

Hematologic Oncology™

U P D A T E

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

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INTERVIEWS

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Hematologic Oncology Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Approximately 135,520 new cases of lymphoid and myeloid cancer and related disorders were identified in the United States in the year 2007, and 52,310 individuals will die from these diseases. Importantly, more than 45 drug products are currently approved for use in the management of hematologic malignancies, comprising more than 55 distinct FDA-approved indications. Although this extensive list of available treatment options is reassuring to patients and oncology healthcare professionals, it poses a challenge to clinicians who must maintain up-to-date knowledge of appropriate clinical management strategies. 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 up-to-date clinical management strategies to facilitate optimal patient care.

LEARNING OBJECTIVES

- Utilize prognostic and predictive clinical and molecular markers to aid in treatment decision-making for patients with hematologic malignancies.
- Demonstrate knowledge of emerging research investigating the role of dose-dense induction therapy and novel targeted agents in the current and future management of non-Hodgkin's lymphoma.
- Plan primary therapy for patients with chronic lymphocytic leukemia (CLL), considering clinical research on the use of novel chemotherapeutics, monoclonal antibodies and immunomodulatory agents.
- Develop an evidence-based approach to the use of BCR-ABL targeted therapies for patients with chronic myelogenous leukemia (CML), based on the clinical characteristics of the disease.
- Formulate therapeutic interventions for patients with imatinib-resistant CML and strategies for monitoring disease progression.
- Devise up-front therapeutic interventions for patients with multiple myeloma who are or are not candidates for stem cell transplantation, based on emerging clinical trial data with novel agents and combinations.
- Develop a therapeutic plan for the treatment of myelodysplastic syndrome, considering recent safety and efficacy data for the novel DNA hypomethylating agent and HDAC inhibitors.
- Counsel appropriately selected patients with myeloid and lymphoid disorders about their potential participation in clinical research studies incorporating novel treatment approaches.

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This program is supported by educational grants from Bayer Pharmaceuticals Corporation, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium Pharmaceuticals — The Takeda Oncology Company and Ortho Biotech Products LP.

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INTERVIEW

Steven D Gore, MD

Dr Gore is Professor of Oncology at Johns Hopkins University and The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland.

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Track 1

► **DR LOVE:** Would you discuss the presentation of the azacitidine trial (AZA-001) at ASH 2007 by Fenaux?

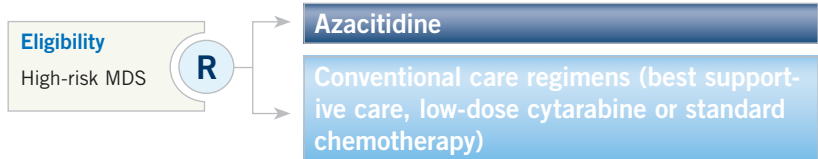
► **DR GORE:** This seminal study was conducted primarily in Europe, and the participating doctors selected one of three conventional care regimens (Fenaux 2007; [1.1]). The trial was set up this way because in Europe a great deal of variability existed in what was considered the standard treatment. For instance, in France they used a lot of low-dose cytarabine, and in Italy almost everyone received supportive care.

The three choices were (1) best supportive care — including growth factors and transfusions, (2) low-dose cytarabine or (3) standard chemotherapy. Once the physician selected one of those three, the patient was randomly assigned to either that choice or azacitidine at the FDA-approved dose and schedule. Patients received azacitidine or the conventional care regimen until disease progression (Fenaux 2007; [1.1]).

This trial enrolled patients with high-risk myelodysplastic syndrome (MDS), and the median overall survival was improved by approximately nine months among those treated with azacitidine. More impressively, overall survival at two years in this high-risk group was approximately doubled, from 26 to 51 percent, which is extraordinary and clinically meaningful (Fenaux 2007; [1.1]).

1.1 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	24.4 months	15 months*
Two-year overall survival	51%	26%†
Median time to AML	26.1 months	12.4 months

* Hazard ratio (95% confidence interval) = 0.58 (0.43-0.77), $p = 0.001$

† $p < 0.0001$

AML = acute myelogenous leukemia

SOURCE: Fenaux P et al. *Proc ASH* 2007; [Abstract 817](#).

Track 2

▶ **DR LOVE:** How do you choose between azacitidine and decitabine in clinical practice?

▶ **DR GORE:** I have conducted a lot of research on these compounds, and it’s my belief that biologically they’re similar. If they were administered in equally toxic or equally effective dosing schedules, they would probably be quite similar. However, they have been developed clinically in highly different schedules.

The FDA-approved schedule for decitabine, a three-day intravenous inpatient schedule administered every six weeks, is probably a more toxic regimen than the azacitidine regimen in terms of hematologic toxicity. Two survival trials used that decitabine regimen. One, published by Kantarjian in *Cancer* a couple of years ago, showed no survival benefit compared to observation (Kantarjian 2006). I believe that the trial showed no survival benefit because the median number of cycles that were administered was only two to three.

For both of these agents, to obtain hematologic benefit you need to use at least four to six cycles. All of the azacitidine trials have, for the most part, enabled patients who didn't achieve a complete remission to receive ongoing therapy. However, none of the decitabine trials have used more than eight cycles of therapy. So the duration of response always appears greater in the azacitidine trials, which I believe suggests that maintenance therapy is important.

The EORTC ran a similar trial comparing supportive care to the FDA-approved regimen of decitabine for patients with high-risk MDS. Although it was only reported as a press release, they didn't meet their target endpoint, which is to say that decitabine did not improve overall survival (Eisai 2008). Hence we have two drugs that biologically are similar but have different doses and schedules. One doubles survival at two years, and one doesn't. To me, it's incumbent on the physician to prescribe azacitidine.

Alternative dosing schedules for decitabine, which are better tolerated — particularly those developed at MD Anderson — have been studied only in Phase II trials (Kantarjian 2007), and they haven't been studied for their impact on survival. Again, I believe that if you're interested in improving a patient's survival, outside of a clinical trial, the data suggest using azacitidine at the FDA-approved dose and schedule.

Tracks 5, 7

▶ **DR LOVE:** Could you discuss entinostat and how it's being evaluated?

▶ **DR GORE:** Entinostat (MS-275) is one of the second-generation histone deacetylase (HDAC) inhibitors. It's been studied in AML in a Phase I study, and it clearly has some monotherapy activity (Gojo 2007). We chose to combine it with azacitidine in a Phase I study, which we presented at ASH. Although one should not extrapolate from a Phase I study, responses were promising (Gore 2006). We're currently conducting a Phase II randomized trial (ECOG-E1905; [1.2]) comparing the combination of azacitidine and entinostat to azacitidine alone in AML and MDS.

▶ **DR LOVE:** What's been observed with the HDAC inhibitors in terms of side effects and toxicities?

▶ **DR GORE:** The HDAC inhibitors tend to induce significant asthenia if the dose is pushed. It is the limiting factor. Even with the FDA-approved dose and schedule of vorinostat for cutaneous T-cell lymphomas, patients are extremely fatigued. Many of them have some nausea, but fatigue is the biggest problem. HDAC inhibitors have also been associated with cardiac QT interval issues. The HDAC inhibitor that's drawn the most attention is romidepsin, also known as depsipeptide. For a while it was thought to be particularly cardiotoxic, but that's probably not true (Klimek 2008; Byrd 2005). Certainly, EKG changes must be monitored, which seems to be a class effect.

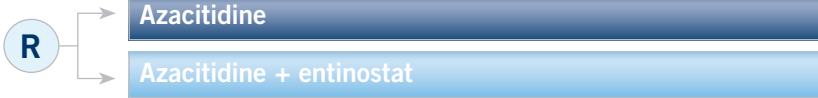
The side-effect profile of our combination of azacitidine and entinostat does not appear to be significantly different from that of azacitidine alone at the

doses of entinostat we're administering, which are low (Gore 2006). Of course, it will require the randomized Phase II trial results to compare the adverse events of the two arms. ■

1.2

Phase II Randomized Study of Azacitidine with or without Entinostat

Protocol ID: ECOG-E1905
Target Accrual: 152 (Open)



Eligibility

- Myelodysplastic syndrome (MDS) or
- Chronic myelomonocytic leukemia (dysplastic subtype) or
- Acute myeloid leukemia with multilineage dysplasia (AML-TLD)

Study Contact

Eastern Cooperative Oncology Group
Steven Gore, MD
Tel: 410-955-8781

SOURCE: NCI Physician Data Query, July 2008.

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INTERVIEW

Michael J Keating, MB, BS

Dr Keating is Professor of Medicine in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas.

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| Track 2 | Prognostic factors in CLL | Track 9 | Future therapeutic approaches for CLL |
| Track 3 | Clinical presentations of CLL | Track 10 | Clinical use of imatinib in chronic myelogenous leukemia (CML) |
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Select Excerpts from the Interview

Track 4

► **DR LOVE:** Would you discuss the evolution of treatment options for patients with chronic lymphocytic leukemia?

► **DR KEATING:** We've gone from single-agent chlorambucil — with a response rate of approximately 50 to 60 percent and a three to five percent complete remission rate — to fludarabine — with a higher overall response rate and a 20 to 25 percent complete remission rate — to the combinations of fludarabine/cyclophosphamide (FC), fludarabine/rituximab (FR), fludarabine/cyclophosphamide/rituximab (FCR) or pentostatin/cyclophosphamide/rituximab. All of these combinations have evolved during the past eight to nine years of clinical trials.

The observation made by the CALGB that fludarabine/rituximab is superior to fludarabine alone (Byrd 2005) has been confirmed by a study performed in Europe (GCLLSG-CLL-8), in which the German CLL Study Group compared FC to FCR. FCR has now been established as having a higher

complete remission rate and a longer progression-free survival rate (Roche 2008). It is now widely accepted that chemoimmunotherapy with rituximab is superior to chemotherapy alone.

Track 5

▶ **DR LOVE:** What about alemtuzumab and bendamustine?

▶ **DR KEATING:** Chlorambucil has been compared to alemtuzumab. The study demonstrated higher complete and overall response rates and a longer progression-free survival rate with alemtuzumab compared to chlorambucil. However, no overall survival advantage has been noted (Hillmen 2007; [2.1]).

2.1

Phase III Randomized Trial of Alemtuzumab versus Chlorambucil as First-Line Therapy for CLL

Results based on independent response review panel

	Alemtuzumab (n = 149)	Chlorambucil (n = 148)	p-value
Overall response rate	83.2%	55.4%	<0.0001
Complete response rate	24.2%	2.0%	<0.0001
MRD-negative	7.4%	0%	0.0008
Median progression-free survival	14.6 months	11.7 months	0.0001

MRD = minimal residual disease

“Our results indicate that alemtuzumab may be the most active single agent for the treatment of patients with CLL, and appears to have an important role in the treatment of patients with poor-risk cytogenetics and in the eradication of MRD.”

SOURCE: Hillmen P et al. *J Clin Oncol* 2007;25(35):5616-23. [Abstract](#)

A presentation at ASH compared bendamustine, which is an alkylating agent, to chlorambucil. That study demonstrated a significantly higher complete response rate, overall response rate and progression-free survival rate with bendamustine (Knauf 2007).

Track 6

▶ **DR LOVE:** Would you discuss how alemtuzumab and bendamustine fit into the overall treatment algorithm for CLL?

▶ **DR KEATING:** In the front-line setting, alemtuzumab may be used for patients who don't want to receive chemotherapy, which may be predominantly the elderly patient population. Whether doctors in the United States will be interested in doing that is questionable. Alemtuzumab is extremely potent in clearing the peripheral blood. In five to six days, all the leukemic cells are gone. It's fairly effective in the marrow and spleen but not effective in bulky lymph nodes.

Bendamustine is generating a lot of interest because of a suggestion that it is a better alkylating agent. In lymphoma, bendamustine seems to be as good or perhaps slightly better than CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in comparisons of CHOP with rituximab to bendamustine with rituximab (Rummel 2007). Bendamustine is administered for two days, so it's relatively convenient. It may cause cumulative suppression of the marrow, but we need more data on this and more US experience before we can draw as many conclusions as we wish.

Track 8

▶ **DR LOVE:** Would you discuss the combination of alemtuzumab with rituximab?

▶ **DR KEATING:** The combination was put together predominantly by our group at MD Anderson on the basis that rituximab performed well in terms of shrinking lymph nodes but did not perform well in the bone marrow, and alemtuzumab performed well in the marrow and not in the lymph nodes. Our thinking was that because we had two antigen targets, CD20 and CD52, it was possible that the two antibodies together would have a greater effect.

We conducted a four-week program with four conventional doses of rituximab and twice-a-week alemtuzumab. You might expect a 20 to 25 percent partial response rate. However, with four weeks of treatment, approximately 40 percent of the patients experienced partial remission and five to 10 percent experienced complete remission (Faderl 2003).

My thought, without direct proof, is that the drugs are greater than additive and are probably synergistic. An advantage is that the whole truncated course is finished in four weeks. Patients have rapid responses, and we don't see any toxicity with the combination beyond what you might see with alemtuzumab or rituximab alone.

Track 10

▶ **DR LOVE:** Let's talk about the management of chronic myelogenous leukemia.

▶ **DR KEATING:** The complete cytogenetic and molecular response rates are so good that imatinib is obviously the treatment of choice. A dose of 400 milligrams is great, but would 600 milligrams or 800 milligrams be better? The responses appear to be quicker but not necessarily better on a long-term basis, and more toxicity appears with the higher doses (Cortes 2008).

Before the new tyrosine kinase inhibitors dasatinib and nilotinib were available, patients who were not faring well would receive imatinib dose escalations, and some responded (Kantarjian 2003). Now a higher dose of imatinib has been compared to dasatinib. The time to treatment failure was superior with dasatinib compared to the higher dose of imatinib (Kantarjian 2007;

[2.2]). I believe that most people are simply switching to a different tyrosine kinase inhibitor rather than increasing the dose of imatinib. ■

2.2

Randomized Phase II Trial Comparing Dasatinib to High-Dose Imatinib for Chronic-Phase CML (CP-CML) After Failure of First-Line Imatinib

“This randomized study confirmed that treatment with dasatinib results in early and complete cytogenetic responses in patients with CP-CML resistant to imatinib at conventional doses of 400 to 600 mg. Dasatinib represents a safe and effective therapy for patients with CP-CML resistant to conventional doses of imatinib with improved cytogenetic and molecular response rates and progression-free survival relative to high-dose imatinib (800 mg). Based on these data, dasatinib appears to be more active than high-dose imatinib for patients who experience imatinib failure.”

SOURCE: Kantarjian H et al. *Blood* 2007;109(12):5143-50. [Abstract](#)

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INTERVIEW

William I Bensinger, MD

Dr Bensinger is Professor of Medicine at the University of Washington and Member of the Hutchinson Cancer Research Center in Seattle, Washington.

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| Track 2 | Incorporation of novel therapeutic agents and strategies by community oncologists in the treatment of MM | Track 10 | ECOG-E4A03: Lenalidomide with high-dose or low-dose dexamethasone in newly diagnosed MM |
| Track 3 | Role of stem cell transplantation for MM in an era of rapidly developing novel therapeutics | Track 11 | Maintenance therapy with IMiDs (thalidomide or lenalidomide) after transplant |
| Track 4 | Impact of lenalidomide and bortezomib on stem cell collection | Track 12 | Incorporation of liposomal doxorubicin in the management of MM |
| Track 5 | Novel combinations with thalidomide, bortezomib or lenalidomide versus VAD-based therapies prior to transplant | Track 13 | Randomized study of “cryotherapy” during administration of high-dose melphalan to decrease oral mucositis |
| Track 6 | FHCRC-2123.00: A Phase II clinical trial of cyclophosphamide, bortezomib, dexamethasone and thalidomide (VEL-CTD) in newly diagnosed MM | Track 14 | Melphalan/prednisone (MP) versus MP/thalidomide or MP/bortezomib for patients with newly diagnosed MM who are ineligible for transplant |
| Track 7 | Use of doublet versus triplet combination therapies in the up-front treatment of MM | Track 15 | Treatment algorithm for patients with newly diagnosed MM |
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| | | Track 17 | Bisphosphonate-associated osteonecrosis of the jaw |

Select Excerpts from the Interview

Track 5

► **DR LOVE:** Can you discuss the recent research reports on using novel biologics in the up-front setting in multiple myeloma?

► **DR BENSINGER:** We have three novel combinations that have been studied to a limited degree in randomized trials: thalidomide and dexamethasone (TD),

bortezomib and dexamethasone (VD) and lenalidomide and dexamethasone (RD). In addition, some early data exist with a triplet regimen combining VTD (bortezomib, thalidomide and dexamethasone; [Wang 2005]), and we have limited data on VRD (bortezomib, lenalidomide and dexamethasone; [Richardson 2007]).

For many years, the combination of vincristine, doxorubicin and dexamethasone (VAD) has been the standard for patients undergoing transplant, but these newer doublets and triplets are producing much higher overall response rates and higher complete remission rates than VAD (3.1). Survival data are at least one to two years off, but considering that the response rates with these doublets and triplets are remarkably higher than what we've seen with VAD-based combinations, I believe that these novel drug combinations are superior to more traditional regimens.

I believe the triplets — VRD or VTD — may be better than the doublets, but we don't know for sure at this time. This is difficult for the oncologist who is considering which sequences to use, how long to treat and when to refer patients for transplants.

3.1

Response and Complete Remission with Bortezomib-Based Primary Therapy in Patients with Newly Diagnosed Multiple Myeloma

	VRD* ¹ (n = 66)	VTD ^{†2} (n = 129)
Complete response (CR)	26%	NR
Near CR (nCR)	11%	NR
CR + nCR	37%	36%
≥VGPR	72%	60%
Partial response	27%	NR

* VRD = bortezomib/lenalidomide/dexamethasone
[†] VTD = bortezomib/thalidomide/dexamethasone
 NR = not reported; VGPR = very good partial response

SOURCES: ¹ Richardson PG et al. *Proc ASCO* 2008; [Abstract 8520](#); ² Cavo M et al. *Proc ASH* 2007; [Abstract 73](#).

 **Track 10**

► **DR LOVE:** Can you discuss the ECOG trial evaluating dose of dexamethasone?

► **DR BENSINGER:** The ECOG-E4A03 trial evaluated lenalidomide in combination with either high-dose dexamethasone or low-dose dexamethasone (Rajkumar 2007, 2008). There were significantly fewer major toxicities, including clotting, infectious complications and cardiac complications, in the low-dose arm.

The overall response rate was less robust in the low-dose arm, but early survival data suggested an advantage for the low-dose arm compared to the high-dose arm despite the lower response rates. Although excess toxicity was associated with an increase in mortality, patients in the high-dose arm actually died more frequently of progression of the myeloma (3.2). However, although they demonstrated robust responses, they had to come off the study more frequently because of toxicity, and they were less tolerant of subsequent therapies because of the early toxicity.

In the low-dose arm, patients were able to tolerate this regimen better, and they could remain on therapy for a longer period.

3.2

Superior Survival with Lenalidomide and Low-Dose versus High-Dose Dexamethasone in Newly Diagnosed MM

“Lenalidomide plus low-dose dexamethasone is associated with superior overall survival compared to lenalidomide plus high-dose dexamethasone. The excess mortality in the high-dose dexamethasone arm was due to both disease progression (myeloma deaths) as well as increased toxicity. This study has major implications for the use of high-dose dexamethasone in the treatment of newly diagnosed MM.”

SOURCE: Rajkumar SV et al. *Proc ASH* 2007; [Abstract 74](#).

3.3

Bortezomib (V) or Thalidomide (T) in Combination with Melphalan/Prednisone (MP) versus MP as First-Line Therapy for Multiple Myeloma

Study/endpoints	Treatment		Hazard ratio
	MPV	MP	
San-Miguel (N = 682) ¹			
Overall survival	Not reached	Not reached	0.61
Time to progression	24.0mo	16.6mo	0.48
At least partial response	71%	35%	
Hulin (N = 229) ²	MPT	MP	
Overall survival	45.3mo	27.7mo	Not reported
Progression-free survival	24.1mo	19.0mo	Not reported
At least partial response	61%	31%	
Facon (N = 447) ³	MPT	MP	
Overall survival	51.6mo	33.2mo	0.59
Progression-free survival	27.5mo	17.8mo	0.51
At least partial response	76%	35%	

SOURCES: ¹ San-Miguel JF et al. *Proc ASH* 2007; [Abstract 76](#); ² Hulin C et al. *Proc ASH* 2007; [Abstract 75](#); ³ Facon T et al. *Lancet* 2007;370(9594):1209-18. [Abstract](#)

 **Track 14**

▶ **DR LOVE:** What’s your first-line approach for patients who are not candidates for transplant?

► **DR BENSINGER:** My approach has changed because of remarkable clinical trial data. Several European trials have resurrected melphalan/prednisone (MP), which, although it has been standard for many years, has also been known as not highly effective. Recent studies have added an IMiD, primarily thalidomide, or bortezomib, to MP (Facon 2007; Hulin 2007; San-Miguel 2007).

All of these studies have shown remarkably improved response rates and improved event-free and overall survival rates. These trials have robust numbers of patients and are definitive in showing that these triplet combinations are superior to standard MP for older patients (3.3). ■

SELECT PUBLICATIONS

Cavo M et al. **Bortezomib (Velcade)-thalidomide-dexamethasone (VTD) vs thalidomide-dexamethasone (TD) in preparation for autologous stem-cell (SC) transplantation (ASCT) in newly diagnosed multiple myeloma (MM).** *Proc ASH 2007*; [Abstract 73](#).

Facon T et al. **Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): A randomised trial.** *Lancet 2007*;370(9594):1209-18. [Abstract](#)

Hulin C et al. **Comparison of melphalan-prednisone-thalidomide (MP-T) to melphalan-prednisone (MP) in patients 75 years of age or older with untreated multiple myeloma (MM). Preliminary results of the randomized, double-blind, placebo controlled IFM 01-01 trial.** *Proc ASCO 2007*; [Abstract 8001](#).

Jagannath S et al. **A phase II study of bortezomib (Velcade®), cyclophosphamide (Cytosan®), thalidomide (Thalomid®) and dexamethasone as first-line therapy for multiple myeloma.** *Proc ASH 2007*; [Abstract 188](#).

Kumar S et al. **Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma.** *Leukemia 2007*;21:2035-42. [Abstract](#)

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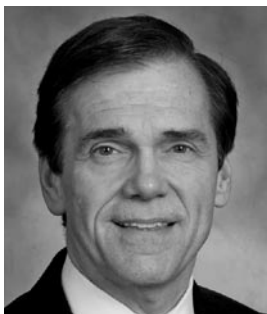
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Rajkumar SV et al. **A randomized trial of lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed multiple myeloma (E4A03): A trial coordinated by the Eastern Cooperative Oncology Group.** *Proc ASH 2007*; [Abstract 74](#).

Richardson PG et al. **Safety and efficacy of lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma: A phase I/II study.** *Proc ASCO 2008*; [Abstract 8520](#).

San-Miguel JF et al. **MMY-3002: A phase 3 study comparing bortezomib-melphalan-prednisone (VMP) with melphalan-prednisone (MP) in newly diagnosed multiple myeloma.** *Proc ASH 2007*; [Abstract 76](#).

Wang M et al. **Rapid control of previously untreated multiple myeloma with bortezomib-thalidomide-dexamethasone followed by early intensive therapy.** *Proc ASH 2005*; [Abstract 784](#).



INTERVIEW

Fredrick B Hagemeister, MD

Dr Hagemeister is Professor of Medicine at The University of Texas MD Anderson Cancer Center's Department of Lymphoma/Myeloma in Houston, Texas.

Tracks 1-9

- | | | | |
|----------------|--|----------------|--|
| Track 1 | New agents being evaluated in the treatment of lymphomas | Track 6 | Impact of rituximab serum levels on disease progression |
| Track 2 | DENSE-R-CHOP-14 trial: Dose-dense rituximab in elderly patients with diffuse large B-cell lymphoma | Track 7 | Bendamustine versus chlorambucil for treatment-naïve patients with B-cell CLL: Pivotal trial results |
| Track 3 | Clinical use of R-CHOP-14 | Track 8 | Bendamustine-R versus CHOP-R in the first-line treatment of indolent and mantle cell lymphomas |
| Track 4 | Tolerability of R-CHOP-14 in older patients | Track 9 | Integration of bortezomib into treatment regimens for lymphomas |
| Track 5 | DENSE-R-CHOP-14 trial: Study design and results | | |

Select Excerpts from the Interview

Tracks 2, 5

► **DR LOVE:** Can you discuss the trial of dose-dense rituximab with CHOP-14 in elderly patients with diffuse large B-cell lymphoma presented at ASCO 2008?

► **DR HAGEMEISTER:** That trial demonstrated that if you administer rituximab more frequently — two times a week — then higher rituximab levels are sustained over a much longer period. Dose-dense rituximab also somehow imparts a better response rate and disease-free survival rate among patients with large-cell lymphoma (Pfreundschuh 2008a; [4.1]). The study was conducted with patients older than age 60, which is the population in which we've been using R-CHOP-14 clinically.

The caveat with this regimen is that you have to use trimethoprim/sulfamethoxazole and acyclovir as prophylaxis (Pfreundschuh 2008a), which we have not normally used with R-CHOP-21 but has been described by Memorial Sloan-Kettering with the use of standard R-CHOP-14. I've

changed my practice — I use prophylactic trimethoprim/sulfamethoxazole and acyclovir for patients who receive standard R-CHOP-14.

► **DR LOVE:** Would you discuss the study design and results?

► **DR HAGEMEISTER:** It was a Phase II trial for which they selected patients with high-risk disease (Pfreundschuh 2008a). They compared these Phase II results to the results from their previous study (RICOVER-60) of R-CHOP-14 versus CHOP-14 (Pfreundschuh 2008b). The patients in the new study who received dose-dense rituximab and had worse risk features, such as more advanced disease, fared better. It was approximately a 10 percent improvement in progression-free survival after a short follow-up (Pfreundschuh 2008a; [4.1]).

I don't know whether they'll fall off eventually or how the data will ultimately appear. However, at an early point, it seems that using rituximab more frequently and obtaining higher rituximab levels in patients with large-cell lymphoma improve disease-free survival, time to relapse and other parameters (Pfreundschuh 2008a). Whether it will improve overall survival, I don't know.

4.1 Comparison of Dose-Dense R-CHOP-14 to R-CHOP-14 for Elderly Patients with Poor-Prognosis Diffuse Large B-Cell Lymphoma (DLBCL)

	DENSE-R-CHOP-14 (n = 124)	RICOVER (R-CHOP-14) (n = 306)	p-value
Complete response rate			
Overall	82%	78%	—
IPI 1 or 2	83%	84%	—
IPI 3, 4 or 5	82%	68%	0.037
Event-free survival			
IPI 1 or 2	78%	81%	0.481
IPI 3, 4 or 5	70%	60%	0.124
Progression-free survival			
IPI 1 or 2	87%	89%	0.557
IPI 3, 4 or 5	80%	70%	0.057

IPI = international prognostic index

“Densification of R results in higher serum levels and in higher complete remission and event-free survival rates in elderly pat. with poor-prognosis DLBCL.”

SOURCES: Pfreundschuh M et al. *Proc ASCO* 2008a; [Abstract 8508](#); Pfreundschuh M et al. *Lancet Oncol* 2008b;9(2):105-16. [Abstract](#)

Tracks 7-8

► **DR LOVE:** Can you review what we know about bendamustine in follicular lymphoma?

► **DR HAGEMEISTER:** The German data comparing bendamustine with rituximab to R-CHOP that were presented at ASH 2007 were interesting. They demonstrated that bendamustine/rituximab was as efficacious as R-CHOP in

patients with a variety of different indolent lymphomas. The data indicated a complete response rate of around 50 percent in patients with indolent or mantle-cell lymphoma (Rummel 2007; [4.2]). They suggest a role for bendamustine, particularly in combination with rituximab.

4.2

Phase III Randomized Trial of Bendamustine with Rituximab (B-R) versus R-CHOP as First-Line Therapy for Patients with Indolent or Mantle-Cell Lymphoma

	B-R (n = 139)	R-CHOP (n = 134)
Overall response rate	94%	93%
Complete response rate	51%	40%
Total alopecia	0%	40%
Grade III/IV leukocytopenia	12%	41%

“In this first interim analysis the combination of bendamustine plus rituximab appears to be non-inferior to the standard CHOP-R while showing a better tolerability profile.”

SOURCE: Rummel MJ et al. *Proc ASH* 2007; [Abstract 385](#).

 **Track 9**

▶ **DR LOVE:** Where are we with bortezomib in lymphoma?

▶ **DR HAGEMEISTER:** Evidence suggests that when you expose rituximab-resistant cell lines to bortezomib, you can make those cell lines rituximab sensitive. Evidence in cell lines also suggests that bortezomib is either additive or synergistic in combination with chemotherapy and other drugs. Ongoing studies are using rituximab with cyclophosphamide, bortezomib and prednisone (R-CBorP) for indolent lymphomas, substituting bortezomib for vincristine (Gerecitano 2008). Other trials are considering the addition of bortezomib in the treatment of mantle-cell lymphoma, indolent lymphoma and large-cell lymphoma. ■

SELECT PUBLICATIONS

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](#).

Pfreundschuh M et al. **Improved outcome of elderly patients with poor-prognosis diffuse large B-cell lymphoma (DLBCL) after dose-dense rituximab: Results of the DENSE-R-CHOP-14 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL).** *Proc ASCO* 2008a; [Abstract 8508](#).

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* 2008b;9(2):105-16. [Abstract](#)

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab in the first-line treatment of patients with indolent and mantle cell lymphomas — First interim results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2007; [Abstract 385](#).

QUESTIONS (PLEASE CIRCLE ANSWER):

- In a Phase III randomized trial for patients with high-risk MDS, _____ significantly improved median overall survival compared to the conventional care regimens of best supportive care, low-dose cytarabine or standard chemotherapy.
 - Decitabine
 - Azacitidine
 - Lenalidomide
 - Both a and b
 - All of the above
- Bendamustine is a(n) _____.
 - Alkylating agent
 - Antimetabolite
 - Monoclonal antibody
 - Vinca alkaloid
 - None of the above
- A Phase II trial demonstrated that time to treatment failure was superior with dasatinib compared to high-dose imatinib for patients with chronic-phase CML after failure on conventional doses of imatinib.
 - True
 - False
- In the Phase II trial of cyclophosphamide, bortezomib, dexamethasone and thalidomide prior to stem cell transplant, _____ of the patients had a complete response or near complete response.
 - 12 percent
 - 22 percent
 - 42 percent
 - 70 percent
- In the ECOG-E4A03 trial, low-dose dexamethasone in combination with lenalidomide was associated with _____ compared to high-dose dexamethasone in combination with lenalidomide.
 - Significantly fewer major toxicities
 - Lower overall response rate
 - Improvement in overall survival
 - All of the above
- The addition of _____ to first-line melphalan and prednisone (MP) improves response rates, event-free survival and overall survival for patients with transplant-ineligible multiple myeloma.
 - Thalidomide
 - Bortezomib
 - Either a or b
 - None of the above
- Elderly patients with diffuse large B-cell lymphoma and poor-risk features in a Phase II trial of dose-dense rituximab in combination with CHOP-14 demonstrated a higher response rate and longer disease-free survival rate when compared to patients on the control arm of the RICOVER-60 trial, who received R-CHOP-14.
 - True
 - False
- Elderly patients with large B-cell lymphoma in a Phase II trial of dose-dense rituximab in combination with CHOP-14 received prophylaxis with _____.
 - Trimethoprim/sulfamethoxazole
 - Acyclovir
 - Both a and b
 - None of the above
- In a Phase III trial, the overall response rate with bendamustine/rituximab was _____ to that with R-CHOP for patients with indolent lymphomas.
 - Comparable
 - Superior
 - Inferior

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 2, 2008

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

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Role of azacitidine in the treatment of high-risk MDS	4	3	2	1
Alemtuzumab and bendamustine in the treatment of CLL	4	3	2	1
Novel first-line therapeutic options for multiple myeloma in patients ineligible for transplant	4	3	2	1
Novel schedules and treatment combinations with rituximab for non-Hodgkin's lymphoma	4	3	2	1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Role of azacitidine in the treatment of high-risk MDS	4	3	2	1
Alemtuzumab and bendamustine in the treatment of CLL	4	3	2	1
Novel first-line therapeutic options for multiple myeloma in patients ineligible for transplant	4	3	2	1
Novel schedules and treatment combinations with rituximab for non-Hodgkin's lymphoma	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 LEARNER statements by circling the appropriate selection:

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

- Utilize prognostic and predictive clinical and molecular markers to aid in treatment decision-making for patients with hematologic malignancies 4 3 2 1 N/M N/A
- Demonstrate knowledge of emerging research investigating the role of dose-dense induction therapy and novel targeted agents in the current and future management of non-Hodgkin's lymphoma 4 3 2 1 N/M N/A
- Plan primary therapy for patients with chronic lymphocytic leukemia (CLL), considering clinical research on the use of novel chemotherapeutics, monoclonal antibodies and immunomodulatory agents 4 3 2 1 N/M N/A
- Develop an evidence-based approach to the use of BCR-ABL targeted therapies for patients with chronic myelogenous leukemia (CML), based on the clinical characteristics of the disease. 4 3 2 1 N/M N/A
- Formulate therapeutic interventions for patients with imatinib-resistant CML and strategies for monitoring disease progression 4 3 2 1 N/M N/A
- Devise up-front therapeutic interventions for patients with multiple myeloma who are or are not candidates for stem cell transplantation, based on emerging clinical trial data with novel agents and combinations 4 3 2 1 N/M N/A
- Develop a therapeutic plan for the treatment of myelodysplastic syndrome, considering recent safety and efficacy data for the novel DNA hypomethylating agent and HDAC inhibitors .. 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with myeloid and lymphoid disorders about their potential participation in clinical research studies incorporating novel treatment approaches .. 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?

.....

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

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Faculty	Knowledge of subject matter				Effectiveness as an educator
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Michael J Keating, MB, BS	4	3	2	1	4 3 2 1
William I Bensinger, MD	4	3	2	1	4 3 2 1
Fredrick B Hagemester, MD	4	3	2	1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the editor and faculty for this activity:

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This program is supported by educational grants from Bayer Pharmaceuticals Corporation, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium Pharmaceuticals — The Takeda Oncology Company and Ortho Biotech Products LP.

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Last review date: September 2008

Release date: September 2008

Expiration date: September 2009

Estimated time to complete: 3 hours