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Hematologic Oncology™ UPDATE

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

EDITOR

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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 the numerous types 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, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Utilize treatment history and disease cytogenetics to individualize the clinical management of myelodysplastic syndrome.
- Describe available evidence-based therapeutic approaches for frequently encountered adult acute and chronic leukemias.
- Formulate optimal front-line and maintenance strategies for patients with follicular lymphoma or diffuse large B-cell lymphoma.
- Summarize emerging data with novel agents and combinations in the setting of newly diagnosed or relapsed/refractory, indolent or aggressive non-Hodgkin lymphoma.
- Integrate innovative combination regimens into the management of multiple myeloma, considering the benefits and risks of proteasome inhibitors and immunomodulatory agents.
- Counsel patients with hematologic cancer about the side effects and toxicities associated with various systemic therapies.

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TABLE OF CONTENTS

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INTERVIEW

Jonathan W Friedberg, MD

Dr Friedberg is Chief of the Hematology/Oncology Division at the James P Wilmot Cancer Center and Associate Professor of Medicine and Oncology at the University of Rochester in Rochester, New York.

CD 1, Tracks 1-12

Select Excerpts from the Interview

CD 1, Track 1

DR LOVE: Would you discuss the CORAL trial for patients with relapsed diffuse large B-cell lymphoma (DLBCL) that was presented at ASCO?

DR FRIEDBERG: This collaborative trial randomly assigned patients with relapsed aggressive lymphomas to R-ICE or R-DHAP chemotherapy prior to autologous stem cell transplant. Investigators sought to answer two questions: (1) What is the optimal salvage regimen? and (2) Does rituximab have a role after autologous transplant?

Data on the second question are not yet mature, but the authors presented response rates of 64 percent for patients treated with R-ICE and 63 percent with R-DHAP (Gisselbrecht 2009). No statistically significant difference in response rates was evident. Furthermore, no statistically significant difference was observed in the number of patients who could subsequently undergo stem cell mobilization and transplant.

One interesting point that might be lost in simply evaluating these results is that this is one of the first studies of salvage therapy in the rituximab era. The majority of these patients had been exposed to rituximab in the past, which means they either experienced relapse after R-CHOP or had primary disease that was refractory to R-CHOP. The outcome for that group of patients after transplant was poor — 30 percent or less.

This suggests that if you don't have a complete response to R-CHOP treatment, your outcome will be poor even with autologous transplant. New treatments are needed for this group of patients with refractory disease.

CD 1, Track 2

DR LOVE: What are your thoughts on the SAKK-35/98 trial, which reported follow-up of prolonged versus short-course rituximab for patients with follicular lymphoma?

DR FRIEDBERG: This Swiss trial for patients with either newly diagnosed or relapsed follicular lymphoma treated all patients with four weekly doses of rituximab. Patients whose disease responded or who had stable disease after the initial four doses were then randomly assigned to either observation or an extended schedule of rituximab — a single dose every two months times four (Ghielmini 2009; [1.1]).

1.1

SAKK-35/98: Long-Term Follow-Up of Prolonged versus Short-Course Rituximab for Patients with Follicular Lymphoma

	Short-course rituximab (n = 78)	Prolonged rituximab (n = 73)	*p*-value
Median event-free survival (EFS)	13 months	24 months	0.0012
EFS*, all patients			
At five years	10%	26%	NR
At eight years	4%	25%	0.0007
EFS in chemotherapy-naïve patients (n = 38)†			
At eight years	Not reported	45%	0.03

* EFS: Time until progression, relapse, second tumor or death
† EFS for patients with chemotherapy-naïve disease with a complete response or partial response at 12 weeks

SOURCE: Ghielmini ME et al. *Proc ASCO* 2009;**Abstract 8512**.

The long-term follow-up was a median of 9.4 years. A continued, significant event-free survival benefit was recorded for patients on the extended rituximab schedule versus patients who received four doses of rituximab, and 25 percent of patients on the extended schedule had disease that remained in remission at eight years (Ghielmini 2009; [1.1]).

In the subset of patients with disease that was chemotherapy naïve, approximately 45 percent remained in remission at eight years (Ghielmini 2009; [1.1]).

A strong trend toward a survival benefit was observed. However, the *p*-value of 0.09 for overall survival was not considered statistically significant.

CD 1, Track 4

DR LOVE: Would you discuss the rationale behind the study comparing R-CHOP-14 to R-CHOP-21 that was presented at ASCO?

DR FRIEDBERG: Preliminary data were presented on the comparison of the 14-day R-CHOP schedule versus the 21-day R-CHOP schedule for patients with newly diagnosed DLBCL (Cunningham 2009). The original standard treatment in this setting was 21-day CHOP, and a later study indicated that R-CHOP-21 provided a benefit compared to CHOP-21 (Feugier 2005).

The German group has reported that CHOP-14 is better than CHOP-21 and that R-CHOP-14 is better than CHOP-14 (Pfreundschuh 2004, 2008). However, what hasn't been shown is whether R-CHOP-21 is inferior or equivalent to R-CHOP-14.

This large Phase III trial is addressing that question and randomly assigned 540 patients to each R-CHOP schedule. The primary overall survival endpoint has not yet been reached, and so far no difference in response rates has been observed (Cunningham 2009), suggesting that for now the R-CHOP-21 regimen remains the standard.

CD 1, Track 8

DR LOVE: Would you provide an overview on the galiximab study that you reported at ASH 2008?

DR FRIEDBERG: Galiximab is a monoclonal antibody directed against CD80, which is present on most malignant B cells and disrupts the co-stimulatory pathway of T-cell activation. In theory, some immune responses may be impaired by blocking CD80.

In a Phase II nonrandomized trial published a couple of years ago, we reported that combination rituximab and galiximab seemed to provide a longer progression-free survival than you would expect with rituximab alone (Leonard 2007). We also reported no additional toxicity with the addition of galiximab to rituximab.

At ASH 2008 we presented long-term follow-up data from this study. Although several patients experienced relapse relatively quickly — within a year of receiving galiximab and rituximab — the lymphomas seemed to "sit still" after relapse.

We reported that a relatively high fraction of these patients did not require additional treatment three years after receiving the combination of galiximab and rituximab (Friedberg 2008; [1.2]). ■

1.2

Durable Responses with Galiximab/Rituximab for Relapsed or Refractory Follicular Lymphoma: Long-Term Follow-Up

"We conclude that the combination of rituximab and galiximab is well-tolerated in long-term follow-up, with a substantial number of durable responses. Almost one-third of patients treated with only 4 weeks of this combination do not require additional lymphoma therapy for more than three years...

These durable responses provide strong rationale for ongoing phase III clinical trials of the galiximab/rituximab combination."

SOURCE: Friedberg JW et al. *Proc ASH* 2008;**Abstract 1004**.

SELECT PUBLICATIONS

Cunningham D et al. **A phase III trial comparing R-CHOP 14 and R-CHOP 21 for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin's lymphoma.** *Proc ASCO* 2009;**Abstract 8506**.

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.

Friedberg JW et al. **Durable responses in patients treated with galiximab (anti-CD80) in combination with rituximab for relapsed or refractory follicular lymphoma: Long-term follow-up of a Phase II clinical trial.** *Proc ASH* 2008;**Abstract 1004**.

Ghielmini ME et al. **Long-term follow-up of patients with follicular lymphoma (FL) receiving single agent rituximab at two different schedules in study SAKK 35/98.** *Proc ASCO* 2009;**Abstract 8512**.

Gisselbrecht C et al. **R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study.** *Proc ASCO* 2009;**Abstract 8509**.

Leonard JP et al. **A phase I/II study of galiximab (an anti-CD80 monoclonal antibody) in combination with rituximab for relapsed or refractory, follicular lymphoma.** *Ann Oncol* 2007;18(7):1216-23.

Palumbo AP et al. **A Phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients.** *Proc ASCO* 2009;**Abstract 8515**.

Pfreundschuh M et al. **Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: A randomised controlled trial (RICOVER-60).** *Lancet Oncol* 2008;9(2):105-16.

Pfreundschuh M et al. **Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: Results of the NHL-B1 trial of the DSHNHL.** *Blood* 2004;104(3):626-33.

INTERVIEW

Nikhil C Munshi, MD

Dr Munshi is Associate Professor of Medicine at Harvard Medical School and Associate Director of the Jerome Lipper Myeloma Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

CD 1, Tracks 13-22 — CD 2, Tracks 1-5

CD 1

Track 13 Combining lenalidomide and bortezomib for multiple myeloma (MM)

Track 14 Clinical trials evaluating lenalidomide/bortezomib/dexamethasone (RVD) for relapsed/refractory or newly diagnosed MM

Track 15 Proposed clinical trial comparing RVD to RVD with transplant for MM

Track 16 EVOLUTION: A Phase I/II trial evaluating bortezomib, dexamethasone, cyclophosphamide and lenalidomide (VDCR) for newly diagnosed MM

Track 17 Cure versus disease control for MM

Track 18 Clinical use of RVD for newly diagnosed MM

Track 19 Phase III randomized trial of bortezomib, melphalan and prednisone (VMP) versus VMP with thalidomide (VMPT) for elderly patients with newly diagnosed MM

Track 20 Bortezomib-related neurotoxicity

Track 21 **Case discussion:** A 73-year-old man with MM with a near complete response to bortezomib/dexamethasone

Track 22 Performance of cytogenetic studies as part of a standard workup for patients with MM

CD 2

Track 1 **Case discussion:** A 39-year-old man with relapsed MM who previously received bortezomib/dexamethasone

Track 2 Testing for serum free light chains in MM

Track 3 New agents being evaluated for bone disease associated with MM

Track 4 Scheduling bisphosphonate administration

Track 5 Dental referrals for patients who will receive bisphosphonates

Select Excerpts from the Interview

CD 1, Tracks 14-15

DR LOVE: What do we know about the combination of lenalidomide, bortezomib and dexamethasone (RVD) for patients with multiple myeloma (MM)?

DR MUNSHI: Two trials evaluating these agents in combination have received the most attention. The first study determined the doses of lenalidomide and

bortezomib that could be combined with dexamethasone and established that we can utilize these drugs in the relapsed/refractory setting.

In this study, treatment with RVD resulted in a response rate of more than 50 percent in a heavily pretreated population. More than 80 percent of these patients had received either thalidomide or lenalidomide previously, and more than half of the patients had received bortezomib (Anderson 2009).

This is an exciting result — although a patient might have been resistant to each drug administered alone, when used in combination lenalidomide and bortezomib helped overcome resistance and provided benefit.

The second trial, a Phase I study presented by Dr Richardson from our group, evaluated the RVD regimen for patients with newly diagnosed MM (2.1). Patients received a three-week cycle of lenalidomide administered 14 days

2.1 **Phase I/II Trial of Lenalidomide, Bortezomib and Dexamethasone (RVD) for Patients with Newly Diagnosed Multiple Myeloma (MM)**

Efficacy data (n = 66)

	All patients	Patients receiving MPD
ORR	98%	100%

Responses by ISS stage

	ISS I (n = 33)	ISS II (n = 21)	ISS III (n = 10)	*p*-value
≥PR	97%	100%	100%	0.385
≥VGPR	51%	57%	80%	0.421

Responses by cytogenic status

	Normal (n = 39)	Abnormal (n = 24)	No 13q deletion (n = 52)	13q deletion (n = 7)	No trans 4;14 (n = 49)	Trans 4;14 (n = 10)
≥PR	100%	96%	100%	86%	98%	100%
	$p = 0.381$		$p = 0.119$		$p = 1.00$	
≥VGPR	69%	79%	75%	57%	73%	70%
	$p = 0.560$		$p = 0.375$		$p = 1.00$	

MPD = maximum planned dose; ORR = overall response rate; ISS = International Staging System; PR = partial response; VGPR = very good partial response

"RVD produces high quality responses and is well tolerated in newly diagnosed MM pts, regardless of their cytogenetic status or ISS stage. MPD has been reached at Len 25 mg, Bz 1.3 mg/m^2, and Dex 20 mg, with phase II enrollment now complete and 100% ORR reported at the MPD.

Stem cell mobilization has been successful in almost all pts, with transplant course in pts otherwise unremarkable."

SOURCE: Richardson P et al. *Proc ASH* 2008;**Abstract 92**.

on and one week off instead of the traditional schedule of three weeks on, one week off. All patients received aspirin for prophylaxis against deep-vein thrombosis.

More than 65 patients underwent treatment and analysis, and a 100 percent overall response rate was reported — all patients achieved a partial response or better (Richardson 2008; [2.1]).

Approximately 25 percent of the patients have now achieved a complete remission. These numbers are similar to those we previously achieved with transplant alone, so the RVD regimen is providing a substantial benefit.

Patients on this study have continued the combination beyond four to six cycles because of a lack of significant neuropathy, which is often observed with single-agent bortezomib administered for a long time. The manageable toxicity and significantly higher response rate make RVD a promising regimen.

It is also important to note that 21 patients in this group had their stem cells successfully mobilized. The patients who underwent transplant received timely engraftment of their bone marrow and recovery of their blood counts. This suggests that RVD can be used as an induction regimen with or without transplant to attain maximum benefit.

DR LOVE: Is the RVD regimen now being evaluated in randomized trials?

DR MUNSHI: A pivotal trial set to open in the next few months is a collaborative effort between the French IFM group and Dana-Farber, in which patients will be randomly assigned to eight cycles of RVD versus RVD and transplant. The target accrual for this trial is 1,000 patients.

All patients will receive maintenance lenalidomide, and this trial will evaluate whether a role exists for transplant when we are already administering an effective regimen and whether transplant adds a benefit to the response rates already reported with the RVD regimen.

CD 1, Track 16

DR LOVE: What other novel combinations are being evaluated for patients with newly diagnosed MM?

DR MUNSHI: A study presented at ASH 2008 by Michele Cavo reported that bortezomib/thalidomide/dexamethasone (VTD) is superior to TD (Cavo 2008).

Now that we have reports that three-drug regimens provide more benefit than two-drug regimens, the next emphasis is to evaluate four-drug combinations. One study is adding cyclophosphamide to the RVD regimen, creating the VDCR combination.

A presentation by Dr Shaji Kumar at ASH 2008 reported on an ongoing three-arm Phase I/II randomized study evaluating RVD, VDCR and bortezomib/cyclophosphamide with dexamethasone — VCD.

The Phase I data established the cyclophosphamide dose at 500 mg/m^2 per week, twice in the cycle for the VDCR regimen, and also reflected high response rates with VDCR. The authors concluded that VDCR can be administered safely (Kumar 2008; [2.2]). A Phase II study is ongoing and will establish which of the three-drug or four-drug combinations might be superior.

2.2

EVOLUTION: Response Rates with Bortezomib, Dexamethasone, Cyclophosphamide and Lenalidomide (VDCR) for Patients with Newly Diagnosed MM (N = 25)

Overall response rate (CR + VGPR + PR)	96%
sCR	20%
≥CR	36%
≥VGPR	64%
≥PR	96%

CR = complete response; VGPR = very good partial response; PR = partial response; sCR = stringent complete response

"VDCR was well tolerated and hematologic toxicities were manageable. The current study shows that the VDCR regimen is feasible and highly active in newly diagnosed myeloma and merits further testing in clinical trials. Enrollment to the 3 arms (VDR, VDC and VDCR) of the phase II portion of the study and testing for minimal residual disease by flow cytometry are ongoing."

SOURCE: Kumar S et al. *Proc ASH* 2008;**Abstract 93**.

CD 1, Tracks 19-20

DR LOVE: Would you discuss the results of the study presented at ASCO that evaluated bortezomib, melphalan and prednisone (VMP) versus VMP and thalidomide (VMPT)?

DR MUNSHI: Dr Palumbo's study also asked the question, is a four-drug regimen better than a three-drug regimen? The authors reported that VMPT was superior to VMP (Palumbo 2009), although I'm not convinced the superiority was high enough to switch to the four-drug regimen.

Interestingly, patients enrolled on this study received bortezomib once weekly instead of the usual twice-a-week administration. A substantial decrease in bortezomib-related neurotoxicity was reported with the weekly regimen (Palumbo 2009; [2.3]). I believe that is an important point as we administer bortezomib more and more.

DR LOVE: Vincent Rajkumar was the discussant on this presentation and called it practice changing. Do you believe, based on these data and others, that it's reasonable to use a weekly bortezomib schedule?

DR MUNSHI: The advantages are clear in terms of neurotoxicity. However, the data do not exist to indicate whether once-a-week bortezomib provides

the same clinical benefit as the twice-weekly regimen, so I cannot suggest changing to the weekly regimen.

In some situations we consider it. We recently published a report in the *Journal of Clinical Oncology* in which we observed that approximately one third of patients have some level of neuropathy at the time of diagnosis (Richardson 2009).

If you decrease the frequency of bortezomib, patients might benefit from a toxicity standpoint and the responses may not be so different. If a patient does not have any significant, clear indication to administer the once-a-week regimen, however, I believe that we should continue with the standard schedule, which has established response rates. ■

2.3

Efficacy and Toxicity According to Bortezomib Infusion Schedule in a Phase III Study of VMPT versus VMP for Newly Diagnosed MM

	VMPT		VMP	
	Twice weekly (n = 71)	Weekly (n = 150)	Twice weekly (n = 64)	Weekly (n = 165)
Complete response	38%	32%	27%	20%
Grade III/IV peripheral neuropathy (PN)	18%	2%	14%	2%
Dose reduction due to PN	42%	11%	35%	13%
Discontinuation due to PN	10%	3%	15%	4%

Twenty-five patients receiving VMPT and 19 patients receiving VMP also received twice- and once-weekly bortezomib.

SOURCE: Palumbo AP et al. *Proc ASCO* 2009;**Abstract 8515**.

SELECT PUBLICATIONS

Anderson KC et al. **Lenalidomide, bortezomib, and dexamethasone in relapsed/refractory multiple myeloma (MM): Encouraging outcomes and tolerability in a phase II study.** *Proc ASCO* 2009;**Abstract 8536**.

Cavo M et al. **Superior complete response rate and progression-free survival after autologous transplantation with up-front Velcade-thalidomide-dexamethasone compared with thalidomide-dexamethasone in newly diagnosed multiple myeloma.** *Proc ASH* 2008;**Abstract 158**.

Kumar S et al. **Safety and efficacy of novel combination therapy with bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in newly diagnosed multiple myeloma: Initial results from the phase I/II multi-center EVOLUTION study.** *Proc ASH* 2008;**Abstract 93**.

Palumbo AP et al. **A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients.** *Proc ASCO* 2009;**Abstract 8515**.

Richardson PG et al. **Single-agent bortezomib in previously untreated multiple myeloma: Efficacy, characterization of peripheral neuropathy, and molecular correlations with response and neuropathy.** *J Clin Oncol* 2009;27(21):3518-25.

Richardson P et al. **Lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma: Encouraging efficacy in high risk groups with updated results of a Phase I/II study.** *Proc ASH* 2008;**Abstract 92**.

INTERVIEW

Vicki A Morrison, MD

Dr Morrison is Associate Professor of Medicine at the University of Minnesota and Staff Physician at the VA Medical Center's Sections of Hematology/Oncology and Infectious Disease in Minneapolis, Minnesota.

CD 2, Tracks 6-13

Select Excerpts from the Interview

CD 2, Tracks 9, 11

DR LOVE: Would you discuss therapeutic options for patients with relapsed or refractory chronic lymphocytic leukemia (CLL)?

DR MORRISON: One option is alemtuzumab, which was developed as a treatment for relapsed or refractory disease and has subsequently been approved as first-line therapy for CLL. The primary issues with administering alemtuzumab are infectious complications and infusion toxicities.

If you're considering alemtuzumab therapy for your patients, you have to carefully consider how closely they can be observed for these infectious complications. In our practice we are also hesitant to administer alemtuzumab therapy to frail patients and reserve it for patients who are more fit.

Another agent under investigation in CLL is ofatumumab. It is a fully humanized anti-CD20 antibody, which might help to circumvent the potential for infusion reactions that are associated with rituximab. The mechanism of action

may be somewhat different from that of rituximab, but the question is whether ofatumumab offers any significant advantages.

CD 2, Tracks 12-13

DR LOVE: What are your thoughts about other agents under investigation for CLL, specifically lenalidomide and bortezomib?

DR MORRISON: Dr Chanan-Khan from Roswell Park and Dr Ferrajoli from the MD Anderson Cancer Center have reported data on lenalidomide in the relapsed/refractory setting in CLL (Chanan-Khan 2006; Ferrajoli 2008; [3.1]).

3.1

Phase II Trials of Lenalidomide for Patients with Relapsed/Refractory CLL

	Chanan-Khan (N = 45)	Ferrajoli (N = 44)
ORR	47%	32%
CR	9%	7%
Nodular PR	—	2%
PR	38%	23%

ORR = overall response rate; CR = complete response; PR = partial response

SOURCES: Chanan-Khan A et al. *J Clin Oncol* 2006;24(34):5343-9; Ferrajoli A et al. *Blood* 2008;111(11):5291-7.

Moving lenalidomide up from the relapsed/refractory setting has received a lot of enthusiasm. It's an oral agent, so it's easily administered. Currently, a three-arm Intergroup trial — CALGB-10404 — is evaluating it for previously untreated patients with CLL. Patients receive induction therapy with fludarabine and rituximab (FR) alone, FR followed by lenalidomide after completion of induction therapy or FR with cyclophosphamide (FCR). So one arm of this trial has what could be considered to be lenalidomide maintenance therapy.

Bortezomib was initially developed for the treatment of multiple myeloma, but it has also been studied in lymphoproliferative disorders, and based on the Phase II trial (Fisher 2006; [3.2]), the drug was approved for patients with mantle-cell lymphoma (MCL).

I am the protocol chair for the current CALGB-50501 trial, which is evaluating the combination of bortezomib and lenalidomide for relapsed or refractory MCL (3.3).

One concern with combining lenalidomide and bortezomib is the lack of safety data with this combination. The only safety data were from Paul Richardson's studies in the relapsed/refractory myeloma setting (Richardson 2006).

The hope is that the combination of lenalidomide and bortezomib will at least be additive, if not synergistic, in terms of response rates. ■

3.2 Multicenter Phase II Study of Bortezomib for Patients with Relapsed or Refractory Mantle-Cell Lymphoma (MCL)

"This study represents the largest prospective study to date in patients with relapsed MCL. In a population typical of the relapsed MCL population, the results demonstrate that bortezomib is effective, with a 33% response rate, including 8% CR/CRu. The median DORs in all responding patients (9.2 months) and patients achieving CR/CRu (13.5 months) are considerable given the median expected survival of 1 to 2 years after initial relapse, suggesting important clinical benefit.

Similarly, median TTP was 10.6 months among responders, 14.6 months in patients achieving CR/CRu, and 6.2 months in all patients. These data are supported by similar results from phase I and II studies of single-agent bortezomib in relapsed MCL."

SOURCE: Fisher RI et al. *J Clin Oncol* 2006;24(30):4867-74.

3.3 Phase II Study of Bortezomib and Lenalidomide for Patients with Relapsed or Refractory Mantle-Cell Lymphoma (MCL)

Protocol IDs: CALGB-50501, NCT00553644; **Target Accrual:** 54 (Open)

Treatment

Induction therapy

[Bortezomib IV (d1, 4, 8, 11) + lenalidomide PO (d1-14)] q3wk x 8

Maintenance therapy*

[Bortezomib IV (d1, 8) + lenalidomide PO (d1-14)] q3wk → 6y

Eligibility

- Histologically confirmed MCL
- Measurable disease, defined as any tumor mass > 1 centimeter
- Prior therapy with at least one single- or multiagent regimen consisting of traditional cytotoxic and/or biologic agents

* Patients achieving a complete or partial response as best response after completion of induction therapy

SOURCE: NCI Physician Data Query, August 2009.

SELECT PUBLICATIONS

Chanan-Khan A et al. **Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: Results of a phase II study.** *J Clin Oncol* 2006;24(34):5343-9.

Ferrajoli A et al. **Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia.** *Blood* 2008;111(11):5291-7.

Fisher RI et al. **Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma.** *J Clin Oncol* 2006;24(30):4867-74.

Richardson PG et al. **Lenalidomide plus bortezomib (Rev-Vel) in relapsed and/or refractory multiple myeloma (MM): Final results of a multicenter phase 1 trial.** *Proc ASH* 2006;**Abstract 405**.

INTERVIEW

Elias Jabbour, MD

Dr Jabbour is Assistant Professor and Internist in the Leukemia Department at The University of Texas MD Anderson Cancer Center in Houston, Texas.

CD 2, Tracks 14-24

Select Excerpts from the Interview

CD 2, Track 15

DR LOVE: How do you utilize hypomethylating agents in the treatment of myelodysplastic syndrome (MDS)?

DR JABBOUR: These agents are effective, but it is important to know how to use them as the myelosuppression is not easy to manage.

The key is to administer the courses back to back every 28 days. We are not certain exactly how these agents work, but translational research suggests that hypomethylation might be one of the mechanisms. Therefore, you have to continue administration from day one to day 28 to allow complete hypomethylation.

DR LOVE: Under what circumstances would you not administer the agent on day 28?

DR JABBOUR: Mainly because of low blood counts, but I counsel community oncologists to consider that myelosuppression may not stem from the treatment but possibly from the disease. At our institution we collect the patient's bone marrow at day 28, and empty marrow indicates myelosuppression.

DR LOVE: Is this routine or only if the patient is experiencing cytopenia?

DR JABBOUR: Usually we do it every month for the first three months until the patient achieves a good response, and then we do it less often. Otherwise we would typically only do so if the patient has a low blood count.

The problem in the community is that the oncologist observes the patient and on day 28, when the patient's counts are evaluated and found to be low, treatment is postponed. This can cause a patient to lose the benefit of the agent and result in disease progression. This is not how you should use these agents. Another factor to consider is that response may take longer with these agents. Therefore, do not stop the treatment before you administer four to six courses, unless the patient experiences disease progression or the treatment is not tolerated.

CD 2, Track 17

DR LOVE: Can you review the clinical research database for decitabine and azacitidine in MDS?

DR JABBOUR: These two agents received approval based on response rates, without survival improvements. Azacitidine was the first to be approved based on randomized trial results, which reported a benefit with azacitidine compared to supportive care (Silverman 2002).

A randomized Phase III study recently reported a survival advantage with azacitidine compared to conventional care (Fenaux 2009; [4.1]). The median survival was 15 months for patients receiving conventional care and 25 months for patients receiving azacitidine. Results with decitabine administered for three days at a dose of 135 mg/m^2 per course were published subsequently (Kantarjian 2006).

MD Anderson later published results of a Phase II randomized study aimed at optimizing the dose and schedule for decitabine. Of three schedules of low-dose decitabine — each totaling 100 mg/m^2 per course — the dose of 20 mg/m^2 IV daily for five days was reported to be superior, with a 39 percent complete response rate (Kantarjian 2007).

Dr Steensma from the Mayo Clinic recently published results from the ADOPT trial in the *Journal of Clinical Oncology* corroborating the efficacy of the five-day decitabine schedule (Steensma 2009). An EORTC randomized Phase III study recently reported no survival advantage with decitabine compared to best supportive care (WijerMans 2008). However, this trial used the three-day decitabine schedule.

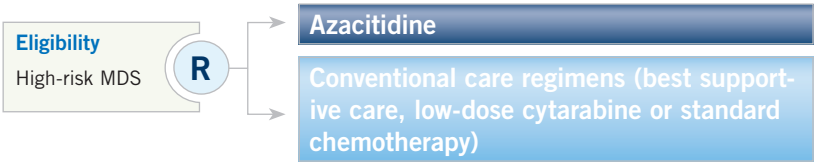
DR LOVE: Is it your impression that these two agents have similar efficacy, side effects and toxicity?

DR JABBOUR: I believe so. I'm comfortable with recommending either. For the community physicians, the choice may be based on route of administration because azacitidine is administered subcutaneously and decitabine by IV infusion. ■

4.1

AZA-001: Azacitidine versus Conventional Care Regimens (CCR) for Patients with High-Risk MDS

Protocol ID: AZA-001
Accrual: 358 (Closed)



	Azacitidine (n = 179)	CCR (n = 179)
Median overall survival	24.5 months	15 months
	HR (95% CI) = 0.58 (0.43-0.77), $p = 0.0001$	
Median time to AML	17.8 months	11.5 months
	HR (95% CI) = 0.50 (0.35-0.70), $p < 0.0001$	

HR = hazard ratio; CI = confidence interval; AML = acute myeloid leukemia

"At 2 years, on the basis of Kaplan-Meier estimates, 50.8% (95% CI 42.1-58.8) of patients in the azacitidine group were alive compared with 26.2% (18.7-34.3) in the conventional care group ($p < 0.0001$)."

SOURCE: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

SELECT PUBLICATIONS

Fenaux P et al; International Vidaza High-Risk MDS Survival Study Group. **Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study.** *Lancet Oncol* 2009;10(3):223-32.

Kantarjian H et al. **Results of a randomized study of 3 schedules of low-dose decitabine in higher risk myelodysplastic syndrome and chronic myelomonocytic leukemia.** *Blood* 2007;109(1):52-7.

Kantarjian H et al. **Decitabine improves patient outcomes in myelodysplastic syndromes: Results of a phase III randomized study.** *Cancer* 2006;106(8):1794-803.

List AF et al. **Effect of azacitidine (AZA) on overall survival in higher-risk myelodysplastic syndromes (MDS) without complete remission.** *Proc ASCO* 2008;**Abstract 7006**.

Martin MG et al. **A phase II study of 5-day intravenous azacitidine in patients with myelodysplastic syndromes.** *Am J Hematol* 2009;84(9):560-4.

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.

Steensma DP et al. **Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: The alternative dosing for outpatient treatment (ADOPT) trial.** *J Clin Oncol* 2009;27(23):3842-8.

WijerMans P et al. **Low dose decitabine versus best supportive care in elderly patients with intermediate or high risk MDS not eligible for intensive chemotherapy: Final results of the randomized phase III study (06011) of the EORTC leukemia and German MDS study groups.** *Proc ASH* 2008;**Abstract 226**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The CORAL trial — comparing R-ICE to R-DHAP prior to autologous stem cell transplant for patients with relapsed diffuse large B-cell lymphoma — reported superior response rates with R-DHAP.**
   a. True
   b. False
2. **The SAKK-35/98 clinical trial evaluated a short course (four weekly doses) of rituximab versus prolonged rituximab for patients with newly diagnosed or relapsed follicular lymphoma.**
   a. True
   b. False
3. **Approximately _____ of patients who received the combination of galiximab and rituximab in a Phase II trial reported by Friedberg and colleagues did not require additional lymphoma therapy for more than three years.**
   a. One fourth
   b. One third
   c. One half
4. **In a Phase I/II study, bortezomib/lenalidomide/dexamethasone (RVD) produced high-quality responses in patients with newly diagnosed multiple myeloma (MM), regardless of _____.**
   a. ISS stage
   b. Cytogenic status
   c. Both a and b
5. **In the Phase I/II trial evaluating RVD for patients with newly diagnosed MM, the regimen adversely affected stem cell harvesting in the majority of patients.**
   a. True
   b. False
6. **A trial evaluating bortezomib, dexamethasone, cyclophosphamide and lenalidomide (VDCR) was discontinued due to excessive, unmanageable hematologic toxicity.**
   a. True
   b. False
7. **Ofatumumab is a fully humanized anti-CD20 monoclonal antibody.**
   a. True
   b. False
8. **Which of the following regimens is being evaluated in the Intergroup trial CALGB-10404 as first-line therapy for chronic lymphocytic leukemia?**
   a. FCR
   b. FR
   c. FR and lenalidomide
   d. All of the above
   e. None of the above
9. **The CALGB-50501 trial is evaluating the combination of bortezomib and _____ for patients with relapsed or refractory mantle-cell lymphoma.**
   a. Lenalidomide
   b. Thalidomide
   c. Rituximab
10. **In the AZA-001 trial, treatment with azacitidine improved median overall survival by approximately _____ compared to conventional care regimens for patients with high-risk myelodysplastic syndrome.**
    a. Three months
    b. Six months
    c. Nine months
    d. 12 months

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 3, 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
Effect of azacitidine on overall survival in myelodysplastic syndrome	4 3 2 1	4 3 2 1
SAKK-35/98: Randomized trial of prolonged versus short-course rituximab for follicular lymphoma	4 3 2 1	4 3 2 1
Phase III randomized trial of R-CHOP-14 versus R-CHOP-21 for diffuse large B-cell lymphoma	4 3 2 1	4 3 2 1
Mechanism of action of galiximab	4 3 2 1	4 3 2 1
Infectious complications associated with fludarabine	4 3 2 1	4 3 2 1
Activity of lenalidomide/bortezomib/dexamethasone (RVD) for newly diagnosed multiple myeloma	4 3 2 1	4 3 2 1
Incidence of neurotoxicity associated with bortezomib weekly versus twice weekly	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 treatment history and disease cytogenetics to individualize the clinical management of myelodysplastic syndrome ..... 4 3 2 1 N/M N/A
- Describe available evidence-based therapeutic approaches for frequently encountered adult acute and chronic leukemias ..... 4 3 2 1 N/M N/A
- Formulate optimal front-line and maintenance strategies for patients with follicular lymphoma or diffuse large B-cell lymphoma ..... 4 3 2 1 N/M N/A
- Summarize emerging data with novel agents and combinations in the setting of newly diagnosed or relapsed/refractory, indolent or aggressive non-Hodgkin lymphoma ..... 4 3 2 1 N/M N/A
- Integrate innovative combination regimens into the management of multiple myeloma, considering the benefits and risks of proteasome inhibitors and immunomodulatory agents ..... 4 3 2 1 N/M N/A
- Counsel patients with hematologic cancer about the side effects and toxicities associated with various systemic therapies ..... 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
Jonathan W Friedberg, MD	4 3 2 1	4 3 2 1
Nikhil C Munshi, MD	4 3 2 1	4 3 2 1
Vicki A Morrison, MD	4 3 2 1	4 3 2 1
Elias Jabbour, 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:

⬭ MD ⬭ DO ⬭ PharmD ⬭ NP ⬭ RN ⬭ PA ⬭ Other .....

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Research To Practice designates this educational activity for a maximum of 2.75 *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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