



Aggressive Lymphomas - Crossing the Bridge between Translational Research and Clinical Treatment

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

Since the mid-1970's, the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen has remained the mainstay of treatment for advanced-stage aggressive lymphomas. Approximately 50% of patients treated with CHOP achieve complete remission and 35% enjoy long-term disease-free survival. Attempts to further improve on these results with second- and third-generation chemotherapeutic regimens have been largely unsuccessful.

Recent clinical and molecular studies have enabled us to revise the classification of non-Hodgkin lymphomas and to define more biologically distinct patient populations. For patients with advanced stages of diffuse large B-cell lymphoma (DLBCL), the most common subtype of aggressive non-Hodgkin lymphoma, a new antibody-based standard has now emerged. Novel drugs are being tested in the clinic, as well, that appear to promise better outcomes for patients with mantle cell lymphoma.

These and other important advances are the focus of this issue of *M. D. Anderson Clinical Perspectives: Lymphoma & Myeloma*. In his article on new treatment strategies for aggressive NHLs, Dr. Luis Fayad describes the latest treatment approaches for diffuse large B-cell lymphoma. In the US, DLBCL accounts for more than 30% of the 55,000 new cases of NHL diagnosed annually



Larry W. Kwak, MD, PhD

(Fayad L et al. *Expert Opin Pharmacother.* 2006;7:733-48.). The substitution of liposomal formulations of vincristine and doxorubicin in standard chemotherapeutic regimens to improve activity and reduce

toxicity, the use of immunotoxins, and the use of intense chemotherapeutic regimens are just some of the strategies that have yielded impressive results in both front-line and salvage treatment of patients with DLBCL.

In his case study, Dr. Jorge Romaguera discusses compelling new therapies for the treatment of mantle cell lymphoma (MCL). MCL is usually diagnosed at an advanced stage and carries a poor prognosis and short survival. Numerous clinical trials examining novel and more aggressive therapies are being conducted in hopes of obtaining better results for patients with this disease. These include more intensive combination chemotherapy regimens, monoclonal antibody therapy in conjunction with other treatments, high-dose chemotherapy followed by autologous or allogeneic stem cell transplantation, and newer targeted therapies such as proteo-

some inhibitors and compounds that inhibit pathways of resistance.

In the next issue of this newsletter, we will explore the latest research in Hodgkin lymphoma. In addition, we will provide a convenient business reply card to gain input from you on the newsletter and to learn if we can improve its usefulness to you. ■

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Continuing Medical Education

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

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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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Aggressive Non-Hodgkin's Lymphomas: New Treatment Strategies

by Luis E. Fayad, MD, Associate Professor of Medicine, Dept of Lymphoma and Myeloma, The University of Texas M. D. Anderson Cancer Center

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL) in the US. Until a few years ago, the standard of care was combination chemotherapy (CHOP). Recently, the addition of the monoclonal antibody rituximab (Rituxan[®]; Genentech; Biogen IDEC) has shown improvement in the overall response (ORR), complete response (CR), failure-free survival (FFS), and overall survival (OS) rates (Coiffier B et al. *NEJM*. 2002;346: 235-242.; Pfreundschuh M et al. *Lancet Oncol*. 2006;7:379-391.).

Despite those encouraging results, many patients will still succumb of their disease. At MDACC, we are trying new strategies to cure more patients, or salvage them at relapse.

In a prospective phase II trial, we replaced the standard vincristine for a liposomal vincristine (VSLI) in the R-CHOP regimen. Sixty-eight evaluable patients with aggressive lymphomas, mostly DLBCL, were treated with this combination chemotherapy. The ORR was 92.6% with 55 (80%) patients achieving a CR with no difference between younger and older patients. Overall survival was 94%, and 3-year PFS was of 84% (Rodriguez MA et al. *Blood, ASH Annual Meeting Abstracts*. 2005;106(11):A943.).

Prospective data was collected from 34 patients with diffuse large B-cell lymphoma treated with rituximab-hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone (R-HCVAD) alternating with rituximab-methotrexate-cytarabine (R-MA). In this series, patients had stage IV disease in 50% of the cases, Ki-67 >70% in 84%, Ki-67 of >90% in 62% of cases, elevated LDH in 65%, International prognostic index (IPI) score of high-intermediate (HI) and high-risk in 53% of patients. The overall response rate of this poor prognostic group was 100%, with a CR rate of 95%. With a median follow-up of 26 months, only 4 patients have failed,



Luis E. Fayad, MD

one died in remission while on treatment secondary to a pulmonary embolism. This patient had COPD and was 72 years-old. The other 3 patients relapsed; two of them are in a second complete remission after salvage treatment followed by high-dose chemotherapy with stem cell transplant and one patient died of progressive disease after relapse. The 4-year FFS and 4-year OS were 70% and 94%, respectively (Fayad L et al. *J Clin Oncol, ASCO Annual Meeting Proceedings*. 2007;25(18S):8058.).

With these promising results, we are currently exploring a phase II study for patients with high-risk factors as defined by an age-adjusted IPI of HI or high-risk will be randomized to R-CHOP standard of care, vs. R-HCVAD alternating with R-MA. The protocol is ongoing and we have 20 patients enrolled.

We have joined an international study for patients with DLBCL with poor prognosis features, as defined by HI or high-risk IPI, who achieve CR after receiving standard R-CHOP every 2 or 3 weeks (either at MDACC or with their local oncologist). If after 6 or 8 cycles, the patient achieves a CR, he/she will be eligible to participate in a randomized 2:1 placebo control maintenance study using a new drug, an oral PKC β inhibitor called enzastaurin (LY317615; Eli Lilly).

This drug was able to produce long-term stable disease in heavily treated DLBCL patients in a multicenter phase II study. Fifty-five patients (median age, 68 years) were enrolled. Patients had received a median number of two prior therapies (range, one to five); six patients relapsed

after high-dose therapy and autologous stem-cell transplantation. Twelve of 55 patients (22%) were free from progression (FFP) for two cycles, and eight patients remained FFP for four cycles (15%). Four patients (7%), including three complete responders and one patient with stable disease, continue to experience FFP 20+ to 50+ months after study entry. The study is exploring the probable benefit of this drug in the adjuvant setting after achieving CR with R-CHOP.

Another study, in collaboration with Memorial Sloan-Kettering Cancer Center, explores the use of the radioimmunotherapy agent Y⁹⁰-ibritumomab (Zevalin[®]; Biogen IDEC) as adjuvant treatment after achieving CR in patients 65 years or older, with an age-adjusted IPI (AAIPI) HI or high, treated with R-CHOP every 21 days. Preliminary results are encouraging in this elderly population. To date, 16 patients who received Zevalin in the study are free of relapse.

Another study for front-line DLBCL explores the replacement of doxorubicin with liposomal doxorubicin (Doxil[®]; OrthoBiotech). The trial is designed to evaluate the effectiveness of the treatment and, hopefully, a decrease in cardiac toxicity. Patients eligible for treatment include those with stage II disease or higher and those \geq 60 years of age.

We are also conducting a supportive care trial for second-line (refractory/recurrent) therapy of DLBCL patients who are candidates for autologous stem cell transplant (ASCT). Patients are treated with R-ICE or R-ESHAP with the addition of a platelet growth factor, AMG-531 (Amgen). This drug has been studied in patients with ITP with exciting results. We hope, AMG-531 will decrease the toxicity associated with the R-ICE and R-ESHAP regimens.

For relapsing patients who are not candidates for combination chemotherapy or

(continued on p. 6)



Lymphoma & Myeloma Clinical Trials at MDACC

NUMBER	PROTOCOL TITLE	TREATMENT	PHASE	PRINCIPAL INVESTIGATOR
INDOLENT LYMPHOMA - UNTREATED				
2008-0042	A Phase II study of Lenalidomide and Rituximab for Indolent Lymphoma	Immunomodulation + Monoclonal Antibody	II	Samaniego
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
2006-0260	CCOP Trial of Rituximab+Sargramostim in Newly Diagnosed Follicular B-cell Lymphoma	Monoclonal Antibody + Cytokine	II	McLaughlin
INDOLENT LYMPHOMA - PREVIOUSLY TREATED				
2008-0124	Velcade+Bendamustine and Rituximab in Subjects with Relapsed or Refractory Follicular Lymphoma	Proteasome Inhibitor + Alkylating Agent + Monoclonal Antibody	II	Fowler
2006-1092	SAR3419 in Relapsed/Refractory B-Cell NHL	Anti-CD19 Immunotoxin	I	Younes
2007-0906	A Phase 1b Study to Evaluate the Safety and Tolerability of AMG 655 in Combination with Bortezomib or Vorinostat in Subjects with Relapsed or Refractory Lymphoma	Trail Antibody	I	Younes
2008-0075	Phase I/II Study of Immunotherapy with Milatizimab in patients with NHL and CLL	Anti-CD74 Monoclonal Antibody	I/II	Samaniego
2008-0105	Ph I of SB1518 for Tx of Advanced Lymphoid Malignancies	HDAC Inhibitor	I	Younes
2008-0278	An Open-Label, Phase I Study of MLN8237, a Novel Aurora A Kinase Inhibitor, in Patients with Advanced Hematological Malignancies	Kinase Inhibitor	I	Fowler
2007-0408	A multi-center, open-label, Phase I study of single agent RO5045337 administered orally in patients with AML, ALL, CML in blast phase, or refractory CLL / SCLL	p53-MDM2 inhibitor	I	Andreef
2006-0313	Rituxan + GM-CSF for Relapsed Indolent Lymphoma	Monoclonal Antibody + Cytokine	II	McLaughlin
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 Liposomal Doxorubicin for Older > 60 Years with Untreated Aggressive B-Cell NHL	Chemotherapy + Monoclonal Antibody	II	Rodriguez
2005-0054	R-HCVAD Alternating with /R-Methotrexate-Cytarabine vs Std R-CHOP for Newly Diagnosed High-Risk Aggressive B-Cell NHL, < 60 Years	Monoclonal Antibody + Combination Chemotherapy	II	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				
2007-0578	Placebo-controlled Study of R-ICE Chemotherapy with and without SGN-40	Anti-CD40 Humanized Monoclonal Antibody	II	Fayad
2005-0579	Depsipeptide, a Histone Deacetylase Inhibitor, in Relapsed/Refractory MCL or DLCLNHL	HDAC Inhibitor	II	Fayad
2005-0461	CC-5013 and Rituxan in Relapsed MCL and Diffuse Large B-cell NHL	Immunomodulation/Thalidomide Analogue	I-II	Wang
2008-0105	Ph I of SB1518 for Tx of Advanced Lymphoid Malignancies	JAK2 Inhibitor	I	Younes
2007-0906	A Phase 1b Study to Evaluate the Safety and Tolerability of AMG 655 in Combination with Bortezomib or Vorinostat in Subjects with Relapsed or Refractory Lymphoma	Trail Ab	I	Younes
2006-1092	SAR3419 in Relapsed/Refractory B-Cell NHL	Anti-CD19 Immunotoxin	I	Younes
2008-0075	Phase I/II Study of Immunotherapy with Milatizimab in patients with NHL and CLL	Anti-CD74 Monoclonal Antibody	I/II	Samaniego
2004-0492	NHL - Chimeric Antibody-CNTO 328 (Anti IL-6)	Anti-IL6 Monoclonal Antibody	I	Kurzrock
MANTLE CELL LYMPHOMA - PREVIOUSLY TREATED				
2005-0461	CC-5013 and Rituxan in Relapsed MCL and Diffuse Large B-cell NHL	Immunomodulation/Thalidomide Analogue	I-II	Wang
2006-1092	SAR3419 in Relapsed/Refractory B-Cell NHL	Anti-CD19 Immunotoxin	I	Younes
2007-0906	A Phase 1b Study to Evaluate the Safety and Tolerability of AMG 655 in Combination with Bortezomib or Vorinostat in Subjects with Relapsed or Refractory Lymphoma	AMG 655	I	Younes
2008-0075	Phase I/II Study of Immunotherapy with Milatizimab in patients with NHL and CLL	Anti-CD74 Monoclonal Antibody	I/II	Samaniego
2008-0105	Ph I of SB1518 for Tx of Advanced Lymphoid Malignancies	JAK2 Inhibitor	I	Younes
2008-0278	An Open-Label, Phase I Study of MLN8237, a Novel Aurora A Kinase Inhibitor, in Patients with Advanced Hematological Malignancies	Kinase Inhibitor	I	Fowler
2004-0792	(NCI#6939) 17-AAG in Relapsed CD30+ ALCL, Relapsed MCL, and Relapsed Classical HL	Heat Shock Protein - 90 inhibitor	II	Younes
2005-0579	Depsipeptide, a Histone Deacetylase Inhibitor, in Relapsed/Refractory MCL or DLCLNHL	HDAC Inhibitor	II	Fayad
2004-0492	NHL - Chimeric Antibody-CNTO 328 (Anti IL-6)	Anti-IL6 Monoclonal Antibody	I	Kurzrock
PRIMARY CNS LYMPHOMA - PREVIOUSLY TREATED				
NABTC05-01	Rituximab and Temozolomide	Monoclonal Antibody + Alkylating Agent	II	Hsu
HODGKIN LYMPHOMA - UNTREATED				
2007-0144	Rituximab + ABVD vs ABVD for Advanced-Stage Classical HL w/ Poor Risk Features (IPS > 2)	Anti-CD20 Antibody	III	Younes



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

NUMBER	PROTOCOL TITLE	TREATMENT	PHASE	PRINCIPAL INVESTIGATOR
HODGKIN LYMPHOMA - PREVIOUSLY TREATED				
2007-0796	A Phase I Study of Every Other Week XmAb2513 to Evaluate the Safety, Tolerability, and Pharmacokinetics in Patients with HL or Anaplastic Large Cell Lymphoma	Anti-CD30 Fc Engineered Humanized Monoclonal Antibody	I	Younes
2008-0401	A Phase II Study of Oral Panobinostat in Adult Patients with Relapsed/Refractory Classical Hodgkin's Lymphoma after Failure of High-Dose Chemotherapy with Autologous Stem Cell Transfusion and a Gemcitabine- or Vinorelbine- or Vinblastine-Containing Treatment/Regimen	HDAC inhibitor	II	Younes
2008-0105	Ph I of SB1518 for Treatment of Advanced Lymphoid Malignancies	JAK2 Inhibitor	I	Younes
2007-0906	A Phase 1b Study to Evaluate the Safety and Tolerability of AMG 655 in Combination with	Trail Antibody	I	Younes
2004-0792	(NCI#6939) 17-AAG in Relapsed CD30+ ALCL, Relapsed MCL, and Relapsed Classical HL	Heat Shock Protein - 90 inhibitor	II	Younes
PERIPHERAL T-CELL LYMPHOMA - UNTREATED				
ID03-0004	Hyper CVID Doxil in Newly Diagnosed PTCL	Combination Chemotherapy	II	Pro
2005-0627	SGN-30 Monoclonal Antibody + CHOP for CD30+ Anaplastic Large Cell Lymphoma	Monoclonal Antibody	II	Pro
PERIPHERAL T-CELL LYMPHOMA - PREVIOUSLY TREATED				
2006-0986	Romidepsin (Depsipeptide, FK228) In Progressive or Relapsed PTCL Following Prior Systemic Therapy	HDAC Inhibitor	II	Pro
2008-0001	A Phase I Dose Escalation Study of Weekly SGN-35 Alone and in Combination with Gemcitabine in Patients with Relapsed/Refractory CD30-Positive Hematologic Malignancies	Anti-CD30 immunotoxin Antibody +/- Antimetabolite	I	Fanale
2004-0792	(NCI#6939) 17-AAG in Relapsed CD30+ ALCL, Relapsed MCL, and Relapsed Classical HL	Heat Shock Protein - 90 inhibitor	II	Younes
2008-0105	Ph I of SB1518 for Tx of Advanced Lymphoid Malignancies	JAK2 Inhibitor	I	Younes
2007-0906	A Phase 1b Study to Evaluate the Safety and Tolerability of AMG 655 in Combination with Bortezomib or Vorinostat in Subjects with Relapsed or Refractory Lymphoma	Trail Antibody	I	Younes
NOVEL THERAPIES FOR LYMPHOMA				
2004-0792	(NCI#6939) 17-AAG in Relapsed CD30+ ALCL, Relapsed MCL, and Relapsed Classical HL	Heat Shock Protein - 90 inhibitor	II	Younes
2005-0579	Depsipeptide, a Histone Deacetylase Inhibitor, in Relapsed/Refractory MCL or DLCLNHL	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
2007-0906	A Phase 1b Study to Evaluate the Safety and Tolerability of AMG 655 in Combination with Bortezomib or Vorinostat in Subjects with Relapsed or Refractory Lymphoma	Trail Antibody	I	Younes
2008-0075	Phase I/II Study of Immunotherapy with Milatizimab in patients with NHL and CLL	Anti-CD74 Monoclonal Antibody	I/II	Samaniego
2008-0105	Ph I of SB1518 for Treatment of Advanced Lymphoid Malignancies	JAK2 Inhibitor	I	Younes
SUPPORTIVE CARE FOR LYMPHOMA				
2005-0698	Zometa on Chemotherapy- Induced Bone Loss in Lymphoma Patients Receiving Chemo	Bisphosphate Derivative	N/A	Hagemester
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
NOVEL THERAPIES FOR MULTIPLE MYELOMA				
2008-0018	Carfilzomib with Len/Dex for Relapsed Multiple Myeloma	Proteasome Inhibitors/Immunomodulatory Agents	I	Wang
2008-0135	An Open-Label, Dose Escalation, Phase 1 Study of MLN4924, A Novel Inhibitor of Nedd8-Activating Enzyme, in Adult Patients with Lymphoma or Multiple Myeloma	NAE inhibitor	I	Shah
2005-0438	Oral Vorinostat (MK-0683) in Combination with Bortezomib in Patients with Advanced MM	HDAC inhibitor	I/II	Weber
2004-0492	NHL - Chimeric Antibody-CNTO 328 (Anti IL-6)	Anti-IL6 Monoclonal Antibody	I	Kurzrock
MYELOMA/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				
2007-0716	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Combination of CNTO 328 and Velcade Versus Velcade Alone in Subjects with Relapsed or Refractory MM	Anti-IL6 Monoclonal Antibody	II	Thomas
2007-0398	Carfilzomib in Patients with Relapsed and Refractory Multiple Myeloma	Proteasome Inhibitor	II	Wang
2007-0479	A Phase 2 Multicenter Study of CNTO 328 (Anti IL-6 Monoclonal Antibody) in Subjects with Relapsed or Refractory Multiple Myeloma	Anti IL-6 Monoclonal Antibody	II	Thomas
2007-0399	An Open-label, Single-arm, Phase 2 Study of Carfilzomib in Patients with Relapsed MM	Proteasome Inhibitor	II	Wang
SUPPORTIVE CARE FOR MYELOMA				
2006-0481	A Randomized, Double-Blind, Multicenter Study of Denosumab Compared w/Zoledronic Acid in the Treatment of Bone Mets in Subjects W/Advanced Cancer or MM	Monoclonal Antibody vs. Bisphosphate Derivative	III	Vadhan



(cont'd from p. 3) Aggressive NHL: New Treatment Strategies

who have already received an autologous stem cell transplant, we have different single agents.

We are looking at immunotoxins as well, such as CMC-544 (Wyeth), a humanized anti-CD22 bound to calicheamicin, with important activity in relapsing follicular lymphoma and in DLBCL. Preliminary data from a study with CMC-544 in combination with rituximab demonstrated a response rate of 59% in follicular lymphomas and close to 30% in recurrent DLBCL in patients with a median of 4 prior treatments.

We are conducting a single center, open label, phase I/II study with lenalidomide (Revlimid®; Celgene) in combination with

rituximab, in patients with up to 4 prior treatments with DLBCL. Lenalidomide is an immunomodulatory drug known to produce durable clinical responses in multiple myeloma, and in 5q- myelodysplastic syndromes. Single agent study with this drug has shown clinical activity in DLBCL.

Other compounds being investigated are HDAC inhibitors, and depsipeptide given by intravenous administration. This drug has shown activity in cutaneous T-cell lymphomas. MBC0106, an oral HDAC inhibitor, has shown clinical activity in patients with Hodgkin, DLBCL and follicular lymphoma.

The inhibitor of mammalian target of rapamycin (mTOR) showed clinical activ-

ity in mantle cell lymphomas, and is now being explored in DLBCL, as well.

Future studies will also incorporate correlative studies with gene profiling, and anti-idiotypic vaccines in the adjuvant front-line setting.

In summary, we are looking to improve the outcomes of patients with DLBCL, who come to us with untreated disease. In addition, we are providing new, exciting therapies for relapsing patients.

For the most current list of clinical trials at the *Department of Lymphoma and Myeloma*, turn to page 4 of this newsletter or log onto our department website at www.mdanderson.org/departments/lymphmyeloma/. ■

Case Study: Novel Therapies in Mantle Cell Lymphoma

by Jorge E. Romaguera, MD, Professor of Medicine, Dept of Lymphoma and Myeloma, The University of Texas M. D. Anderson Cancer Center

A 62 year-old asymptomatic healthy male presented to the physician with a history of an enlarged lymph node in the neck for more than 2 weeks. Physical examination revealed generalized adenopathy and splenomegaly. Laboratory tests revealed that his white cell count was elevated. His serum LDH was above normal and his β_2 microglobulin was 3.4 mg/L. A lymph node biopsy revealed mantle cell lymphoma.



Jorge E. Romaguera, MD

Discussion

Mantle cell lymphoma (MCL) has the poorest prognosis among malignant lymphomas, with a failure-free survival and survival of 1 and 3-4 years, respectively, after treatment with doxorubicin-containing chemotherapy regimens.

Untreated MCL

Recent introduction of the monoclonal antibody rituximab (Rituxan®; Genentech; Biogen-IDEC), as well as more intense chemotherapy regimens with or without stem cell rescue, have improved the outcomes.

Table 1 shows selected studies in mantle cell lymphoma.

Nucleoside analogs such as fludarabine (Fludara®; Bayer) and 2-CDA produce complete remission rates of 29-40% lasting 14-

24 months. Newer approaches include the addition of the proteasome inhibitor bortezomib (B; Velcade®, Millennium), which has shown 40% overall response (OR) in salvage therapy (Fisher RI et al. *J Clin Oncol.* 2006;30:4867.). Bortezomib-containing frontline chemotherapy regimens currently under investigation include:

- B + rituximab + CHOP (Leonard JP et al. *ASH.* 2005;A491.)
- B + rituximab + DA EPOCH (Wilson W et al. *Nat. Cancer Institute*)

- B + rituximab + hyperCVAD (Khal B et al. *Wisconsin*)

- B + rituximab + hyperCVAD + methotrexate/ara-C (soon to start. Romaguera JE and Goy A. M. D. *Anderson Cancer Center and Hackensack UMC*)

New radiolabeled monoclonal antibodies exploit the radiosensitivity of MCL. ¹³¹I-tositumomab produced an 87% overall OR and a 50% CR when given as frontline therapy (Zelenetz et al. *Ann Oncol.* 2005;A64.).

Previously Treated MCL

Rituximab given concomitantly and as maintenance improves response rates and response duration after combination chemotherapy (Forspointner et al. *Blood.* 2006; 108:4003.). The radiolabeled monoclonal antibody 90Y-ibritumomab produced 41% OR in pre-treated patients (Younes A et al. *Ann Oncol.* 2005;A201.). Exciting new

(continued on back cover)



Continuing Medical Education Evaluation & Post-Test

Post-Test [Course Code: MEMV1070, December 2008]

Read each question and circle the letter next to the correct answer. There is only one correct answer per question. A score of 80% must be obtained to receive *AMA PRA Category 1 credit™*. Once reviewed, you will receive a certificate documenting your participation in this CME activity.

- In the US, DLBCL accounts for more than ___% of the 55,000 new cases of NHL diagnosed annually:*
 - 30%
 - 50%
 - 75%
 - 90%
- In patients with untreated mantle cell lymphoma, nucleoside analogues produce complete remission rates of __%, lasting ___ months.*
 - 70-90%, 49-76 months
 - 51-68%, 38-55 months
 - 49-57%, 28-34 months
 - 29-40%, 14-24 months
- Which type of lymphoma has the poorest prognosis of all malignant lymphomas?*
 - Hodgkin lymphoma
 - diffuse, large B-cell lymphoma
 - mantle cell lymphoma
 - follicular lymphoma
- Which of the following agents are in development for aggressive non-Hodgkin lymphoma?*
 - HDAC inhibitors
 - mTOR inhibitors
 - immunomodulatory agents
 - PKC inhibitors
 - monoclonal antibodies
 - all of the above
 - a and d
- In an MDACC study of 34 poor-prognoses patients with diffuse large B-cell lymphoma, treated with R-HCVAD alternating with R-MA, the 4-year FFS and 4-year OS were:*
 - disappointing - only 10% and 23%, respectively
 - comparable to the current standard of care in this population - 50% and 55%, respectively
 - good - 65% and 75%, respectively
 - very promising - 70% and 94%, respectively
 - none of the above

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
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(cont'd from p. 6) **Case Study: Mantle Cell Lymphoma**

drugs are being tested which inhibit pathways of resistance, including temsirolimus (CCI-779; Wyeth), an mTOR inhibitor, which achieves a 38% OR (Witzig TE et al. *J Clin Oncol.* 2005;23:5347.). Other drugs being tested include second generation proteasome inhibitors, Akt inhibitors, histone deacetylase inhibitors, bcl-2 inhibitors, protein kinase C inhibitors, cyclin D kinase inhibitors such as flavopiridol (Alvocidib; Sanofi-Aventis), inhibitors of angiogenesis, and small inhibitory RNA molecules. Combination, such as bortezomib with rituximab and dexamethasone, have produced responses in 7/8 patients (Drach et al. ASCO. 2006;A7532.).

Immunomodulators such as thalidomide (Thalomid®; Celgene), in combination with rituximab, produce an 81% response rate (Kaufmann H et al. *Blood.* 2004;104:2269.). A more potent immunomodulator, Revlimid is being tested in combination with rituximab at M. D. Anderson Cancer Center with exciting preliminary results. Several anti-idiotypic (Neelapu SS et al. *Nat. Med.* 2005;11:986.) and dendritic-based (Munger CM et al. *Int. J Oncol.* 2006;28:1337.) vaccines are currently being tested in patients with MCL.

The best chance for cure, however, will be after consolidation of a response with high

Table 1. Selected Mantle Cell Lymphoma Studies

Regimen	(Author)	(n)	SCT	% CR	Outcome	F/U
HCVAD Mtx/Ara-C	(Khour ¹)	(33)	Cy/TBI	100	5-yr DFS 43%	49 months
RCHOP	(Lenz ²)	(58)	N	34	2-yr PFS 30%	18 months
REPOCH-Id	(Neelapu ³)	(25)	N	92	4-yr EFS 19%	48 months
RHCVD/ R-Mtx/AraC ≤ 65 yrs	(Romaguera ⁴)	(97) (65)	N	87 89	5-yr FFS 50% 61%	57 months ^a
Modified RHCVD +R	(Kahl ⁵)	(22)	N	64	3-yr PFS 50%	37 months
RCHOP ≤ 65 yrs	(Dreyling ⁶)	(32)	Cy/TBI	81	2-yr PFS 51%	25 months
Chemo ≤ 60 yrs	(Gianni ⁷)	(28)	Cy/AraC Mel/MiMe	100	4-yr EFS 60%	48 months ^b
R-HCVAD R-Mtx/AraC < 65 yrs	(Ritchie ⁸)	(13)	Bu/Mel	92	3-yr EFS 92%	36 months
R-DHAP	(DeGuibert ⁹)	(24)	BEAM	92	3-yr PFS 70%	NA

^aUpdate. JE Romaguera ■ ^bPersonal communication, Dr. C Tarella.

Bu/Mel - Busulfan/melphalan ■ CR: complete remission ■ Cy/AraC/Mel/MiMe: cyclophosphamide, cytarabine, melphalan, mitoxantrone, melphalan ■ Cy/TBI: cyclophosphamide/total body irradiation ■ EFS: event-free survival ■ DFS: disease-free survival ■ PFS: progression-free survival ■ R: rituximab ■ RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone ■ RDHAP: rituximab, dexamethasone, cytarabine, cisplatin ■ REPOCH-Id: rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin, anti-idiotypic antibody ■ RHCVD: rituximab, cyclophosphamide, doxorubicin, vincristine, dexamethasone ■ R-Mtx/AraC: rituximab, methotrexate, cytarabine ■ SCT: stem cell transplant ■ RDHAP: rituximab, dexamethasone, cytarabine, cisplatin ■ REPOCH-Id: rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin, anti-idiotypic antibody

¹Khour¹ IF et al. *J Clin Oncol.* 1998;12:3803-9. ■ ²Lenz G et al. *J Clin Oncol.* 2005;23(9):1984-92. ■ ³Neelapu SS et al. *Nat Med.* 2005;11(9):986-91. ■ ⁴Romaguera JE et al. *J Clin Oncol.* 2005;23(28):7013-23. ■ ⁵Kahl BS et al. *Ann Oncol.* 2006;17(9):1418-23. ■ ⁶Dreyling M et al. *Blood.* 2005;105(7):2677-84. ■ ⁷Gianni AM et al. *Blood.* 2003;102(2):749-55. ■ ⁸Ritchie DS et al. *Ann Hematol.* 2007;86(2):101-5. ■ ⁹De Guibert S et al. *Haematologica.* 2006;91(3):425-6.

doses of chemotherapy. Recent investigations center around combinations of radioimmunotherapy with high doses of chemotherapy as part of the conditioning regimen given prior to an autologous stem cell transplant (Gopal A et al. *Blood.* 2002;99.; Weigert et al. ASCO. 2006;A7533.), and an exploitation of the known graft vs lymphoma effect of donor stem cell infusions in MCL (Khour

I et al. *J Clin Oncol.* 2003;21.). A reduced intensity conditioning regimen decreases the immediate mortality associated with it, but there is controversy about long term graft vs host toxicity.

In conclusion, the coming years promise to bring a true potential for improved outcome and cure for this dreaded disease. ■