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Hematologic Oncology™ UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

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INTERVIEWS

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CME Certified

Hematologic Oncology Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Over 45 pharmaceutical agents with more than 55 distinct FDA-approved indications are currently available for the management of hematologic cancer. This extensive armamentarium of treatment options poses a challenge to clinicians who must maintain up-to-date knowledge of optimal therapeutic algorithms for diverse tumor types. To bridge the gap between research and patient care, this issue of *Hematologic Oncology Update* features one-on-one discussions with leading oncology investigators. By providing information on the latest research developments in the context of expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of state-of-the-art clinical management strategies to facilitate optimal patient care.

LEARNING OBJECTIVES

- Utilize prognostic markers to determine the timing and selection of treatment for chronic lymphocytic leukemia (CLL).
- Develop an algorithm for the evaluation, classification and treatment of myelodysplastic syndrome (MDS).
- Counsel patients with acute myeloid leukemia (AML) about the risks and benefits of innovative, evidence-based therapeutic approaches.
- Formulate up-to-date induction, consolidation and maintenance strategies for acute promyelocytic leukemia (APL).
- Apply emerging data with novel agents and regimens to the care of patients with newly diagnosed or relapsed/refractory indolent or aggressive non-Hodgkin lymphomas (NHL).
- Integrate currently available therapeutic strategies into the management of cutaneous T-cell lymphoma.
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate.

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FACULTY — **Dr Tallman** had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Rai** — Honoraria: Bayer Pharmaceuticals Corporation, Celgene Corporation, Cephalon Inc, Genentech BioOncology, GlaxoSmithKline. **Dr Moskowitz** — Advisory Committee: Amgen Inc, GlaxoSmithKline; Clinical Trial Support: Celgene Corporation, Eli Lilly and Company, Genentech BioOncology. **Dr Rosen** — Clinical Trial Grants: Berlex Inc, Celgene Corporation, Wyeth; Consulting Agreements: Abbott Laboratories, Allos Therapeutics, Berlex Inc, BioCryst Pharmaceuticals Inc, Celgene Corporation, CT International, Eli Lilly and Company, Genentech BioOncology, Genta Inc, Ligand Pharmaceuticals, Pharmion Corporation, Sigma-Tau Pharmaceuticals Inc, SuperGen Inc, Therakos Inc, Wyeth; Honoraria: Celgene Corporation, Genentech BioOncology, Ligand Pharmaceuticals; Speakers Bureau: Merck and Company Inc.

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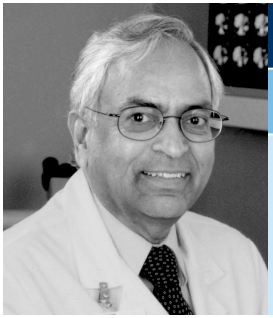

INTERVIEW

Kanti R Rai, MD

Dr Rai is Chief of the Division of Hematology-Oncology at Long Island Jewish Medical Center in New Hyde Park, New York and Joel Finkelstein Cancer Foundation Professor of Medicine at Albert Einstein College of Medicine in Bronx, New York.

Tracks 1-14

Select Excerpts from the Interview

Track 7

DR LOVE: Would you review the Intergroup study CALGB-10404 evaluating fludarabine/cyclophosphamide/rituximab (FCR) versus fludarabine/rituximab (FR) → lenalidomide versus FR?

DR RAI: It's a randomized Phase II trial for patients with newly diagnosed, previously untreated chronic lymphocytic leukemia (CLL) who need to start systemic therapy. It is an important trial because both FCR and FR are effec-

tive, but we do not know whether one is superior in terms of toxicities, remission rates and long-term duration of response.

These two combinations have not yet been tested head to head, but in viewing the data for each one, I believe that FR is less myelotoxic than FCR. The relative proportion of complete remissions, however, is dramatically greater with FCR, with approximately a 70 percent complete response rate according to the MD Anderson data (Tam 2008) compared to about 47 percent with FR in a multi-institutional trial, CALGB-9712 (Byrd 2003).

The data from a prospectively randomized study from Germany, presented at ASH 2008, in which FCR was compared to fludarabine/cyclophosphamide (FC), demonstrated that FCR was significantly superior in remission induction. However, the percentage of complete responses with FCR in this multi-institutional trial was approximately 50 percent (Hallek 2008; [1.1]).

1.1

Phase III Randomized Trial of Fludarabine/Cyclophosphamide/ Rituximab (FCR) versus Fludarabine/Cyclophosphamide (FC) as First-Line Therapy for Advanced CLL

Efficacy	FCR (n = 390)	FC (n = 371)	*p*-value
Overall response rate	95.0%	88.0%	0.001
Complete response rate	52.0%	27.0%	<0.0001
	(n = 400)	(n = 387)	
Two-year PFS	76.6%	62.3%	<0.0001
Two-year OS	91.0%	88.0%	0.18

PFS = progression-free survival; OS = overall survival

"Treatment with FCR chemoimmunotherapy improves response rates and PFS when compared to the FC chemotherapy. FCR caused more neutropenia/leukopenia without increasing the incidence of severe infections.

These results suggest that FCR chemoimmunotherapy might become the new standard first-line treatment for physically fit CLL patients."

SOURCE: Hallek M et al. *Proc ASH* 2008;**Abstract 325**.

Tracks 9-10

DR LOVE: What are your thoughts about the role of bendamustine in the treatment of CLL?

DR RAI: Bendamustine is an important entry in the armamentarium for CLL. Without question, bendamustine emerged as significantly superior to chlorambucil as first-line therapy for CLL (Knauf 2008; [1.2]).

DR LOVE: How do you see bendamustine being used in practice?

DR RAI: Some clinicians have started to use bendamustine and rituximab as front-line therapy. Other clinicians have reserved it for use after a fludarabine-containing regimen when more treatment is necessary. I believe its use is justifiable in both settings. However, we don't have enough long-term experience with bendamustine.

1.2

Bendamustine versus Chlorambucil as First-Line Treatment for B-Cell Chronic Lymphocytic Leukemia: An Updated Analysis from an International Phase III Study

	Bendamustine (n = 162)	Chlorambucil (n = 157)	*p*-value
ORR	67%	30%	<0.0001
Median PFS	21.5 months	8.3 months	<0.0001
OS	Not reported	Not reported	Nonsignificant

ORR = overall response rate; PFS = progression-free survival; OS = overall survival

"This study has shown that bendamustine offers significantly greater efficacy than chlorambucil, with manageable toxicity, and should be considered as first-line chemotherapy for patients with advanced B-CLL."

SOURCE: Knauf WU et al. *Proc ASH* 2008;**Abstract 2091**.

Track 11

DR LOVE: Can you review what we know about ofatumumab?

DR RAI: Ofatumumab is a novel monoclonal antibody generating a high degree of excitement and interest. It is an anti-CD20 monoclonal antibody, but it targets a slightly different epitope of CD20 than rituximab. It also differs from rituximab in that it is a completely humanized anti-CD20 monoclonal antibody, whereas rituximab is a chimeric anti-CD20 monoclonal antibody.

The data presented at ASH 2008 were interesting. The trial included a large sample of patients with CLL who were divided into two broad categories. Those patients for whom both fludarabine-based combinations and alemtuzumab had failed were considered to have double-refractory CLL. About half of the patients belonged to the double-refractory category, and this group had a poor prognosis (Osterborg 2008).

DR LOVE: Was their disease also refractory to rituximab?

DR RAI: Patients were not certified as having rituximab-refractory disease, but those with disease that had been refractory to or relapsed after fludarabine might also have received rituximab in combination with fludarabine. Being previously exposed to rituximab, however, was acceptable.

The other category included patients with bulky lymphadenopathy for whom alemtuzumab would be contraindicated and who therefore simply had fluda-

rabine-refractory disease (Osterborg 2008). In both groups, ofatumumab demonstrated a noticeable, high level of activity (Osterborg 2008; [1.3]). The upshot of this trial was that ofatumumab should be further investigated. Another anti-CD20 molecule available for clinical use would be most welcome. ■

1.3

Ofatumumab for Fludarabine- and Alemtuzumab-Refractory or Bulky Fludarabine-Refractory CLL

	Fludarabine- and alemtuzumab-refractory CLL (n = 59)	Bulky fludarabine-refractory CLL (n = 79)
Received prior rituximab	59%	54%
Overall response rate	51%	44%
Complete response rate	0%	1%
Partial response rate	51%	43%
Stable disease rate	39%	43%
Median overall survival	13.7 months	15.4 months
Median time to next CLL therapy	9.0 months	7.9 months

"These results demonstrate the effectiveness of ofatumumab in patients with double-refractory CLL or bulky fludarabine-refractory disease. Ofatumumab was well tolerated with no unexpected toxicities. This monoclonal antibody potentially represents an active treatment option with clinical benefit for patients with poor prognosis who have exhausted standard treatment options."

SOURCE: Osterborg A et al. *Proc ASH* 2008;**Abstract 328**.

SELECT PUBLICATIONS

Byrd JC et al. **Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: Results from Cancer and Leukemia Group B 9712 (CALGB 9712).** *Blood* 2003;101(1):6-14.

Cheson BD, Rummel MJ. **Bendamustine: Rebirth of an old drug.** *J Clin Oncol* 2009;27(9):1492-501.

Coiffier B et al. **Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: A phase 1-2 study.** *Blood* 2008;111(3):1094-100.

Hallek M et al. **Immunochemotherapy with fludarabine (F), cyclophosphamide (C), rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL).** *Proc ASH* 2008;**Abstract 325**.

Knauf WU et al. **Bendamustine versus chlorambucil as first-line treatment in B cell chronic lymphocytic leukemia: An updated analysis from an international phase III study.** *Proc ASH* 2008;**Abstract 2091**.

Osterborg A et al. **Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL refractory to both fludarabine and alemtuzumab or bulky fludarabine-refractory disease: Results from the planned interim analysis of an international pivotal trial.** *Proc ASH* 2008;**Abstract 328**.

Tam CS et al. **Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia.** *Blood* 2008;112(4):975-80.

INTERVIEW

Martin S Tallman, MD

Dr Tallman is Professor of Medicine at the Northwestern University Feinberg School of Medicine at Robert H Lurie Comprehensive Cancer Center in Chicago, Illinois.

Tracks 1-22

Track 1 **Case discussion:** A 48-year-old woman with myelodysplastic syndrome (MDS) and chromosome 5q deletion

Track 2 Counseling patients after the diagnosis of MDS

Track 3 Treatment algorithm for MDS

Track 4 Therapeutic agents available for patients with MDS who are not candidates for transplant

Track 5 Mechanism of action for lenalidomide in MDS

Track 6 Considerations for allotransplant in patients with severe cytopenias without 5q deletions

Track 7 Decitabine versus azacitidine for MDS without 5q deletion

Track 8 Unresolved clinical issues regarding the use of hypomethylating agents

Track 9 Typical treatment course for a patient with MDS receiving lenalidomide

Track 10 **Case discussion:** A 38-year-old man who has newly diagnosed acute myeloid leukemia (AML) with translocation 8;21

Track 11 Prognostic factors for AML

Track 12 Addition of gemtuzumab to induction chemotherapy for AML

Track 13 ECOG-E1900: Induction therapy with two different doses of daunorubicin for newly diagnosed AML

Track 14 Novel targeted agents being evaluated for AML

Track 15 Clofarabine for older patients with previously untreated AML

Track 16 Clinical experience with clofarabine in hematologic cancer

Track 17 Clinical trials of maintenance decitabine for AML

Track 18 **Case discussion**: A 33-year-old man diagnosed with acute promyelocytic leukemia (APL)

Track 19 Tolerability of all-trans retinoic acid (ATRA)

Track 20 Arsenic trioxide alone or in combination with ATRA for APL

Track 21 Potential mechanisms of action of arsenic trioxide

Track 22 **Case discussion:** A 48-year-old woman with newly diagnosed, intermediate-risk AML

Select Excerpts from the Interview

Tracks 3-4, 7

DR LOVE: What is your treatment algorithm for myelodysplastic syndrome (MDS)?

DR TALLMAN: The only curative strategy for MDS is allogeneic hematopoietic stem cell transplantation, but unfortunately it tends to be a disease in older patients who are often not candidates for transplant. The mortality rate associated with transplant may be as high as 20 or 25 percent for older patients, and until four or five years ago the alternatives to transplant were limited. Most patients were treated with supportive care, which was relatively unsatisfying for patients and physicians alike.

Since 2004 three drugs have been approved for patients with MDS, and we're enthusiastic about these agents. Two are hypomethylating agents, 5-azacitidine and decitabine, and the third drug, lenalidomide, is an immunomodulatory agent.

The good news is that these drugs are efficacious for some patients. They can improve blood counts, and they can render some patients transfusion independent. The not-so-good news is that these are not curative and they don't work for all patients. Still, we finally have some tools to treat an otherwise generally untreatable, incurable hematologic disorder.

We tend to consider the hypomethylating agents for older adults who may not be candidates for transplant or for patients who are transplant eligible but have no suitable donors. In some patients, the hypomethylating agents improve peripheral blood counts and marrow function, and some patients experience complete remissions.

Lenalidomide, however, is particularly effective for patients with a specific disorder — the 5q-minus syndrome. For these patients, the drug not only improves blood counts, but it also has a high complete remission rate in the bone marrow by morphology in addition to a high complete chromosome remission rate. In fact, in the majority of such patients the chromosome can be eradicated.

DR LOVE: When selecting a hypomethylating agent, how do you decide between azacitidine and decitabine?

DR TALLMAN: It hasn't been determined which one is superior for treating MDS, and I don't have a strong preference. Data suggest a survival advantage with 5-azacitidine. However, the studies have been difficult to conduct and the results are subject to interpretation.

I believe that we have more experience with 5-azacitidine. The CALGB conducted an often-quoted prospective, randomized trial comparing 5-azacitidine to best supportive care (CALGB-9221), which suggested that it improved time to progression to acute leukemia (Silverman 2002). I'm not aware of data demonstrating a survival advantage with decitabine.

We also have data that demonstrate a response rate with decitabine for patients after azacitidine failure (Borthakur 2008; [2.1]). However, I'm not aware of data on the response rate with azacitidine after decitabine failure. Therefore, at my institution we tend to start with 5-azacitidine.

2.1

Activity of Decitabine in Patients with Myelodysplastic Syndrome Previously Treated with Azacitidine

"Fourteen patients with MDS post-azacitidine failure/lack of response/intolerance were treated with decitabine. Overall three patients achieved a complete remission, and one patient had hematologic improvement, for an overall response rate of 28%. Of the responders, one stopped prior 5-azacitidine owing to disease progression, two for no response and one for severe skin toxicity. Grade 3-4 drug related side-effects were minimal.... We conclude that clinically significant responses with decitabine can be seen in patients post-azacitidine failure without significant toxicity."

SOURCE: Borthakur G et al. *Leuk Lymphoma* 2008;49(4):690-5.

Tracks 12-13

DR LOVE: Can you review where we are currently in the treatment of acute myeloid leukemia (AML)?

DR TALLMAN: During the past 30 to 35 years we had not seen any changes in induction chemotherapy for AML. However, two recent studies suggest promising new agents. First, a large, randomized study from the Medical Research Council in the United Kingdom showed that the addition of gemtuzumab ozogamicin to induction chemotherapy improved disease-free survival for patients with favorable- and intermediate-prognosis karyotypes (Burnett 2006).

The other trial, ECOG-E1900, examined dose intensification of daunorubicin. Although the current approved dose is 45 mg/m^2, many investigators and physicians use between 45 and 60 mg/m^2. In this large, randomized trial, 45 mg/m^2 was compared to 90 mg/m^2 for patients younger than age 61 with newly diagnosed disease.

Previous studies published by the CALGB had suggested that the higher dose resulted in a higher remission rate without excessive cardiac toxicity (Kolitz 2004). In November 2008 the National Cancer Institute revealed the results of E1900 in a press release (NCI 2008). The study was stopped early because the 90-mg/m^2 dose resulted in a higher remission rate and improved overall survival. Patients with favorable-risk cytogenetics fared particularly well.

Track 15

DR LOVE: What's the role of clofarabine in treating AML?

DR TALLMAN: An important abstract was presented at ASH 2008 that evaluated the role of clofarabine for previously untreated older adults with AML who were unfit for intensive chemotherapy (Erba 2008). The data showed that approximately 40 percent of the patients achieved remission or near remission. Even patients with complex karyotypes (three or more abnormalities) had significant remission rates.

The Eastern Cooperative Oncology Group is about to embark on a new study for older patients with previously untreated AML that will compare induction with single-agent clofarabine to standard daunorubicin/cytarabine therapy in a randomized fashion. In a second randomization patients will be consolidated, and those whose disease remains in remission will then be randomly assigned to maintenance therapy with decitabine versus observation.

Track 20

DR LOVE: How is arsenic being used for the treatment of acute promyelocytic leukemia (APL)?

DR TALLMAN: Arsenic trioxide is an old drug that has been revisited in the treatment of APL. I believe that it's the single most active drug in APL — more active than all-trans retinoic acid (ATRA) — and it's the treatment of choice for patients with relapsed APL. It induces remission in 85 to 90 percent of patients with relapsed disease, and essentially no primary resistance to arsenic is evident.

The early studies combined ATRA, arsenic and chemotherapy. Then several other studies combined ATRA/arsenic and minimal chemotherapy. However, the exciting data came from several sources in which arsenic was combined with ATRA without chemotherapy, and finally several more studies used arsenic alone as induction therapy. Indeed, a number of patients with low-risk disease appear to be cured with single-agent arsenic.

Many investigators and physicians are now using the combination of ATRA/arsenic as initial therapy for APL, which has allowed us to minimize chemotherapy. In fact, this is the only type of AML in which we can obtain cures using no chemotherapy at all.

This combination is emerging as an effective, acceptable strategy for newly diagnosed APL. It is not yet considered standard therapy, but I believe it will be soon. ■

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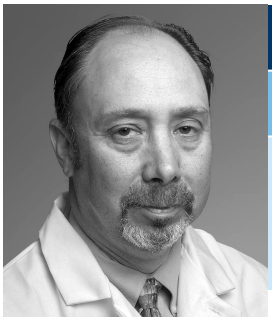
Burnett AK et al. **The addition of gemtuzumab ozogamicin to induction chemotherapy for AML improves disease free survival without extra toxicity: Preliminary analysis of 1115 patients in the MRC AML15 trial.** ASH 2006;**Abstract 13**.

Erba HP et al. **Phase II study of single agent clofarabine in previously untreated older adult patients with acute myelogenous leukemia (AML) unlikely to benefit from standard induction chemotherapy.** *Proc ASH* 2008;**Abstract 558**.

Kolitz JE et al. **Dose escalation studies of cytarabine, daunorubicin, and etoposide with and without multidrug resistance modulation with PSC-833 in untreated adults with acute myeloid leukemia younger than 60 years: Final induction results of Cancer and Leukemia Group B Study 9621.** *J Clin Oncol* 2004;22(21):4290-301.

Silverman LR et al. **Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the Cancer and Leukemia Group B.** *J Clin Oncol* 2002;20(10):2429-40.



INTERVIEW

Craig Moskowitz, MD

Dr Moskowitz is Clinical Director of the Division of Hematologic Oncology and Member of the Lymphoma Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-7

Track 1 **Case discussion:** A 49-year-old woman with p53-positive diffuse large B-cell lymphoma (DLBCL) who was initially treated with R-CHOP-14

Track 2 Clinical use of R-CHOP-14 for DLBCL

Track 3 Tolerability of R-CHOP-14 versus R-CHOP-21

Track 4 **Case discussion:** A 62-year-old man with mantle-cell lymphoma (MCL) who was treated with R-CHOP-14 and R-ICE

Track 5 **Case discussion:** A 70-year-old man with diffuse, nonbulky follicular lymphoma that progressed through several therapies and went into remission after bendamustine/rituximab

Track 6 Role of bendamustine in follicular lymphoma

Track 7 Single-agent bortezomib for patients with chemotherapy-refractory mantle-cell or follicular lymphoma

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: What is your experience with patient tolerability of R-CHOP-14 versus R-CHOP-21?

DR MOSKOWITZ: Younger patients tolerate it well. I don't administer it to older patients. We are awaiting further safety and efficacy results from the GELA (NCT00144755) 600-patient study evaluating R-CHOP-14 versus R-CHOP-21 (3.1). It will probably be reported at the 2010 ASH meeting or the 2011 Lugano session.

Track 7

DR LOVE: Your group recently published a paper in the *British Journal of Haematology* on bortezomib for patients with chemotherapy-refractory mantle-cell lymphoma (O'Connor 2009; [3.2]). Would you summarize your experience with bortezomib for patients with mantle-cell or follicular lymphoma?

DR MOSKOWITZ: We've conducted a series of studies with bortezomib in mantle-cell lymphoma and follicular lymphoma — the initial Phase I study and then a study evaluating lymphoma subtypes at standard bortezomib dosing (Orlowski 2002; O'Connor 2005).

A study on rituximab/cyclophosphamide/bortezomib/prednisone is ongoing — a drug-substitution study, eliminating vincristine and adding bortezomib on a day-one and day-eight schedule (NCT00859443; Gerecitano 2008). We also have a prospective comparison of weekly bortezomib versus bortezomib administered in a standard fashion (O'Connor 2007).

Bortezomib has been approved as a single agent for mantle-cell lymphoma. It has good features and bad features, but what I like best is that if it doesn't work, you know immediately. In patients with mantle-cell lymphoma that responds to bortezomib, the responses occur by the first restaging, which is usually performed after six to eight weeks.

If you can make it past the first restaging, then some patients can receive bortezomib for up to one year. It's a difficult schedule, however, so only approximately one third of patients pass the first restaging.

When treating follicular lymphoma, you do not want to stop bortezomib prematurely because most of the responses are delayed. Some patients respond after having stable disease with bortezomib for two to four months.

DR LOVE: What's the overall activity in follicular lymphoma?

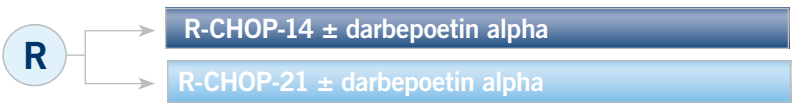
DR MOSKOWITZ: These studies are ongoing. For us it's close to 40 percent, but we're administering it as combination therapy. The key factor to remember with bortezomib is that more side effects occur than with rituximab.

Patients exhibit neuropathy, but the major side effect in my experience is fatigue. Patients just "have had enough of it" after a while because the dose administered to patients with lymphoma is much higher than the dose administered to patients with myeloma. ■

3.1

A Phase III, Multicenter, Randomized, Open-Label Trial of Dose-Dense versus Conventionally Scheduled R-CHOP

Protocol IDs: LNH03-6B, NCT00144755 Target Accrual: 600 (Closed)



Select Eligibility Criteria

- 66 to 80 years old; ECOG PS 0 to 2
- Previously untreated CD20+ diffuse large B-cell lymphoma with age-adjusted IPI = 1, 2 or 3

Trial Lead Organization

Groupe d'Etudes de Lymphomes de L'Adulte (GELA)

SOURCE: NCI Physician Data Query, June 2009.

3.2

Efficacy of Single-Agent Bortezomib for Patients with Chemotherapy-Refractory or Relapsed Mantle-Cell Lymphoma (MCL)

	Relapsed (n = 23)	Refractory (n = 16)	*p*-value
Overall response rate, %	50	43	0.74
Progression-free survival (PFS), months	5.6	3.8	0.81

"Responding patients experienced a PFS from bortezomib that was similar to their line of prior therapy (7.8 months vs 8.4 months, respectively). The data showed similar responses in patients with relapsed and refractory disease as well as remission durations similar to prior therapy, suggesting that there may be little cross-resistance with other conventional cytotoxic agents.

Importantly, these data suggest that MCL patients with refractory or poorly responsive disease may still derive meaningful clinical benefit from treatment with bortezomib."

SOURCE: O'Connor OA et al. *Br J Haematol* 2009;145(1):34–9.

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Feugier P et al. **Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d'Etude des Lymphomes de l'Adulte.** *J Clin Oncol* 2005;23(18):4117–26.

Gerecitano JF et al. **A phase I study evaluating two dosing schedules of bortezomib (Bor) with rituximab (R), cyclophosphamide (C) and prednisone (P) in patients with relapsed/refractory indolent and mantle cell lymphomas.** *Proc ASCO* 2008;**Abstract 8512**.

Habermann TM et al. **Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma.** *J Clin Oncol* 2006;24(19):3121–7.

O'Connor OA et al. **Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following treatment with single agent bortezomib: Results of a multicentre Phase 2 clinical trial.** *Br J Haematol* 2009;145(1):34–9.

O'Connor O et al. **Schedule of bortezomib administration may be an important determinant of single-agent activity in patients with relapsed or refractory follicular (FL) lymphoma and mantle cell lymphoma (MCL).** *Proc ASCO* 2007;**Abstract 8051**.

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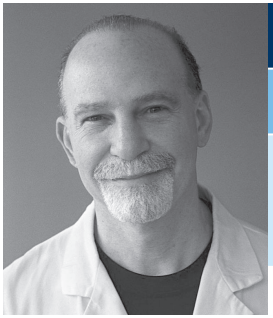

INTERVIEW

Steven T Rosen, MD

Dr Rosen is Genevieve Teuton Professor of Medicine and Director of the Robert H Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois.

Tracks 1-12

Select Excerpts from the Interview

Tracks 4-8

DR LOVE: Would you discuss the treatment alternatives for patients with mycosis fungoides?

DR ROSEN: We have various local options for dealing with plaques and tumor lesions, including topical corticosteroids, which are effective for patch disease, and bexarotene gel, which we'll sometimes administer for isolated patches, plaques or small tumor lesions. Bexarotene gel should only be used to treat a localized area because of the associated inflammation.

Topical nitrogen mustard has been used for several decades. It can be applied extensively and is most effective in patch/plaque disease. It is less effective for tumor lesions.

Another treatment option, known as PUVA, exposes the patient to ultraviolet light after administration of the photoactivatable oral compound psoralen. This method is used for thin plaques or patches and is not effective for tumor lesions.

Although we're often directing therapies to the skin, systemic therapies can also enhance the efficacy of skin therapies. Interferon, which is probably the most active agent for treating this disease, or bexarotene, can be combined with PUVA in particular.

Spot radiation therapy can be administered to large, isolated or ulcerated tumor lesions. Some institutions use entire-body electron-beam radiation therapy. We stopped using that approach a number of years ago. At times you may see dramatic responses, but the disease is more difficult to treat upon recurrence. In select instances, we administer total body irradiation with a modest number of rads per treatment.

Another alternative for treating extensive plaque and tumor lesions is denileukin diftitox — a recombinant DNA-derived cytotoxic protein that links the interleukin-2 molecule to diphtheria toxin. Response rates for denileukin diftitox are in the range of 25 to 30 percent (Olsen 2001; [4.1]).

The majority of responses are short lived, although I have seen more durable remissions. The main toxicities are elevated liver function enzymes and peripheral edema. In general, it's a well-tolerated treatment, particularly when combined with steroids, which seem to ameliorate some of the toxicities. I tend to reserve denileukin diftitox for patients whose disease has progressed on other effective therapies.

4.1

Pivotal Phase III Trial of Two Dose Levels of Denileukin Diftitox for the Treatment of Cutaneous T-Cell Lymphoma (CTCL)

	Denileukin diftitox		
Response	9 ug/kg per day (n = 35)	18 ug/kg per day (n = 36)	Total (n = 71)
Overall response*	23% (n = 8)	36% (n = 13)	30% (n = 21)
Median duration of response Range (minimum-maximum)	6.8mo 2.7-46.1+mo	6.9mo 4.0-17.5mo	6.9mo 2.7-46.1+mo

* No statistically significant difference between dose groups

"In the current study, by using rigorous standardized measures to assess both tumor burden and symptom status, denileukin diftitox has been shown to induce a 30% objective response (21 of 71) in CTCL patients with mycosis fungoides or Sézary's syndrome who were heavily pretreated and/or had advanced disease...

In general, clinical benefit is evident after the first or second course of therapy, allowing the informed clinician to rapidly make decisions regarding continued treatment and to adjust the dose and/or frequency of denileukin diftitox or adjuvant medications should side effects occur.

Denileukin diftitox is an important new agent for patients with advanced or recurrent CTCL, particularly those in whom there is a high degree of symptomatology and disfigurement and those who have a potentially life-threatening disease."

SOURCE: Olsen E et al. *J Clin Oncol* 2001;19(2):376-88.

Our most effective therapy at Northwestern has been the combination of interferon and PUVA therapy, which we reported on 20 years ago (Kuzel 1990) and which has been verified by a number of investigators.

DR LOVE: What would normally be your choice for second-line systemic therapy?

DR ROSEN: For a patient whose disease progresses on interferon/PUVA, we may administer topical mustard or spot radiation therapy to isolated lesions but would most likely switch to the rexinoid treatment bexarotene, possibly in combination with ultraviolet light. If that therapy is ineffective or if the disease progresses, we will proceed to administering vorinostat.

The beauty of bexarotene and vorinostat is that they are administered orally. The issue with bexarotene is that it can cause lipid abnormalities. We've noted at least three ischemic events in patients, although we've tried our best to manage their lipid levels.

Another issue is central hypothyroidism. All of these patients are receiving antihypolipidemic medications in addition to thyroid replacement therapy. We prefer to use bexarotene in combination with light therapy and at a low dose, which we believe may minimize the ischemic events.

With vorinostat, only a minority of patients experience dramatic responses. Responses have been short lived, but with some patients it's been a home run, with extensive remissions.

Denileukin diftitox is also an option, and we consider the use of chemotherapy in some instances. Probably the two most active therapeutic drugs in our experience have been gemcitabine and liposomal doxorubicin, the latter of which is useful because of its skin homing capability. It's also wonderful that it doesn't cause alopecia in patients already traumatized by extensive skin problems.

Track 11

DR LOVE: What are the treatment options for patients with Sézary syndrome?

DR ROSEN: Patients with Sézary syndrome are often miserable because of the intense pruritus associated with this syndrome. The traditional remedies used for patients with pruritus from other causes, such as antihistamines or neurologic medications like pregabalin or gabapentin, usually aren't effective. The only way to affect the pruritus is to treat the disease.

The strategy for the patient with Sézary syndrome is similar in some ways to the strategy for a patient with the more traditional mycosis fungoides. High-dose steroids, which are cytotoxic to the malignant cells, can provide short-term relief for pruritus and provide effective control of the disease. We can also use interferon therapy or retinoid/rexinoid therapy with or without

PUVA. Sometimes these patients are more sensitive to light therapy and are prone to burning of the skin.

Another treatment option is extracorporeal photopheresis. We harvest the patient's peripheral mononuclear cells. Those cells are exposed to a psoralen-like compound and ultraviolet light, which essentially kills the cells. The cells are then reinfused into the patient, theoretically creating an immune response. Whether or not that's the mechanism remains unclear, but clinical benefit has been reported for these patients (Dani 2009). You can also combine extracorporeal photopheresis with interferon or bexarotene.

The other effective therapy for patients with Sézary syndrome is alemtuzumab, which provides effective relief usually within days or weeks. We reported a median duration of response in the range of six to nine months, with some patients in remission for a few years (Querfeld 2006; [4.2]). Patients can be retreated at relapse.

4.2

Efficacy of Alemtuzumab in Patients with Heavily Pretreated Advanced Mycosis Fungoides/Sézary Syndrome

	Alemtuzumab (N = 19)
Median overall survival	18 months
Median duration of response	7 months
Overall response rate	79%
Complete response	47%
Partial response	32%

SOURCE: Querfeld C et al. *Proc ASH* 2006;**Abstract 2732**.

Alemtuzumab, in addition to affecting the malignant CD4 cell, also will affect normal T and B cells, macrophages and monocytes. I have concerns with immunosuppression associated with alemtuzumab, and some investigators have taken an approach of administering a limited number of weeks of therapy only until the patients gain relief and demonstrate clinical improvement. Alemtuzumab therapy is only resumed at the time of disease progression.

The most significant issue associated with alemtuzumab use is reactivation of cytomegalovirus (CMV). We note the appearance of CMV either because we're monitoring for it via PCR or, upon development of fever of unknown origin in the patient, CMV is found to be activated. We've not seen any associated mortality, and we effectively treat this problem by administering valganciclovir. ■

SELECT PUBLICATIONS

Dani T, Knobler R. **Extracorporeal photoimmunotherapy-photopheresis.** *Front Biosci* 2009;14:4769-77.

Kuzel TM et al. **Interferon alfa-2a combined with phototherapy in the treatment of cutaneous T-cell lymphoma.** *J Natl Cancer Inst* 1990;82(3):203-7.

Olsen E et al. **Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma.** *J Clin Oncol* 2001;19(2):376-88.

Querfeld C et al. **Alemtuzumab (Campath-1H) in patients with erythrodermic cutaneous T-cell lymphoma (ECTCL): The Northwestern University experience.** *Proc ASH* 2006;**Abstract 2732**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following regimens is being evaluated in the Intergroup trial CALGB-10404 as first-line therapy for CLL?**
   a. FCR
   b. FR
   c. FR → lenalidomide
   d. All of the above
   e. None of the above

2. **Ofatumumab is a humanized anti-CD20 monoclonal antibody.**
   a. True
   b. False

3. **A clinical trial demonstrated that ofatumumab has activity in patients with _____ CLL.**
   a. Fludarabine- and alemtuzumab-refractory
   b. Bulky fludarabine-resistant
   c. Newly diagnosed
   d. Both a and b
   e. None of the above

4. **Which of the following drugs approved for the treatment of myelodysplastic syndromes is a hypomethylating agent?**
   a. Azacitidine
   b. Decitabine
   c. Lenalidomide
   d. Both a and b

5. **Which of the following drugs approved for myelodysplastic syndromes is particularly effective in treating patients with the 5q-minus syndrome?**
   a. Azacitidine
   b. Decitabine
   c. Lenalidomide
   d. Both a and b

6. **Borthakur and colleagues have published data demonstrating clinically significant responses with decitabine in patients with myelodysplastic syndrome after azacitidine failure.**
   a. True
   b. False

7. **The GELA trial, evaluating R-CHOP versus CHOP for the treatment of elderly patients with DLBCL, reported that _____ more patients were alive on the R-CHOP arm after a median follow-up of five years.**
   a. Eight percent
   b. 12 percent
   c. 26 percent
   d. 40 percent

8. **Bortezomib has been approved by the FDA for the treatment of _____ lymphoma.**
   a. Follicular
   b. Mantle-cell
   c. Diffuse large B-cell
   d. None of the above

9. **Which of the following is a treatment option for localized skin treatment in patients with mycosis fungoides?**
   a. Bexarotene
   b. Denileukin diftitox
   c. Topical nitrogen mustard
   d. PUVA
   e. All of the above

10. **The response rate for patients with mycosis fungoides treated with denileukin diftitox is approximately _____.**
    a. 10 percent
    b. 30 percent
    c. 45 percent
    d. 55 percent

11. **The median duration of response with alemtuzumab for heavily pretreated patients with advanced mycosis fungoides/Sézary syndrome was _____.**
    a. Three months
    b. Seven months
    c. 12 months

Post-test answer key: 1d, 2a, 3d, 4d, 5c, 6a, 7c, 8b, 9e, 10b, 11b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 2, 2009

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Activity of ofatumumab for relapsed/refractory CLL	4 3 2 1	4 3 2 1
Efficacy of lenalidomide for MDS with 5q deletion	4 3 2 1	4 3 2 1
Activity of decitabine for patients with MDS that progresses on azacitidine	4 3 2 1	4 3 2 1
Outcomes associated with the addition of gemtuzumab to induction therapy for AML	4 3 2 1	4 3 2 1
Data with arsenic trioxide/ATRA for newly diagnosed APL	4 3 2 1	4 3 2 1
Activity of bortezomib for refractory mantle-cell lymphoma	4 3 2 1	4 3 2 1
Use of denileukin diftitox for mycosis fungoides	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:. . . . . .

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:. . . . . .

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:. . . . . .

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Utilize prognostic markers to determine the timing and selection of treatment for chronic lymphocytic leukemia (CLL). . . . . 4 3 2 1 N/M N/A
- Develop an algorithm for the evaluation, classification and treatment of myelodysplastic syndrome (MDS) . . . . . 4 3 2 1 N/M N/A
- Counsel patients with acute myeloid leukemia (AML) about the risks and benefits of innovative, evidence-based therapeutic approaches . . . . . 4 3 2 1 N/M N/A
- Formulate up-to-date induction, consolidation and maintenance strategies for acute promyelocytic leukemia (APL). . . . . 4 3 2 1 N/M N/A
- Apply emerging data with novel agents and regimens to the care of patients with newly diagnosed or relapsed/refractory indolent or aggressive non-Hodgkin lymphomas (NHL) . . . . . 4 3 2 1 N/M N/A
- Integrate currently available therapeutic strategies into the management of cutaneous T-cell lymphoma. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate . . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

What additional information or training do you need on the activity topics or other oncology-related topics?

Additional comments about this activity:

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Kanti R Rai, MD	4 3 2 1	4 3 2 1
Martin S Tallman, MD	4 3 2 1	4 3 2 1
Craig Moskowitz, MD	4 3 2 1	4 3 2 1
Steven T Rosen, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

Other comments about the faculty and editor for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: ..... Specialty: .....

Professional Designation:

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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

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