



Discovering Novel Treatments for Lymphoma and Myeloma

by Larry W. Kwak, MD, PhD, Professor and Chairman, Lymphoma and Myeloma, The University of Texas M. D. Anderson Cancer Center

A large portion of my career has been devoted to the discovery and development of patient-specific idiotype vaccines for the treatment of patients with lymphoma. This approach was first explored nearly 30 years ago in mice after the discovery of a very well-defined lymphoma tumor antigen.

From Stanford to the NCI and now here at M. D. Anderson, we have taken the clinical development of idiotype vaccines many steps further. For example, phase II results showed that patient-specific vaccination with the Id-KLH plus granulocyte-macrophage colony-stimulating factor (GM-CSF) vaccine was able to induce complete molecular remissions in patients with B-cell lymphomas following complete clinical remission with chemotherapy (Bendandi M et al. *Nat Med.* 1999;5:1171-7.).

This and other promising results from other phase II trials stimulated the initiation of three phase III studies comparing Id-KLH plus GM-CSF with either KLH or placebo (Genitope, Biovest and Favril).



Larry W. Kwak, MD, PhD

class researchers and clinicians at M. D. Anderson. Together, we hope to continue in our efforts to develop breakthrough treatments for patients with lymphoma and myeloma.

Along these lines, this issue of *Lymphoma & Myeloma: M. D. Anderson Clinical Perspectives* marks the debut of a quarterly publication designed to provide the practicing oncologist with timely information surrounding the treatment of patients with lymphoma/myeloma. The newsletter features *Original Articles* authored by M. D. Anderson Faculty, *Comprehensive Clinical Trial Listings*

Results from the first phase III trial should be available later this year.

As we move forward into the future, it is my privilege to work together with this group of world-

and in-depth *Case Studies* that describe real-life applications of cutting edge management approaches. The overall purpose of the publication is to provide a concise forum for oncologists to share in recent clinical advances and to participate in ongoing research in an effort to accelerate development of novel drugs and regimens that may benefit patients with these diseases. I look forward to your input on the newsletter and any suggestions that you may have to improve its usefulness to you. ■

Novel Agents for Relapsed/Refractory Hodgkin and Non-Hodgkin Lymphoma

by Anas Younes, MD, Director, Clinical & Translational Research, Professor of Medicine, Dept of Lymphoma and Myeloma, The University of Texas M. D. Anderson Cancer Center

The first convincing data of curing patients with advanced stage Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) were reported in the late 1960s and early 1970s using the MOPP (nitrogen mustard, vincristine, prednisone and procarbazine) and the CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimens. With time, ABVD (doxorubicin, bleomycin,

vinblastine and dacarbazine) replaced MOPP as the most widely used regimen and remains in use today. Similarly, CHOP is still used even after three decades of its introduction but is now combined with the anti-CD20 monoclonal antibody rituximab (Rituxan®; Genentech, Biogen-Idex). Thus, although our understanding of cancer

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biology and immunology has significantly improved since the introduction of these curative regimens, the treatment of HL and NHL did not drastically change in more than 30 years. Furthermore, these regimens do not cure all patients with HL and NHL, and continue to have late toxicities that may shorten patients' survival. The current approach is focusing on more targeted therapies that can preferentially kill tumor cells while sparing normal cells. This approach is likely to improve the cure rate and reduce treatment-related toxicity. Novel drugs are currently being explored in phase I and phase II trials to target the cancer cells or their

microenvironment (Figure 1). Here we will summarize some of these new strategies that are currently being studied in the Department of Lymphoma/Myeloma at M. D. Anderson.

Novel Agents for NHL

The success of the monoclonal antibody rituximab in the management of patients with B-cell lymphoma led to the development of novel antibodies that target surface proteins and receptors that are commonly expressed by B and T cell lymphomas (Figure 2). These antibodies can be used in three major ways:

- 1) naked or unconjugated antibodies that primarily kill by antibody-dependent cellular cytotoxicity (ADCC) mechanism. Examples of this approach are rituximab (anti-CD20), galiximab (anti-CD80; Biogen-Idec), epratuzumab (anti-D22; Immunomedics), and antibodies targeting TRAIL death receptors 1 and 2, CD30 and CD40 receptors;
- 2) antibodies that are conjugated to radioisotopes, such as ¹³¹I tositumomab (Bexxar®; GlaxoSmithKline) and ⁹⁰Y ibritumomab tiuxetan (Zevalin®; Biogen-Idec);

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Program Goal

This newsletter describes some of the significant changes and ongoing research surrounding the treatment of patients with hematologic cancers. The purpose is to provide participants with important information regarding treatment advances and ongoing clinical programs at The University of Texas M. D. Anderson Cancer Center.

Continuing Medical Education

The University of Texas M. D. Anderson Cancer Center is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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Target Audience

The newsletter is intended for physicians and other healthcare professionals specializing in medical oncology, hematology/oncology, general surgery, internal medicine and general practice.

No specific knowledge other than a basic familiarity with the principles and practice of hematology/oncology is required for successful participation in this program.

Educational Objectives

After reading this newsletter, participants should be able to:

- Describe some of the latest therapeutic approaches in the treatment of lymphoma and myeloma.
- Identify the current standards and management approaches for patients with lymphoma and myeloma.
- Outline the therapeutic implications of recent clinical trial findings and future treatment strategies.
- Describe regimens that have benefits for patients with lymphoma and myeloma and how patients should be selected and managed appropriately.

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In compliance with this policy, a superscript number has been placed by the name of the program chair, planning committee member, teacher, or author who has indicated that he/she has an affiliation with a commercial interest which have interests related to the content of the presentation or that may financially support the activity.

The University of Texas M. D. Anderson has, through a formal review process, made every attempt to resolve all potential conflicts of interest prior to this activity. For information on this process, please contact the Department of CME/Conference Services at 713/792-5357.



(cont'd from p. 2) Novel Agents for Refractory Lymphoma

3) antibodies that are conjugated to toxins, such as CMC-544 (anti-CD22 conjugated to calichamicin) and SGN-35 (anti-CD30 conjugated to an auristatin derivative). Many of these antibodies are also being combined with other active drugs in phase I and phase II clinical trials.

In addition to monoclonal antibodies, small molecule inhibitors that target specific signaling proteins that promote tumor cell survival and growth are currently being explored in clinical trials. The best and most advanced example is the recent use of the proteasome inhibitor bortezomib (Velcade[®]; Millennium), a small molecule inhibitor that is currently approved by the *Food and Drug Administration* for the treatment of patients with multiple myeloma. Bortezomib activity was recently evaluated in patients with relapsed NHL, and was found to have significant anti-tumor activity in patients with relapsed mantle cell lymphoma.

clinical activity in patients with relapsed mantle cell lymphoma and is currently being evaluated in patients with other types of NHL. Another example is 17-AAG, a small molecule that inhibits the heat shock protein-90 (HSP-90). HSPs are required for maintenance and function of a variety of client proteins that regulate cell cycle, survival and apoptosis, and HSP-90 is one of the most abundant cellular chaperone proteins. Although both benign and malignant cells express HSP-90, cancer cells primarily express the active form which has an increased affinity to HSP inhibitors, therefore, making the cancer cells more sensitive to HSP inhibition compared with normal cells. We are currently conducting a phase II study of 17-AAG in patients with relapsed mantle cell lymphoma and anaplastic large cell lymphoma. Finally, recent studies demonstrated that histone acetylation, which is mediated by histone acetyltransferases (HATs), leads to DNA relaxation enabling transcription factors to have greater access to the DNA with subsequent increase in gene transcription. HATs are opposed by histone deacetylases (HDACs), which decrease histone acetylation leading to chromatin condensation and repression of gene expression. Abnormalities in the function of both HATs and HDACs have been observed in a variety of cancers, including lymphoma. HDACs can be pharmacologically inhibited by a diverse natural or synthetic compounds leading to altered expression of cell cycle regulatory genes, including p21, p27, p53, Rb, BCL6, BCL2, BCL-XL, MCL-1, cyclin D1 and HSP-90. Furthermore, HDAC inhibitors can induce apoptosis by caspase-dependent and caspase-independent mechanisms. We are currently conducting a phase II study of a selective HDAC inhibitor MCGD-0103 in patients with relapsed follicular and DLBCL. Early results suggest a potent clinical activity with minimal toxicity.



Anas Younes, MD

Our group is also evaluating the activity of another HDAC inhibitor, depsipeptide.

Our group is also investigating the role of the angiogenesis inhibitors bevacizumab (Avastin[®]; Genentech) and lenalidomide (Revlimid[®]; Celgene) in combination with rituximab in patients with relapsed aggressive B-cell lymphoma, in addition to several vaccine strategies that are currently being examined by our group in patients with follicular lymphoma and DLBCL.

Novel Agents for HL

The *World Health Organization* classification of Hodgkin lymphoma distinguished between two major subtypes, classical HL and nodular lymphocyte predominant HL. Approximately 95% of patients with HL will have the classical HL histology, which is characterized by the presence of rare malignant Hodgkin and Reed Sternberg (HRS) cells among an overwhelming number of benign reactive cells. In recent years, new studies have shed more light on the biological and molecular features of HRS cells, providing hope that new targeted therapy may be developed to enhance the cure rate and to reduce treatment-related toxicity. HRS cells express several receptors, including pro-survival receptors (CD30, CD40) and pro-death receptors (TRAIL death receptors 1 and 2), in addition to CD20 and CD80 antigens that can be therapeutically targeted with monoclonal antibodies. Antibodies targeting CD30 are currently being examined in clinical trials. The results of the unconjugated anti-CD30 antibodies have been somewhat disappointing in patients with relapsed classical HL. A novel anti-CD30 conjugated to an auristatin derivative toxin (SGN-35) will soon be examined in a phase I/II study. HRS cells express IL-13 and IL-13 receptors, creating an autocrine loop that promotes their survival. Our group is currently evaluating the activity of a novel fully human monoclonal antibody targeting IL-13 in patients with relapsed HL. The antibody is administered every 2 weeks by short infusion.

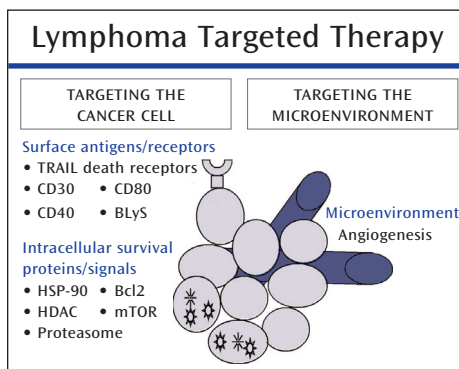


Figure 1. A number of new molecular targets are being explored for lymphoma. Investigational therapies include those targeting malignant cells as well as those targeting the microenvironment.

Bortezomib-based combination trials with rituximab and a variety of chemotherapy regimens including the R-Hyper-CVAD regimen, are currently being explored in phase I and phase II studies.

Other small molecules are currently being evaluated in patients with relapsed NHL with promising early results. For example, CCI-779 (temsirolimus; Wyeth) which inhibits the mammalian target of rapamycin (mTOR), have demonstrated significant

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Lymphoma & Myeloma Clinical Trials at MDACC

NUMBER	PROTOCOL TITLE	TREATMENT	PHASE	PRINCIPAL INVESTIGATOR
INDOLENT LYMPHOMA - UNTREATED				
2003-0696	Zevalin for Low-Grade Follicular NHL of the Orbit	Radioimmunotherapy	PILOT	Esmaeli
2005-0512	Zevalin for Newly Diagnosed Low-Grade Indolent Lymphomas Stage I-II (Follicular Lymphoma Extranodal Marginal Lymphoma of MALT type Nodal Marginal Zone B-cell Lymphoma and Splenic Marginal B-cell Lymphoma)	Radioimmunotherapy	II	Samaniego
ID03-0287	R-FND Zevalin then Rituxan for Advanced Stage Follicular Lymphoma with High-Risk Features	Immunochemotherapy + Radioimmunotherapy	II	McLaughlin
2005-0170	PACE w/FNHL1d1 Vaccine w/GM-CSF In Follicular Lymphoma in First Complete Remission	Chemotherapy + Vaccine	III	Neelapu
2006-0260	CCOP Trial of Rituximab+Sargramostim in Newly Diagnosed Follicular B-cell Lymphoma	Monoclonal Antibody + Cytokine	II	McLaughlin
2004-0818	Nipent Cytozan Rituxan (PCR) Stage III or IV Low-grade NHL or Bulky Lymphoma	Chemotherapy + Monoclonal Antibody	II	Samaniego
INDOLENT LYMPHOMA - PREVIOUSLY TREATED				
2006-0417	Oral MG-0103- a HDAC inhibitor in Relapsed Follicular Lymphoma	Oral HDAC inhibitor	II	Younes
2006-0258	Apo2L/TRAIL with Rituxan in NHL that Has Progressed Following Previous Rituxan	Apoptosis Inducer	I-II	Fanale
2004-0818	Nipent Cytozan Rituxan (PCR) Stage III or IV Low-grade NHL or Bulky Lymphoma	Chemotherapy + Monoclonal Antibody	II	Samaniego
2006-0313	Rituxan + GM-CSF for Relapsed Indolent Lymphoma	Monoclonal Antibody + Cytokine	II	McLaughlin
2004-0612	CCI-779 in B-Cell NHL + CLL (NCI-CTEP Study)	mTor Inhibitor	II	Pro
2005-0571	Zevalin in Relapsed/Refractory Indolent Lymphoma: Extranodal Marginal Lymphoma of MALT type Nodal Marginal Zone B-cell and Splenic Marginal B-cell Lymphoma	Radioimmunotherapy	II	Samaniego
2006-0415	CMC-544 with Rituximab for CD20/CD22+ Follicular NHL	Anti-CD22 Immunotoxin Antibody	I-II	Fayad
2004-0953	Dose Escalation Safety/Tolerance Study of PPI-2458 in NHL	MetAP2 inhibitor	I	Fayad
2005-0046	Immunotherapy with hA20 Once Weekly for 4 Weeks in CD20+ B-Cell NHL	Anti-CD20 Monoclonal Antibody	I	Fayad
2004-0492	NHL - Chimeric Antibody-CNTO 328 (Anti IL-6)	Anti-IL6 Monoclonal Antibody	I	Kurzrock
INTERMEDIATE/HIGH GRADE LYMPHOMA - UNTREATED				
2004-0305	R-CHOP + Peg Lipo Doxorubicin for Older > 60 Years with Untreated Aggressive B-Cell NHL	Chemotherapy + Monoclonal Antibody	II	Rodriguez
2004-0683	R-CHOP/Zevalin for Elderly > 60 Years Previously Untreated DLBCL (High IPI Only)	Monoclonal Antibody + Chemo + RIT	II	Rodriguez
2005-0054	R-HCVAD alternating with R-Methotrexate-Cytarabine vs Standard R-CHOP for Newly Diagnosed High Risk Aggressive B-Cell NHL < 60 Years	Monoclonal Antibody + Combination Chemotherapy	II	Fayad
2005-0908	Double-blind Randomized Placebo-controlled Trial of Favld + GM-CSF after R-CHOP as First-line Therapy in High-intermediate and High-Risk DLBCL	Monoclonal Antibody + Chemo + Vaccine	III	Fayad
2006-0207	PRELUDE: Prevention of Relapse in Lymphoma Using Daily Enzastaurin	Anti PKC-beta Small Molecule	III	Fayad
INTERMEDIATE/HIGH GRADE LYMPHOMA - PREVIOUSLY TREATED				
2005-0749	AMG-531 for Severe Thrombocytopenia due to Chemotherapy in Relapsed Aggressive Lymphoma	Platelet Growth Factor	I-II	Fanale
2006-0417	Oral MG-0103/HDAC inhibitor in Relapsed DLBCL	Oral HDAC inhibitor	II	Younes
2005-0579	Depsipeptide a Histone Deacetylase Inhibitor in Relapsed/Refractory MCL or DLC	NHL HDAC Inhibitor	II	Fayad
2006-0415	CMC-544 with Rituximab with CD20/CD22 positive Diffuse Large B-Cell NHL	Anti-CD22 Immunotoxin Antibody	I-II	Fayad
2003-0520	Avastin + Rituxan in Relapsed and Chemo- or Rituxan-Refractory Aggressive B-Cell NHL	Anti-Angiogenesis	II	Pro
2004-0612	CCI-779 in B-Cell NHL + CLL (NCI-CTEP Study)	mTor Inhibitor	II	Pro
2004-0953	Dose Escalation Safety/Tolerance Study of PPI-2458 in NHL	MetAP2 inhibitor	I	Fayad
2005-0433	Single Dose Escalation Study of BI 2536 BS in Refractory/Relapsed NHL	Mitotic Kinase Inhibitor	I	Younes
2005-0046	hA20 Immunotherapy, Once Weekly x 4 Weeks in CD20+ B-Cell NHL	Anti-CD20 Monoclonal Antibody	I	Fayad
2006-0475	Study of SGN-35 in Relapsed or Refractory CD30+ Hematologic Malignancies	Anti-CD30 immunotoxin antibody	I	Younes
2004-0492	NHL - Chimeric Antibody-CNTO 328 (Anti IL-6)	Anti-IL6 Monoclonal Antibody	I	Kurzrock
HODGKIN LYMPHOMA - UNTREATED				
ID00-218	Rituxan + ABVD	Anti-CD20 antibody	II	Younes



(cont'd from p. 4) **Lymphoma & Myeloma Clinical Trials**

NUMBER	PROTOCOL TITLE	TREATMENT	PHASE	PRINCIPAL INVESTIGATOR
HODGKIN LYMPHOMA - PREVIOUSLY TREATED				
2004-0792	17-AAG in Relapsed CD30+ ALCL Relapsed MCL & Relapsed Classical HL	Heat Shock Protein - 90 inhibitor	II	Younes
2005-0749	AMG-531 for Severe Thrombocytopenia due to Chemotherapy in Relapsed Aggressive Lymphoma	Platelet Growth Factor	I-II	Fanale
2006-0011	Non-Randomized Multiple-Dose Dose-Escalation Study of the Safety Pharmacokinetics Pharmacodynamics and Efficacy of TNX-650 in Refractory HL	Anti IL-13 Humanized Monoclonal Antibody	I-II	Younes
2006-0441	GX15-070MS/24-hour Infusion Q2 Weeks in Relapsed or Refractory Hodgkin Lymphoma	BCL-2 family Small Molecule inhibitor	II	Younes
2006-0465	MGCD0103 in Relapsed or Refractory Hodgkin Lymphoma	Oral HDAC inhibitor	II	Younes
2006-0475	SGN-35 in Relapsed or Refractory CD30+ Hematologic Malignancies	Anti-CD30 immunotoxin antibody	I	Younes
MANTLE CELL LYMPHOMA - PREVIOUSLY TREATED				
2004-0930	CCI-779 at 2 Dose Levels vs Investigator Choice (1 of 8) in Relapsed/Refractory MCL	mTor Inhibitor	III	Romaguera
2005-0461	CC-5013 and Rituxan in Relapsed MCL	Immunomodulation/Thalidomide Analogue	I-II	Wang
2004-0792	17-AAG in Relapsed CD30+ ALCL Relapsed MCL and Relapsed Classical HL	Heat Shock Protein - 90 inhibitor	II	Younes
2003-0520	Avastin + Rituxan in Relapsed and Chemo- or Rituxan-Refractory Aggressive B-cell NHL	Anti-Angiogenesis	II	Pro
2005-0579	Depsipeptide a Histone Deacetylase Inhibitor in Relapsed/Refractory MCL or DLC	NHL HDAC Inhibitor	II	Fayad
2005-0433	Single Dose Escalation Study of BI 2536 BS in Ref/Relapsed NHL	Mitotic Kinase Inhibitor	I	Younes
2005-0046	Immunotherapy with hA20 Once Weekly for 4 Weeks in CD20+ B-Cell NHL	Anti-CD20 Monoclonal Antibody	I	Fayad
2005-0749	AMG-531 for Severe Thrombocytopenia due to Chemotherapy in Relapsed Aggressive Lymphoma	Platelet Growth Factor	I-II	Fanale
2004-0492	NHL - Chimeric Antibody-CNTO 328 (Anti IL-6)	Anti-IL6 Monoclonal Antibody	I	Kurzrock
PERIPHERAL T-CELL LYMPHOMA - UNTREATED				
2005-0627	SGN-30 Monoclonal Antibody + CHOP for CD30+ Anaplastic Large Cell Lymphoma	Monoclonal Antibody	II	Pro
ID03-0004	Hyper CVID-Doxil in Newly Diagnosed PTCL	Combination Chemotherapy	II	Pro
PERIPHERAL T-CELL LYMPHOMA - PREVIOUSLY TREATED				
2005-0327	Dose Escalation Study of MEDI-507 in CD2+ T-Cell Lymphoma/Leukemia	Anti-CD2 Humanized Monoclonal Antibody	I	Pro
2005-0433	Single Dose Escalation Study of BI 2536 BS in Refractory/Relapsed NHL	Mitotic Kinase Inhibitor	I	Younes
2006-0336	(RS)-10-Propargyl-10-Pralatrexate with Vit B12 and Folic Acid in Relapsed/Refractory PTCL	Folate Analog	II	Pro
PRIMARY CNS LYMPHOMA - PREVIOUSLY TREATED				
NABTC05-01	Rituximab and Temozolomide	Monoclonal Antibody + Alkylating Agent	II	Hsu
CASTLEMAN'S DISEASE				
2004-0492	Chimeric Antibody Against IL-6 (CNTO 328) in NHL, MM or Castleman's Disease	Anti-IL-6 Monoclonal Antibody	I	Kurzrock
WALDENSTROM'S - UNTREATED				
2005-0733	Primary Treatment of Waldenstrom's Macroglobulinemia with Bortezomib and Rituximab followed by Autologous Stem Cell Collection	Immunomodulation + Monoclonal Antibody + Auto Stem Cell	II	Thomas
MYELOMA/WALDENSTROM'S - PREVIOUSLY TREATED				
2005-0438	SAHA + Bortezomib in Advanced Multiple Myeloma	HDAC Inhibitor	I	Weber
2005-0831	Denosumab (AMG 162) in Relapsed or Plateau-Phase Multiple Myeloma	Anti-RANKL Monoclonal Antibody	II	Vadhan
2003-0964	Oral Atiprimod in Relapsed or Refractory Multiple Myeloma	IL-6 Inhibitor	I	Wang
2004-0492	NHL - Chimeric Antibody-CNTO 328 (Anti IL-6)	Anti-IL-6 Monoclonal Antibody	I	Kurzrock
SUPPORTIVE CARE STUDIES				
2005-0698	Zometa on Chemotherapy- Induced Bone Loss in Lymphoma Patients Receiving Chemotherapy	Bisphosphonate Derivative	N/A	Hagemeister
2006-0243	PROCRIT 80,000 Units Q4W vs. 40,000 Units Q2W in Non-Chemotherapy Anemia	Colony-Stimulating Factor	Pilot	Hagemeister



(cont'd from p. 3) Novel Agents for Refractory Lymphoma

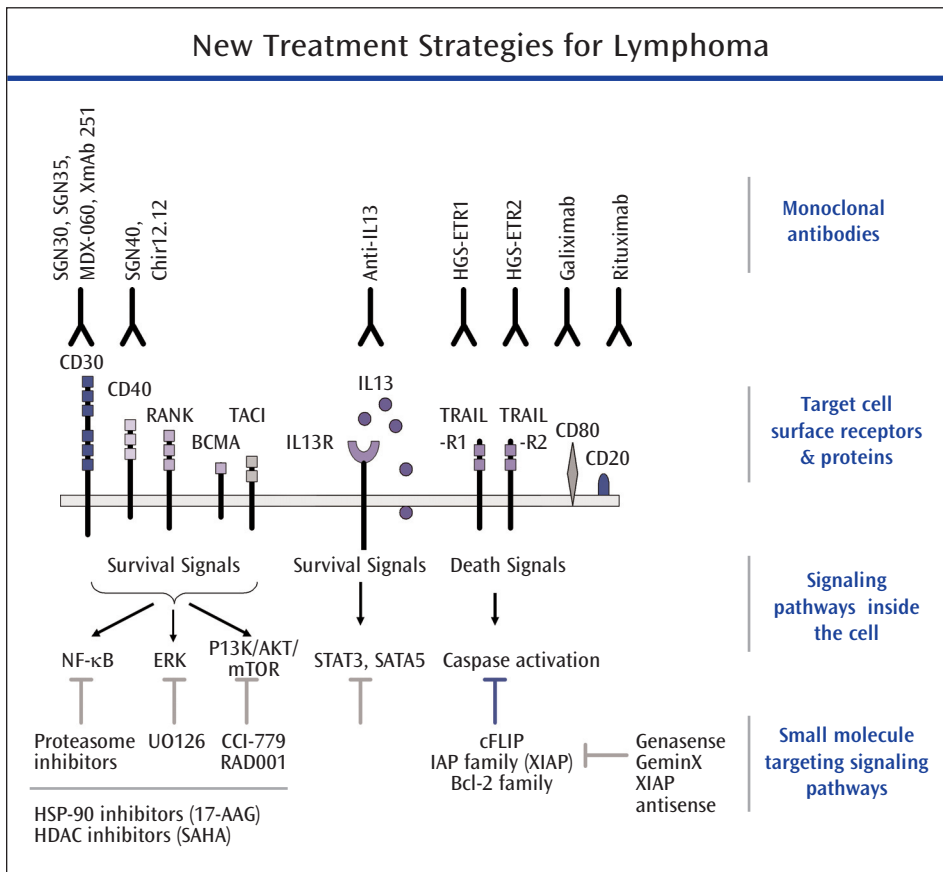


Figure 2. Two major treatment strategies are currently being explored in patients with lymphoma. In the first, monoclonal antibodies are used to target specific receptors and proteins found on the surface of the lymphoma cells. In the second, small molecule drugs are used to enter the lymphoma cells and target specific signaling proteins that promote cell survival.

Dose escalation is ongoing to identify the maximum tolerated dose.

In a different approach, our group pioneered the use of rituximab in patients with classical HL to target the reactive B-cells in HRS cells microenvironment. We are currently combining rituximab with ABVD in patients with poor-risk classical HL, and soon will conduct a randomized study comparing rituximab plus ABVD with ABVD alone in patients with newly diagnosed classical HL.

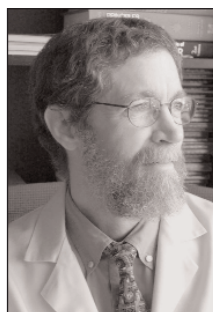
Finally, we are examining the role of several small molecule inhibitors in patients with relapsed HL, including the HSP-90 inhibitor 17-AAG, the HDAC inhibitor MCGD-0103, and the pan-Bcl2 inhibitor GX15-070. These studies are likely to improve the future treatment strategies of patients with relapsed HL.

For more information or patient referrals, please contact Dr. Anas Younes, team leader of the drug development program at ayounes@mdanderson.org, or any of the following members of the drug development team: Luis Fayad, lfayad@mdanderson.org; Barbara Pro, bpro@mdanderson.org; Michelle Fanale, mfanale@mdanderson.org; and, Sheeba Thomas, sthomas@mdanderson.org. ■

Case Study: Targeted Combination Therapy for a Patient with Untreated Follicular Lymphoma

by Peter McLaughlin, MD, Associate Professor, Department of Lymphoma and Myeloma, The University of Texas M. D. Anderson Cancer Center

The traditional management of patients with advanced stage indolent lymphoma has been based on alkylating agents, either single agent oral regimens or combinations. Chemotherapeutic options have been substantially enhanced with the availability of nucleoside analogs including fludarabine. Effective combinations with fludarabine (Fludara[®]; Berlex) have been developed, both with and without concurrent alkylating agents (McLaughlin P et al. *J Clin Oncol.* 1996;14:1262-1268; Zinzani PL et al. *J Clin Oncol.* 2004;22:2654-2661.; Forstpointner R et al. *Blood.*



Peter McLaughlin, MD

body rituximab (Rituxan[®]; Genentech), and radioimmunoconjugates (McLaughlin

2006;Aug 31; [Epub ahead of print]). Another major improvement in the therapy of patients with indolent lymphoma has been the incorporation of monoclonal antibodies, including the unconjugated anti-CD20 anti-

P et al. *J Clin Oncol.* 1998;16:2825-2833.; Kaminski MS et al. *N Engl J Med.* 2004;352:441-449.). The net effect of these new therapeutic options has been a trend, which has been noted by several groups of investigators, for improving outcomes for patients with indolent lymphoma (Swenson WT et al. *J Clin Oncol.* 2005;23:5019-5026.; Fisher RI et al. *J Clin Oncol.* 2005;23:8447-8452.; Liu Q et al. *J Clin Oncol.* 2006;24:1582-1589.).

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(cont'd from p. 6) **Case Study: Targeted Combination Therapy**

Case Report

A 33-year old woman presented with a two month history of malaise, fatigue and sweats. She was found to be pancytopenic and had lymphadenopathy. A cervical lymph node biopsy revealed follicular lymphoma, grade two. Lab data included LDH 646 (top normal 618), hemoglobin 8.2, platelets 77,000 and WBC 4.1 with 77% lymphocytes. The circulating lymphocytes were small cleaved cells, and were monoclonal by flow cytometry. The bone marrow showed extensive involvement by small cleaved cell lymphoma with a 70% infiltrate. Radiographic studies showed widespread adenopathy, some up to 4 cm in diameter, and splenomegaly. Her stage was IV-B. The FLIPI score was 4: advanced stage; >5 nodal sites; elevated LDH; and low hemoglobin (Solal-Celigny P et al. *Blood*. 2004;104:1258-1265.).

Because of geographic issues, the patient was unable to participate in available protocol options for patients with high-risk follicular lymphoma. After discussion of established options, it was elected to proceed with R-FND (rituximab, fludarabine, mitoxantrone, dexamethasone; McLaughlin 1996; Zinzani 2004; McLaughlin P et al. *Semin Oncol*. 2000;27(Suppl 12):37-41.).

She tolerated therapy well and attained complete remission. She completed 6 cycles. At that point, based on concerns about protracted R-FND therapy (McLaughlin P et al. *Blood*. 2005;105:4573-4575.), and based on encouraging data with maintenance rituximab (Forstpointner 2006), it was elected to shift to a schedule of rituximab maintenance. She completed 12 months of maintenance therapy. Since then, she has been observed off therapy and she has

remained in complete remission for over two years.

Discussion

Therapeutic options for patients with advanced stage indolent lymphoma have been improving. There still can be a role for a palliative approach for patients with non-threatening disease, particularly for elderly patients. But patients such as the one reported here need prompt and highly effective therapy. Our current protocol for such a high-risk patient (**Figure 1**) would have been R-FND followed by 90Y-ibrutinomab tiuxetan (Zevalin[®]; Biogen-Idec), and rituximab maintenance. But this patient elected to proceed with off-protocol standard therapy. After weighing options

(continued on back cover)

Continuing Medical Education

Post-Test [Course Code: MEMV1070, February 2007]

Read each question and circle the letter next to the correct answer. There is only one correct answer per question. A score of 75% must be obtained to receive category I CME credit. Once reviewed, you will receive a certificate documenting your participation in this CME activity.

- The success of the monoclonal antibody rituximab in the management of patients with B-cell lymphoma led to the development of novel antibodies that target surface proteins and receptors expressed by B- and T-cell lymphomas:
 - true
 - false
- For patients with advanced stage indolent lymphomas:
 - fludarabine-containing chemotherapy combinations have emerged as highly effective options to CHOP regimens
 - chemo-immunotherapy is the treatment of choice for most patients with high-risk disease (eg, R-CHOP, R-FND)
 - palliative therapy may play a role for elderly patients or those with non-threatening disease
 - all of the above
- Phase II results with patient-specific vaccination with the Id-KLH plus GM-CSF vaccine showed the following in patients with B-cell lymphomas:
 - vaccination failed to induce remission in this population
 - vaccination induced complete molecular remission following complete clinical remission with chemotherapy
 - were inconclusive
 - none of the above
- Bortezomib is:
 - a small molecule, proteasome inhibitor
 - used for treatment of patients with multiple myeloma
 - active in patients with relapsed mantle cell lymphoma
 - a and b
 - all of the above
- Patient-specific idiotype vaccines were first explored:
 - nearly 30 years ago in human trials
 - following the discovery of a very well-defined lymphoma tumor antigen
 - nearly 30 years ago in animal models
 - b and c
- What percentage of patients with Hodgkin lymphoma have classical HL histology (characterized by the presence of rare malignant Hodgkin & Reed Sternberg cells and benign reactive cells)?
 - 5%
 - 75%
 - 95%
 - 100%

Evaluation

- The educational objectives were achieved by the newsletter.

Strongly Agree Agree Disagree Strongly Disagree
- As a result of reading this newsletter, do you feel that you:
 - have increased your professional knowledge? Yes No
 - will change your management approach? Yes No
 - will start patients on new trials or research? Yes No
 - will use new pharmacologic therapies? Yes No
 - will apply the information learned in another way? Yes No

If yes, please explain _____
- Was any commercial or promotional bias noted in the information provided in this newsletter? Yes No If yes, explain _____
- Suggested topics or comments for future publications: _____

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(cont'd from p. 7) Case Study: Targeted Combination Therapy

(mainly R-CHOP (Hiddemann W et al. *Blood*. 2005;106:3725-3732.) or R-FND), we chose R-FND.

The CHOP regimen is an established standard for both aggressive and indolent lymphoma. Combinations which include fludarabine have emerged as highly effective alternative options; the FM (fludarabine, mitoxantrone) regimen compares very favorably with the CHOP regimen (Zinzani 2004). The incorporation of rituximab into a variety of combination regimens has shown a clear impact. In the front-line setting, R-CVP, R-CHOP and R-FND have been shown to be superior to the respective combinations without rituximab (Hiddemann 2005; Marcus R et al. *Blood*. 2005;105:1471-1423; McLaughlin P et al. *Ann Oncol*. 2005; 16(Suppl 5):v109.).

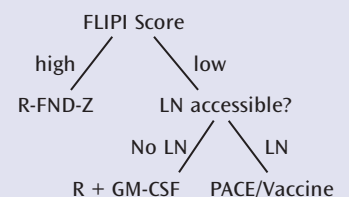
There has been intense interest in the incorporation of rituximab maintenance into the therapy of patients with indolent lymphoma. In the context of single agent rituximab therapy, prolongation of remission has been demonstrated in two trials (Hainsworth JD et al. *J Clin Oncol*. 2005;23:1088-1095.; Ghilmini M et al. *Blood*. 2004;103: 4416-4423.). Following combination chemotherapy that did not include rituximab, the addition of rituximab maintenance has been shown to prolong remission duration

(Hochster HS et al. *Proc ASCO*. 2004;23: 556.). Following chemo-immunotherapy (eg, R-CHOP), the use of additional rituximab in the maintenance setting has so far only been studied in a limited fashion. Two recent trials, both in the setting of recurrent follicular lymphoma, have shown that rituximab maintenance prolongs remission duration after chemo-immunotherapy with R-CHOP and with R-FCM (Forstpointner 2006; van Oers MHJ et al. *Blood*. 2005;106(Suppl 1): 107a.). Trials are ongoing to define whether the same benefit of rituximab maintenance can be demonstrated after front-line chemo-immunotherapy.

In addition to unconjugated anti-CD20 antibody rituximab, there is also intense interest in the incorporation of radio-immunotherapy strategies into the front-line management of patients with indolent lymphoma. The *Southwest Oncology Group* is studying the incorporation of ¹³¹I-tositumomab monoclonal antibody therapy into front-line therapy (Press OW et al. *J Clin Oncol*. 2006;24:4143-4149.). At M. D. Anderson, a trial is underway for patients with high-risk follicular lymphoma, incorporating ⁹⁰Y-ibritumomab tiuxetan consolidation after R-FND therapy (Figure 1). In selected patients, radioimmunotherapy alone may also be an option (Kaminski 2004).

The widespread availability of these anti-CD20 monoclonal antibodies has meaningfully improved the therapy options for patients with follicular lymphoma. Ironically, the commercial availability of these agents, coupled with the exciting clinical results, has stymied the accrual of patients in North America to the clinical trials that are needed to prove and improve their role in the management of these patients. Encouraging anecdotal experiences, such as the one summarized here, are exciting. But it will take participation in clinical trials to truly define and refine our use of these agents. ■

Figure 1. Follicular Lymphoma Front-Line Trials: Stage III-IV



PCR is also an option and is the preferred option for small lymphocytic lymphoma.

FLIPI: Follicular Lymphoma International Prognostic Index; LN: lymph node; R-FND-Z: rituximab, fludarabine, mitoxantrone, dexamethasone and ⁹⁰Y-ibritumomab tiuxetan; R: rituximab; PACE: prednisone, doxorubicin, cyclophosphamide and etoposide; Vaccine: conjugated follicular lymphoma-derived idiotype (FNHLId1) vaccine