes that characterize these tumors. This is key to finding appropriate therapies. (*To view abstracts visit: www.hematology.org*)

RADIOIMMUNOTHERAPY VS. RITUXIMAB: A RETROSPECTIVE REVIEW

The optimal therapy for patients with relapsed follicular lymphoma is still undefined. Many patients are treated with rituximab, but radioimmunotherapy is also an option. No trials have yet compared radioimmunotherapy to rituximab in this population.

Dr. Josiah Orina (Emory U. School of Medicine) conducted a review of existing data to determine if any differences could be seen between the two treatments. His analysis suggested that radioimmunotherapy can improve the likelihood of response and the likelihood of achieving a complete response, when compared to rituximab. Treatment practices will not change based on this type of retrospective analysis of different studies, but the results suggest that there may be an important role for radioimmunotherapy, at least in some patients. (*Abstract 3113*)

NEW THERAPIES

BORTEZOMIB: A PROTEASOME INHIBITOR

Dr. John Leonard (Weill Cornell; member of the LRF Scientific Advisory Board and the LRF Mantle Cell Lymphoma Consortium Executive Committee) presented the work of investigators conducting a Phase I/II trial of bortezomib combined with R-CHOP in DLBCL and mantle cell lymphoma.

Bortezomib (trade name: Velcade) is a drug currently approved for the treatment of multiple myeloma that works through a completely different mechanism than other drugs currently available for lymphoma. Bortezomib is called a proteasome inhibitor. It works by preventing the destruction of certain proteins in cancer cells which results in cell death.

While R-CHOP is standard therapy for DLBCL it is less useful in mantle cell lymphoma. Dr. Leonard presented only the results of the Phase I portion of this study,

which included 20 patients not previously treated, 16 with DLBCL and 4 with mantle cell lymphoma. Half of the patients were considered high-intermediate or high risk on the standard International Prognostic Index. There was a 95% response rate, with 80% of patients having a complete response. While the toxicity was acceptable when combining these three agents, 75% of the patients had peripheral neuropathy, and 35% had severe hematologic toxicity. However, the data are promising. Dr. Leonard and his colleagues are continuing with the Phase II portion of the study that will evaluate 44 patients already enrolled. (Abstract 491)

Dr. Sven de Vos (UCLA) reported on a Phase II study being conducted in several U.S. hospitals. The study is testing the value of treating patients with indolent NHL with bortezomib plus rituximab. Patients had relapsed follicular or marginal zone lymphoma, and had previously responded to a rituximab-based treatment.



They were treated with two different doses of bortezomib, either once weekly or twice weekly, and the same dose of rituximab. Dr. de Vos presented data for 81 patients, half of whom were over 60 years of age. The response rate was essentially the same in both arms (54% and 51%). More follow-up is needed to assess time to progression and duration of response. The treatment was well tolerated in both arms, with the most common adverse events being gastrointestinal complaints, low white blood cell count, low platelet count and

peripheral neuropathy. The side effects were less in the once weekly treatment arm. Because of the activity of this regimen, it will be studied in a Phase 3 trial. (Abstract 17, data reported here is as presented at the meeting. It differs slightly from what is presented in the abstract.)

VACCINE AGAINST FOLLICULAR LYMPHOMA

Researchers in Spain and the United States, through the National Cancer Institute (NCI), have been working on vaccine therapy for follicular lymphoma. The vaccine is produced from a protein on the surface of follicular lymphoma cells. This protein is attached to another called keyhole limpet hemocyanin (KLH) that is obtained from mollusks. The KLH helps trigger an immune response to the tumor cells when the vaccine is administered. Data from the U.S. group's work on 20 patients, with an average follow-up of just over 9 years, was presented at the meeting. Nine of the patients given the vaccine remain in complete remission. There is an ongoing Phase III trial sponsored by the NCI that will enroll 375 patients. Of the 187 patients entered, 145 have achieved a complete response.

(Abstract 2441)

ENZASTAURIN, A PROTEIN KINASE INHIBITOR, IN THE TREATMENT OF RELAPSED DLBCL

Another new therapy for DLBCL was described by **Dr. Margaret A. Shipp** (Dana-Farber/Harvard Cancer Center; SAB member). She along with her colleagues who include another SAB member, **Dr. Julie Vose** (U. of Nebraska) and LRF Fellows **Dr. Sven de Vos** (UCLA) and **Dr. Kerry Savage** (British Columbia Cancer Agency), presented data from a phase II clinical trial of an investigational compound from Lilly Oncology called enzastaurin HCl. Dr. Shipp pointed out that the use of this drug in relapsed DLBCL is important because it is an inhibitor of an identified target in this disease, and several patients not responding to other therapies have had prolonged responses to this single oral agent.

(Abstract 934)

EDUCATION PROGRAM

Several SAB members and LRF awardees participated in the education program and their papers can be found in the Education Program Book on the ASH website.



Dr. Joseph Connors

(University of British Columbia; SAB member) and **Dr. Nancy L. Bartlett** (Washington University School of Medicine; 1992-93 LRF Fellow) both published papers in the Education Book discussing treatment of Hodgkin's Lymphoma. Dr. Connors paper, "Evolving Approaches to Primary Treatment of T-cell", emphasized the need to choose a treatment program that will offer a high probability of cure while minimizing late toxicities (including infertility, premature menopause, cardiovascular disease and second neoplasms). Patients with limited stage Hodgkin's Lymphoma should be treated with brief chemotherapy augmented by radiation therapy only if an early complete remission is not achieved. Most patients with advanced stage disease can be cured with an extended course of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine). Dr. Connors pointed out that fortunately the results of extensive clinical trials and the knowledge of prognostic factors have provided available therapies, which allow the majority of patients complication-free long-term survival.

Dr. Bartlett's paper, "Therapies for Relapsed Hodgkin's Lymphoma: Transplant and Non-Transplant Approaches Including Immunotherapy", explains that while the current standard of care for relapsed Hodgkin's Lymphoma is autologous stem cell transplant, there is no consensus on the optimal pre-transplant therapy and there has been no randomized trial comparing the effectiveness of various regimens. However, the less toxic combinations seem to be equivalent to more aggressive treatment. New approaches such as monoclonal antibodies and new chemotherapy agents are being studied, but the early results have been disappointing. Further work is needed to find new therapies for patients with relapsed Hodgkin's Lymphoma.

Dr. Randy D. Gascoyne (British Columbia Cancer Agency; current MCL awardee) addresses diagnosis and treatment of indolent B-cell lymphomas in his paper in the Education Book entitled:

"Hematopathology Approaches to Diagnosis and Prognosis of Indolent B-Cell Lymphomas." He describes the various disorders that fall within the indolent B-cell lymphomas (Follicular Lymphoma, Extranodal MALT Lymphomas, Small Lymphocytic Lymphoma, Splenic Marginal Zone Lymphoma, Nodal Marginal Zone Lymphoma and Lympho-plasmacytic Lymphoma) and points out that these are distinct diseases with different clinical behaviors resulting from the genetic changes within the tumor cells. Recent



Dr. Randy Gascoyne (British Columbia Cancer Agency)

advances in the genetics of cancer and the development of laboratory techniques such as microarray analysis (DNA chips) have contributed to the improvement in diagnosis and classification of non-Hodgkin's lymphomas. Understanding of the biology and genetics of lymphoid tumors will allow better diagnosis and outcome prediction as well as the development of specific therapies for these diseases.

Dr. Jonathan W. Friedberg (JP Wilmot; 2002-2005 LRF Career Development Awardee), and Dr. John P. Leonard (Weill Cornell) have both published papers in the Education Book discussing the use of monoclonal antibody therapy for lymphoma. Dr. Friedberg points out in his paper, "Unique Toxicities and Resistance Mechanisms Associated with Monoclonal Antibody Therapy", that anti-CD20 therapy with Rituximab has had a dramatic effect in the treatment of patients with follicular lymphoma. Rituximab has a number of means of producing its effects and these are affected by mechanisms in the cellular environment in individual patients. These environments have an effect on which mechanism of action dominates and may also contribute to resistance to antibodies such as rituximab. The ability to overcome resistance will require a further understanding of the pathways involved in antibody therapy and an understanding of the interactions between the cellular environment and the multiple mechanisms of action of monoclonal antibody therapy.

Dr. Leonard's paper, "Targeting CD20 in Follicular NHL: Novel Anti-CD20 Therapies, Antibody Engineering, and the Use of Radio-immunoconjugates", addresses some of the methods that are being investigated to improve antibody therapy and overcome development of resistance. These include changes in dosage and scheduling, as well as combining anti-CD20 antibodies like Rituximab with other antibodies or biologic agents which may have an enhanced effect when used in combination. Another approach being taken is the re-engineering of anti-CD20 antibodies to optimize particular modes of action. Other studies have shown that radio-labeled anti-CD20 antibodies seem to be useful in relapsed and refractory NHL. They may be useful as part of initial therapy as well. Further study of these modified anti-CD20 anti-bodies is ongoing.

IN CONCLUSION

ASH 2005, like its predecessors, attracted the top scientists working on hematologic cancers as well as students entering the field. It is to be hoped that the exchange of information and the stimulation afforded by presentation of the leading work in this field will lead to future breakthroughs in diagnosis and treatment of these diseases.



NEW RESEARCH GRANTS

The LRF is delighted to announce that, thanks to the generosity and vision of our donors, we are greatly extending our research grant program. This year, in addition to our Fellowships and Career Development Awards, we will be offering grants, each for \$250,000 per year for up to 3 years, for original research in the following fields:

- ⇒ Follicular Lymphoma: awards for innovative approaches to the treatment of FL.
- ⇒ Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma: projects involving novel therapeutic approaches to CLL/SLL will be chosen.
- ⇒ Mantle Cell Lymphoma Research Initiative: awards will go to major research projects covering the spectrum from laboratory studies to the identification of new therapeutic strategies.
- ⇒ Additionally, grants of \$75,000 are being made available to fund correlative studies to enhance MCL research already in progress.

LRF is very excited about these grants, because the more research we can enable, the closer we will get to finding a cure for lymphoma.

MCL WEBSITE AND CLINICAL TRIALS LISTING

The newly-launched mantle cell lymphoma website at www.mantlecelllymphoma.org includes, in addition to core information on the disease, a listing of clinical trials. This pilot project is still under construction. When completed, it will offer patients and their loved ones a simple way to access trials that are accepting MCL patients. LRF will include only trials that have been verified by the research team as currently open to MCL patients. A search engine will allow users to search for trials by trial type and geographic location, and by disease status. The listing will provide details on the trial as well as contact information for enrollment.

SCIENCE UPDATE

One of the areas of highest priority for indolent lymphomas is to gain an improved understanding of the biology of the disease, in order to better determine prognosis and select appropriate therapeutic strategies for each individual patient. Gene expression studies are becoming more commonplace. Clinical and biologic markers help to predict in whom the disease will be more aggressive, and therefore allow the physician and patient to make more informed treatment decisions.

Lymphoma arises from genetic mishaps (translocations) when B-cells are being rapidly produced in the germinal center of lymph nodes. The most common of these is the t14/t18 translocation that causes production of a protein BCL-2. BCL-2 is inappropriately produced in DLBCL and other lymphomas. BCL-2 prevents cell death. This protein has been a therapeutic target for several years. Current drugs aimed at shutting off BCL-2 include oblimersen (trade name: Genasense). Research is also aimed at looking for other targets of BCL-2 that will shut down this protein and cause the death of the lymphoma cells. Several compounds are currently in early development, including BH3i, Gossypol, GX01 and ABT-737.

Recent work has identified another protein, BCL-6, that also plays a role in lymphoma. BCL-6 suppresses responses to DNA breaks and represses another factor, c-myc, present in the germinal center. In lymphoma, BCL-6 and c-myc work synergistically to stabilize one another. There are several pathologic consequences of this BCL-6/c-myc complex. These new findings may lead to therapies specifically targeted to c-myc/BCL-6.

(Abstract 2)

Transformation from indolent to aggressive disease is most common in follicular lymphoma. The disease most often transforms to DLBCL. Because the prognosis of patients following transformation is typically poor, an enhanced understanding of the transformation process should help physicians and researchers to better manage the disease. Physicians are studying the time to

transformation, the gene expression profiles in patients who transform to DLBCL (compared to those who have DLBCL at their first diagnosis), and the types of genetic changes that occur in patients who transform (Abstracts 602, 604). DLBCL is a highly varied disease both biologically and in how it acts clinically. As a result it is sometimes difficult for physicians to determine the prognosis for individual patients and the likely response to any particular course of treatment. Currently, patients with transformed DLBCL are generally treated the same as those who had DLBCL at diagnosis – usually with CHOP regimens or CHOP plus rituximab, but use of these therapies has not been able to prevent relapse in most patients.



Clinical factors described in the International Prognostic Index have been used to determine individual patient risk for relapse for over 10 years. These criteria are now being supplemented with data from other sources. Researchers are evaluating PET scans, gene expression profiling, and expression of particular cell markers as predictors. Additional work needs to be done before these methods can be clinically useful to physicians. For example, there is currently no evidence to show that

additional treatment at the point of a positive PET scan can change outcomes. Physicians continue to use the Internal Prognostic Index until these new techniques are evaluated in clinical trials and proven to have clinical value.

Ongoing studies are attempting to find better treatment for patients with transformed disease. One study is evaluating the radioimmunotherapy drug, Zevalin. New therapies may also be found based on genetic abnormalities discovered through gene expression profiling. Aurora kinase, MAP kinase, and histone deacetylase inhibitors are current targets, but these potential therapies are several years away from large clinical trials.

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