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Hematologic Oncology™ UPDATE

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

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Hematologic Oncology Update

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OVERVIEW OF ACTIVITY

More than 45 drug products are currently labeled for use in the management of hematologic malignancies, comprising more than 55 distinct FDA-approved indications. This extensive list of available treatment options poses a challenge to clinicians who must maintain current 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.
- Recall the emerging data for novel agents and combinations in the treatment of indolent and aggressive non-Hodgkin lymphoma (NHL).
- Appraise the role of maintenance rituximab in the management of follicular lymphoma.
- Counsel patients with chronic myelogenous leukemia (CML) about the long-term outcomes associated with the use of tyrosine kinase inhibitors for PDGFR- and c-kit-mediated cellular events.
- Formulate therapeutic interventions for patients with imatinib-resistant CML, and delineate strategies for monitoring disease progression.
- Recommend primary therapy for patients with chronic lymphocytic leukemia (CLL), considering emerging clinical research on the use of novel chemotherapeutics, monoclonal antibodies and immunomodulatory agents.
- Develop an algorithm for the diagnosis, genomic classification and risk-stratified treatment of myelodysplastic syndrome (MDS).
- Devise individualized treatment plans for patients with multiple myeloma (MM), considering baseline eligibility for stem cell transplant and emerging clinical trial data with active novel agents.
- Counsel appropriately selected patients about participation in ongoing clinical research studies.

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INTERVIEW

Bruce D Cheson, MD

Dr Cheson is Head of Hematology and Director of Hematology Research at Georgetown University Hospital's Lombardi Comprehensive Cancer Center in Washington, DC.

Tracks 1-16

Select Excerpts from the Interview

Track 1

DR LOVE: Would you review what we know about bendamustine and NHL?

DR CHESON: In two trials for patients with rituximab-refractory disease, bendamustine alone was active, with overall response rates higher than 70 percent (Friedberg 2008; Kahl 2007). Rummel evaluated the combination of rituximab/bendamustine in patients with a variety of histologies of previously

treated indolent lymphoma or mantle-cell lymphoma. The overall response rate was 90 percent, with a complete remission rate of 60 percent (Rummel 2005).

We were able to reproduce these findings with rituximab/bendamustine in patients with indolent histologies, particularly follicular lymphoma or mantle-cell lymphoma. Surprisingly, the response rates were identical in the two populations — approximately 92 to 93 percent. These patients had relapsed/refractory disease, although patients with disease that was refractory to rituximab, defined by a less than partial response or a response lasting less than six months, were excluded (Robinson 2008; [1.1]).

These data suggest we have a new option — now that bendamustine has been approved — for patients with non-Hodgkin lymphoma that has failed prior therapies, particularly those with mantle-cell lymphoma, which is an incurable disease without many active therapies.

1.1

Phase II Trials of Bendamustine/Rituximab in Patients with Relapsed Lymphoma

	N	ORR	CR	CRu	PR
Pathologic subtype					
Indolent lymphoma	54	93%	41%	13%	39%
Mantle-cell lymphoma	12	92%	42%	17%	33%
Rituximab exposure					
Prior rituximab	37	87%	35%	14%	38%
No prior rituximab	29	100%	48%	14%	38%

N = number of patients; ORR = overall response rate; CR = complete response rate; CRu = complete response unconfirmed; PR = partial response

SOURCE: Robinson KS et al. *J Clin Oncol* 2008;26(27):4473-9. **Abstract**

Track 3

DR LOVE: What are the side effects and toxicities of bendamustine?

DR CHESON: Primarily myelosuppression — neutropenia and thrombocytopenia. The frequency with which these occur depends on the trial and the disease. In one of our trials, the most common reason for patients coming off the study was Grade III/IV thrombocytopenia, but that occurred in only about 10 percent of the patients.

Nausea and vomiting can occur but are unpredictable, so we recommend that all patients receive prophylactic antiemetics. An infusion reaction — associated with fevers, chills and muscle aches — has been reported in a small number of patients. In a couple of patients, the serum creatinine increased. This reaction subsides if you discontinue the drug or administer corticosteroids.

Whether the risk of secondary malignancies is associated with bendamustine is not clear.

Tracks 6-7

DR LOVE: Would you discuss the use of lenalidomide in B-cell malignancies?

DR CHESON: Lenalidomide is a second-generation immunomodulatory drug that has been approved for the treatment of multiple myeloma and myelodysplastic syndrome (MDS) in patients with the 5q deletion. It has also been evaluated in patients with indolent (Witzig 2007) and aggressive (Czuczman 2008) non-Hodgkin lymphoma, for which it has response rates of about 30 percent, depending on the histology.

Lenalidomide is also an interesting agent in chronic lymphocytic leukemia (CLL). Two studies using different doses and schedules have demonstrated activity in this setting. Chanan-Khan demonstrated a response rate of approximately 50 percent among patients with relapsed/refractory disease (Chanan-Khan 2006; [1.2]). Ferrajoli from MD Anderson achieved responses in around 35 percent of patients with relapsed/refractory disease (Ferrajoli 2008; [1.2]). We don't know whether the difference in response rates was due to patient selection, dose or schedule, but lenalidomide is active. Lenalidomide also appears to be active in patients with CLL who have adverse cytogenetics, such as the 11q abnormality and the 17p deletion (Ferrajoli 2007).

1.2 Phase II Trials of Lenalidomide in 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. **Abstract**; Ferrajoli A et al. *Blood* 2008;111(11):5291-7. **Abstract**

You have to be cautious with lenalidomide in patients with CLL. It has the usual side effects of myelosuppression, but two additional adverse effects are of particular concern. The first is a tumor flare reaction. Patients receive the agent for a couple of weeks, and suddenly their nodes increase markedly in size and become painful. The white blood cell count is also elevated. A few days or a week or two later, however, the nodes shrink, the pain goes away, the white count comes down and the patient is well and may even be in remission.

The second potentially serious adverse effect is tumor lysis syndrome, which appears to be dose independent. It has been reported at all doses, including doses as low as 2.5 milligrams per day. It can be life threatening or fatal (Moutouh-de Parseval 2007). The risk of tumor lysis syndrome appears to be especially high for patients with CLL, and we are most concerned about those patients who have increased tumor bulk.

Tracks 13-14

DR LOVE: What are some common questions you receive from oncologists with regard to patients who have follicular lymphoma?

DR CHESON: The big question is, "What is the best initial therapy for these patients?" Patients can receive R-CHOP, R-CVP or single-agent rituximab. Right now we don't know whether initial therapy will make any difference 10 or 15 years down the line, because we have many effective salvage therapies. I practice a risk-adapted approach.

If patients have bulky disease or need immediate therapy because they are symptomatic or organs are compromised, I lean toward R-CHOP. If the patient has progressive disease that's not big but probably needs to be treated, I may use R-CVP. I rarely use single-agent rituximab. It has a reasonable response rate, but the responses tend to be short-lived.

Other questions include, "What is the role of maintenance rituximab in follicular lymphoma?" and, "What is the optimal schedule for maintenance rituximab?"

Five different strategies have been published for maintenance rituximab: four doses every six months for two years, one dose every two months times four, one dose every three months for two years, one dose every three months until disease progression and a regimen based on serum rituximab levels. We don't know which is the best approach. We don't know which patients, if any, benefit from maintenance rituximab.

We also don't know whether maintenance rituximab benefits patients who have been treated with rituximab/chemotherapy. This question is being addressed by the PRIMA trial, in which patients were treated with a regimen selected by their institution — R-CHOP, R-CVP or R-FCM — and then randomly assigned to maintenance rituximab or not. The data from this study are maturing. If they show a meaningful benefit, it will certainly affect practice.

Maintenance rituximab is not innocuous. It is expensive and requires patients to come in to the office for an injection. More neutropenic infections and hospitalizations are reported with maintenance rituximab than without it. An increased risk of progressive multifocal leukoencephalopathy has also been reported in a small number of patients with lymphoma who received rituximab.

Data in the relapse setting suggest a survival benefit with maintenance rituximab. In a study of CHOP versus R-CHOP and maintenance rituximab versus no maintenance for patients with follicular lymphoma, a progression-free and overall survival benefit was found with maintenance rituximab (van Oers 2006; [1.3]). ■

1.3

Phase III Randomized Trial of CHOP versus R-CHOP with or without Rituximab (R) Maintenance for Patients with Relapsed Follicular Lymphoma (FL)

"The final analysis of the European Organisation for Research and Treatment of Cancer (EORTC) 20981 Intergroup study has shown several important findings. Firstly, in patients with relapsed/resistant FL, remission induction with R-CHOP results in a highly significant increase in CR rate as compared with CHOP; secondly, R maintenance treatment significantly improves PFS and OS in patients responding to induction treatment; thirdly, R maintenance treatment achieves a considerable increase in PFS not only after remission induction with chemotherapy (CHOP) but also after immunochemotherapy (R-CHOP)."

CR = complete response; PFS = progression-free survival; OS = overall survival

SOURCE: Van Oers MH et al. *Blood* 2006;108(10):3295-301. **Abstract**

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. **Abstract**

Czuczman MS et al. **International study of lenalidomide in relapsed/refractory aggressive non-Hodgkin's lymphoma.** *Proc ASCO* 2008;**Abstract 8509**.

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. **Abstract**

Ferrajoli A et al. **Lenalidomide is active in patients with relapsed/refractory chronic lymphocytic leukemia carrying unfavorable chromosomal abnormalities.** *Proc ASH* 2007;**Abstract 754**.

Friedberg JW et al. **Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: Results from a phase II multicenter, single-agent study.** *J Clin Oncol* 2008;26(2):204-10. **Abstract**

Kahl B et al. **Bendamustine is safe and effective in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma.** *Proc ASH* 2007;**Abstract 1351**.

Moutouh-de Parseval LA et al. **Tumor lysis syndrome/tumor flare reaction in lenalidomide-treated chronic lymphocytic leukemia.** *J Clin Oncol* 2007;25(31):5047. No abstract available

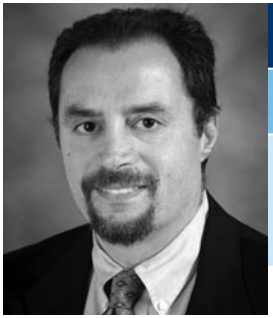
Robinson KS et al. **Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma.** *J Clin Oncol* 2008;26(27):4473-9. **Abstract**

Rummel MJ et al. **Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma.** *J Clin Oncol* 2005;23(15):3383-9. **Abstract**

Van Oers M et al. **Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin's lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 Intergroup trial.** *Blood* 2006;108(10):3295-301. **Abstract**

Weide R et al. **High anti-lymphoma activity of bendamustine/mitoxantrone/rituximab in rituximab pretreated relapsed or refractory indolent lymphomas and mantle cell lymphomas. A multicenter phase II study of the German Low Grade Lymphoma Study Group (GLSG).** *Leuk Lymphoma* 2007;48(7):1299-306. **Abstract**

Witzig TE et al. **Preliminary results from a phase II study of lenalidomide oral monotherapy in relapsed/refractory indolent non-Hodgkin lymphoma.** *Proc ASCO* 2007;**Abstract 8066**.



INTERVIEW

Hagop M Kantarjian, MD

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

Tracks 1-20

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What are some of the key clinical research issues related to the use of imatinib in patients with chronic myelogenous leukemia (CML)?

DR KANTARJIAN: Current questions include whether we can discontinue a patient's therapy with imatinib after a certain period. We're working on

immune stimulation of the host with either vaccines or peginterferon. Otherwise, patients will receive imatinib for a lifetime, as people receive medications for hypertension or diabetes.

Also significant is the issue of pregnancy in women receiving imatinib. Most women who become pregnant but stop imatinib deliver normal babies. A recent publication, however, reported three children with a syndrome of skeletal, kidney and eye malformations (Pye 2008). So we cannot confirm that women who are receiving imatinib will have safe pregnancies.

Another question involves resistance to imatinib, which occurs at a rate of approximately four percent per year. Several new-generation tyrosine kinase inhibitors are more potent than imatinib. Some of them are pure BCR-ABL inhibitors similar to imatinib. One of them, nilotinib, is FDA approved and has shown good results in patients for whom imatinib has failed. Among such patients, approximately 50 percent reachieve a complete cytogenetic response, and two-year overall survival is approximately 90 percent (Kantarjian 2008).

A second FDA-approved drug, dasatinib, produces similar results to nilotinib, with a complete cytogenetic response rate of approximately 60 percent and an estimated two-year overall survival of approximately 90 percent (Mauro 2008).

Still another question is whether any of these new-generation tyrosine kinase inhibitors can be moved up to front-line therapy. My assessment is that the results with imatinib are so good that it will be difficult to beat — it will take large, randomized trials with a follow-up of five to seven years. So I believe imatinib is well established as front-line therapy.

DR LOVE: What are some of the important clinical issues in caring for patients who receive imatinib for long periods?

DR KANTARJIAN: One of the most important issues is compliance. Approximately 70 percent of the patients are reported to have some form of noncompliance (Halpern 2007). It doesn't mean they stop taking imatinib completely, but they do miss days of the medication. If we have a patient who shows resistance to imatinib, the first possibility to consider is noncompliance. A test to measure plasma imatinib levels is available to determine whether the resistance is due to noncompliance or other factors, such as the development of mutations.

A second important issue is intolerance. Perhaps five percent of patients are completely intolerant. Most patients demonstrate this intolerance up front with skin rashes, liver function abnormalities or fluid retention.

Track 5

DR LOVE: What are some of the recent important research developments in the treatment of CLL?

DR KANTARJIAN: I have seen much progress since the discovery of the activity of fludarabine and the value of adding rituximab to fludarabine. Front-line treatment for patients with CLL who require therapy is usually a combination of fludarabine/rituximab or fludarabine/cyclophosphamide and rituximab.

Two other drugs have shown a great deal of promise in the setting of refractory disease. Alemtuzumab is approved for the treatment of refractory disease, and lenalidomide has shown activity across a range of disorders, such as multiple myeloma, MDS with the 5q abnormality, CLL and some lymphomas.

So the current question is, can we improve on the durability of responses? If a patient with CLL receives FCR therapy, we know the remissions will last for a median of six to eight years. Can we use alemtuzumab or lenalidomide as treatment for minimal residual disease rather than in the setting of failure of front-line therapy (2.1)?

Bendamustine, an old drug with the properties of alkylating agents and adenosine nucleoside analogs, was known to be active by investigators in East Germany about 30 years ago. Bendamustine emerged as one of the most powerful drugs in lymphoid malignancies. A study comparing bendamustine to chlorambucil as front-line therapy for CLL demonstrated its superiority and led to the approval of this indication for bendamustine (Knauf 2007).

We have moved away from chlorambucil in the United States. The approval for bendamustine is somewhat awkward because it is for front-line therapy, but US oncologists universally use fludarabine/rituximab-based therapy before considering bendamustine.

2.1

Toward Defining the Role of Alemtuzumab in CLL

"Although [alemtuzumab] already has an important role in the treatment of chronic lymphocytic leukemia (CLL), many of its uses are still being defined. Early trials showed alemtuzumab's value in refractory disease and helped to define its excellent activity in the bone marrow, spleen and 17p deleted patients. The CAM307 trial has demonstrated alemtuzumab's efficacy as monotherapy in the front-line setting, and ultimately led to its FDA approval as frontline therapy. Especially promising is the trend toward improved response in patients with high risk cytogenic abnormalities (17p del, 11q del, trisomy 12). The various consolidation trials have also provided promising results of achieving eradication of minimal residual disease (MRD). Although the ultimate benefit of achieving MRD negativity remains under investigation, alemtuzumab's potent activity on the bone marrow will likely make it an important part of combination therapy."

SOURCE: Kaufman M, Rai KR. *Ther Clin Risk Manag* 2008;4(2):459-64. **Abstract**

Track 18

DR LOVE: Let's talk about recent progress in the treatment of MDS.

DR KANTARJIAN: The first important building block was the discovery of the activity of the hypomethylating agents, azacitidine and decitabine. An international study comparing azacitidine to a conventional care regimen — low-dose ara-C, intensive chemotherapy or best supportive care — demonstrated a distinct survival advantage with azacitidine.

This is the first agent, outside of the setting of allogeneic transplantation, that changes the natural course of MDS. The median overall survival was approximately 25 months with azacitidine compared to 15 months with the standard treatment, and the two-year overall survival almost doubled from 26 to 51 percent (List 2008; Fenaux 2007; [2.2]).

Among patients with lower-risk MDS and a chromosome 5q deletion who were transfusion dependent, lenalidomide has shown a transfusion-independence rate of 66 percent, a complete cytogenetic response rate of about 45 percent and a median duration of response in terms of transfusion independence of approximately 27 months (List 2006; [2.3]).

Tracks 19-20

DR LOVE: Would you discuss your clinical strategy for patients wth MDS?

DR KANTARJIAN: Once the diagnosis is confirmed, we usually observe patients or, if indications for treatment are present, such as significant anemia, we use growth factors — erythropoietin with or without G-CSF. Transfusions are used as needed. We check every patient with MDS for chromosomal abnormalities for several reasons.

The first reason is prognostication. The chromosomal abnormalities are part of the International Prognostic Scoring System. Patients with a chromosome seven abnormality or more than three abnormalities have an average survival of less than one year. You must intervene rapidly for those patients. The second reason to conduct the chromosomal studies is to identify the patients with 5q deletions, who will benefit from lenalidomide (List 2006; [2.3]).

For elderly patients who do not respond to growth factors and require transfusions, if the blasts in the bone marrow are in the range of seven percent or less, I would try some form of immunotherapy, such as cyclosporine, steroids or antithymocyte globulin (ATG), before proceeding with hypomethylating agents.

If patients experience disease progression on these strategies or if they present with higher-risk MDS, then the first choice should be a hypomethylating agent, such as azacitidine because it has demonstrated a survival advantage (List 2008; Fenaux 2007; [2.2]). ■

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

	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), $p = 0.0001$; † $p < 0.0001$

AML = acute myelogenous leukemia

SOURCE: Fenaux P et al. *Proc ASH* 2007;**Abstract 817**.

2.3 Lenalidomide in MDS with Chromosome 5q Deletion

"In this study of transfusion-dependent patients with the myelodysplastic syndrome and chromosome 5q deletion, most patients had had no response to treatment with recombinant erythropoietin and had a substantial need for transfusions, with a median of 3 units per month. Seventy-six percent of the patients who were given lenalidomide needed fewer transfusions than they did before entering the study, and 67% became transfusion-independent, with a rise in hemoglobin to a nearly normal range. The response to treatment was rapid (median interval between initiation of treatment and response, 4.6 weeks) and durable; 61 patients (62%) who had a response to treatment remained transfusion-free for at least 1 year, and the median duration of transfusion independence had not been reached after a median follow-up of 2 years."

SOURCE: List A et al. *N Engl J Med* 2006;355(14):1456-65. **Abstract**

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Fenaux P et al. **Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): Results of the AZA-001 phase III study.** *Proc ASH* 2007;**Abstract 817**.

Halpern R et al. **Relationship between compliance with imatinib mesylate and medical costs for patients with CML and GIST.** *Proc ASCO* 2007;**Abstract 6618**.

Kantarjian HM et al. **Nilotinib in patients with imatinib-resistant or -intolerant chronic myelogenous leukemia in chronic phase (CML-CP): Updated phase II results.** *Proc ASCO* 2008;**Abstract 7010**.

Knauf WU et al. **Bendamustine versus chlorambucil in treatment-naive patients with B-cell chronic lymphocytic leukemia (B-CLL): Results of an international phase III study.** *Proc ASH* 2007;**Abstract 2043**.

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**.

List A et al. **Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion.** *N Engl J Med* 2006;355(14):1456-65. **Abstract**

Mauro MJ et al. **Dasatinib 2-year efficacy in patients with chronic-phase chronic myelogenous leukemia (CML-CP) with resistance or intolerance to imatinib (START-C).** *Proc ASCO* 2008;**Abstract 7009**.

Pye SM et al. **The effects of imatinib on pregnancy outcome.** *Blood* 2008;111(12):5505-8. **Abstract**

INTERVIEW

Sagar Lonial, MD

Dr Lonial is Associate Professor and Director of Translational Research for the B-Cell Malignancy Program in the Department of Medical Oncology and Hematology at the Emory University School of Medicine's Winship Cancer Institute in Atlanta, Georgia.

Tracks 1-18

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss recent research results in induction therapy for patients with multiple myeloma?

DR LONIAL: Historically, the selection of agents as induction therapy did not matter because transplant was the big hammer that equalized whatever was used and few induction regimens resulted in high complete response (CR) rates. Now regimens such as bortezomib/dexamethasone, lenalidomide/dexamethasone and lenalidomide/bortezomib/dexamethasone (RVD) are achieving much higher CR rates (Harousseau 2008; Zonder 2007; Richardson 2008).

This leads to questions such as, how can we maximize the CR rates up front, and does every patient need a transplant if we achieve that depth of response up front? We are also beginning to evaluate the depth of the CR, and I believe that's a testament to the success of our new drugs.

Track 4

DR LOVE: Would you discuss the ECOG-E4A03 study, which evaluated lenalidomide combined with high-dose versus low-dose dexamethasone in patients with multiple myeloma?

DR LONIAL: The most recent analysis suggested that approximately 22 percent of the patients achieved a CR or near CR and about half achieved a very good partial response or better (≥VGPR) when they received primary therapy with lenalidomide and low-dose dexamethasone beyond four cycles (Rajkumar 2008). Controversy remains regarding high-dose versus low-dose dexamethasone, but I believe tolerability is clearly better with the low dose. The first analysis of ECOG-E4A03 evaluated overall survival and demonstrated superiority for low-dose dexamethasone compared to high-dose dexamethasone.

It is interesting that when those data are parsed by age, no difference is evident between high-dose and low-dose dexamethasone for patients younger than age 65 compared to the older patients, among whom we clearly saw a big difference (Rajkumar 2007; [3.1]). Age and performance status are important determinants for dexamethasone dosing in my opinion.

3.1

ECOG-E4A03: Low-Dose versus High-Dose Dexamethasone (Dex) in Combination with Lenalidomide (Len) in Newly Diagnosed Multiple Myeloma

	N	12-month survival probability (95% CI)	24-month survival probability (95% CI)
Age < 65			
Len/high dex	104	0.92 (0.87-0.97)	0.85 (0.78-0.93)
Len/low dex	108	0.97 (0.94-1.00)	0.91 (0.84-0.98)
		$p = 0.13$	$p = 0.16$
Age ≥ 65			
Len/high dex	119	0.84 (0.77-0.91)	0.67 (0.56-0.77)
Len/low dex	114	0.95 (0.84-1.00)	0.82 (0.74-0.91)
		$p = 0.01$	$p = 0.009$

SOURCE: Rajkumar SV et al. *Proc ASH* 2007;**Abstract 74**.

The other aspect of those data is that the response rate was higher for the patients receiving lenalidomide/high-dose dexamethasone than for those receiving lenalidomide/low-dose dexamethasone. In fact, the ≥VGPR rate was approximately 10 to 12 percent higher with high-dose dexamethasone.

This is one of the few trials in which the response rate did not appear to correlate with survival, and I believe that has to do partly with the effect of age (Rajkumar 2007).

Track 6

DR LOVE: Would you discuss the trial (IFM 2005/01) comparing bortezomib/dexamethasone to vincristine/doxorubicin/dexamethasone (VAD) as induction therapy prior to autologous stem cell transplant (ASCT) in multiple myeloma?

DR LONIAL: The investigators reported superior up-front responses with bortezomib/dexamethasone compared to VAD. The CR/near-CR rate with bortezomib/dexamethasone was about 20 percent, and — a unique finding — the up-front response translated to a better post-transplant response (Harousseau 2008).

IFM 2005/01 was the first trial to demonstrate that the agents you use as induction therapy make a difference in terms of long-term outcomes. The difference between IFM 2005/01 and all of the preceding trials that didn't show a difference was that bortezomib/dexamethasone had a higher CR/near-CR rate than the regimens used in those older trials.

Tracks 7-8

DR LOVE: What are your thoughts about the trial by Cavo evaluating bortezomib/thalidomide/dexamethasone (VTD)?

DR LONIAL: The Cavo trial takes what is now my second-preferred regimen, VTD, and compares it to thalidomide/dexamethasone. A number of trials have evaluated thalidomide/dexamethasone versus VAD or dexamethasone as induction therapy. While the response rates with thalidomide/dexamethasone were better up front, after transplant they were all nullified.

Cavo reported that the CR/near-CR rates were significantly higher for VTD up front, almost 36 percent. This also translated to better post-transplant CR/near-CR rates (Cavo 2007). This was the second trial to report that the agents administered as induction therapy affect post-transplant outcomes.

DR LOVE: What is your preferred regimen for treating patients with newly diagnosed multiple myeloma?

DR LONIAL: My first-choice regimen is RVD, which is a combination of our most active drugs — lenalidomide, bortezomib and dexamethasone. I believe the real power of RVD lies in the high responses reported with that regimen.

The overall response rate was 98 percent in the Phase II portion of the trial evaluating that regimen, and the VGPR or better rate for induction was higher than 70 percent (Richardson 2008).

The question we are now asking is, do all patients who achieve a CR up front need to proceed to transplant? For some of the patients we've treated, we've elected to delay the transplant, not completely omitting it. We're critically evaluating the timing of the transplant, early versus late.

DR LOVE: How do you approach harvesting stem cells for these patients?

DR LONIAL: We harvest them all after four cycles, which is important because it can be more difficult to harvest after four cycles. This is true with the other newer regimens also. I've heard some concern about thalidomide and stem cell collection or mobilization. Data suggest perhaps you don't collect quite as many cells, but clinically it is not a significant problem, so I don't believe an issue exists in harvesting stem cells in patients receiving thalidomide.

Bortezomib does not appear to be associated with any problems in stem cell mobilization. Lenalidomide, while it's not a stem cell toxin, does appear to arrest maturation of cells in the bone marrow, which is why some myelosuppression is observed. It appears that it can complicate the collection of stem cells with growth factors alone, but most patients can be rescued with either AMD3100 or cyclophosphamide.

Track 9

DR LOVE: Can you discuss the next generation of ongoing or planned studies in the up-front setting?

DR LONIAL: A Phase III SWOG trial (SWOG-S0777) is evaluating RVD versus RD as induction therapy in order to evaluate the number and depth of CRs. The transplantation question is not built into that trial, but it is important to investigate the tolerability of RVD in a Phase III trial. ECOG-E1A05 is also a Phase III study, which is evaluating RVD versus VD as up-front therapy. It was initially designed as a trial of consolidation therapy but has been changed to address these regimens as induction therapy. These are both important clinical trials.

The French are designing a trial in which most patients will receive RVD up front as their induction therapy, with a secondary assignment, based on response, to transplant or not. This is the important question: If a patient with low-risk disease achieves a CR, does he or she need to have an immediate transplant or can it wait? Do patients with high-risk disease who achieve a CR need an immediate transplant, or will they fare better with continued RVD and avoidance of exposure to melphalan, as cytotoxic agents don't appear to be beneficial to these patients?

Track 13

DR LOVE: What's your clinical algorithm for patients who relapse after transplantation?

DR LONIAL: My questions are, how long was that first remission, which induction therapy did they receive and what response was achieved?

If patients are in an unmaintained remission and they relapse, and they received RVD up front, then you can consider a doublet combination — bortezomib/pegylated liposomal doxorubicin (PLD), bortezomib/dexamethasone or lenalidomide/dexamethasone. The utility of bortezomib/PLD has clearly been established in the relapsed setting, with an improvement in overall survival compared to bortezomib alone (Orlowski 2007). Data are also emerging for PLD in combination with lenalidomide.

In the up-front setting, a couple of trials have evaluated bortezomib/PLD and dexamethasone, or bortezomib/PLD alone, which is a steroid-sparing induction regimen that can be attractive for diabetic patients. In a trial through the Multiple Myeloma Research Consortium, we're combining PLD with the RVD regimen to determine whether we can go to a four-drug CHOP-like regimen that will result in a significantly higher rate of complete remissions. ■

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**.

Harousseau JL et al. **Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): Updated data from IFM 2005/01 trial.** *Proc ASCO* 2008;**Abstract 8505**.

Orlowski RZ et al. **Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: Combination therapy improves time to progression.** *J Clin Oncol* 2007;25(25):3892-901. **Abstract**

Rajkumar SV et al. **Randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group: Analysis of response, survival, and outcome.** *Proc ASCO* 2008;**Abstract 8504**.

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. **Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma.** *N Engl J Med* 2008;359(9):906-17. **Abstract**

Zonder JA et al. **Superiority of lenalidomide (L) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma: Results of the randomized, double-blinded, placebo-controlled SWOG trial S0232.** *Proc ASH* 2007;**Abstract 77**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following tyrosine kinase inhibitors is approved by the FDA for the treatment of CML that has failed imatinib?**
   a. Nilotinib
   b. Dasatinib
   c. Bosutinib
   d. Both a and b
   e. All of the above

2. **Bendamustine was found to be superior to _____ as first-line therapy for patients with CLL.**
   a. Fludarabine
   b. Alemtuzumab
   c. Chlorambucil
   d. All of the above

3. **For patients with high-risk MDS, _____ demonstrated a significant improvement in overall survival compared to a conventional care regimen consisting of either low-dose ara-C, intensive chemotherapy or best supportive care.**
   a. Lenalidomide
   b. Decitabine
   c. Azacitidine
   d. Both a and b
   e. All of the above

4. **Among patients with lower-risk MDS and a chromosome 5q deletion who were transfusion dependent, lenalidomide has shown a transfusion-independence rate of 66 percent.**
   a. True
   b. False

5. **In ECOG-E4A03, induction therapy with lenalidomide and low-dose dexamethasone resulted in a lower overall response rate but better overall survival compared to lenalidomide with high-dose dexamethasone.**
   a. True
   b. False

6. **In the IFM 2005/01 trial, patients with previously untreated multiple myeloma were randomly assigned to _____ versus VAD as induction therapy prior to stem cell transplant.**
   a. Thalidomide/dexamethasone
   b. Bortezomib/dexamethasone
   c. Bortezomib/thalidomide/dexamethasone (VTD)

7. **In a trial evaluating thalidomide/dexamethasone with or without bortezomib (VTD or TD) prior to ASCT, Cavo and colleagues reported _____ CR/near-CR rates with VTD as compared to TD.**
   a. Comparable
   b. Superior
   c. Inferior

8. **Rituximab/bendamustine is associated with overall response rates of approximately 90 percent among patients with relapsed/refractory _____.**
   a. Indolent B-cell lymphoma
   b. Mantle-cell lymphoma
   c. Both a and b

9. **Which of the following side effects is associated with bendamustine?**
   a. Myelosuppression
   b. Nausea
   c. Infusion reaction
   d. All of the above
   e. None of the above

10. **The PRIMA trial will evaluate maintenance rituximab versus observation for patients with _____.**
    a. Follicular lymphoma
    b. Mantle-cell lymphoma
    c. CLL

11. **Clinical trials have evaluated consolidation therapy with alemtuzumab in attempts to eradicate minimal residual disease after up-front therapy for patients with CLL.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 3, 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

- **Bendamustine and rituximab in relapsed indolent B-cell and mantle-cell lymphoma** 4 3 2 1
- **Lenalidomide for the treatment of B-cell malignancies** 4 3 2 1
- **Data for maintenance rituximab in follicular lymphoma** 4 3 2 1
- **Role of azacitidine, decitabine and lenalidomide in the treatment of MDS** 4 3 2 1
- **ECOG-E4A03: Lenalidomide with high-dose versus low-dose dexamethasone in newly diagnosed multiple myeloma** 4 3 2 1
- **Role of up-front triplet therapy with RVD or VTD for multiple myeloma** 4 3 2 1

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

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- **Lenalidomide for the treatment of B-cell malignancies** 4 3 2 1
- **Data for maintenance rituximab in follicular lymphoma** 4 3 2 1
- **Role of azacitidine, decitabine and lenalidomide in the treatment of MDS** 4 3 2 1
- **ECOG-E4A03: Lenalidomide with high-dose versus low-dose dexamethasone in newly diagnosed multiple myeloma** 4 3 2 1
- **Role of up-front triplet therapy with RVD or VTD for multiple myeloma** 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:

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

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
- Recall the emerging data for novel agents and combinations in the treatment of indolent and aggressive non-Hodgkin lymphoma (NHL) ..... 4 3 2 1 N/M N/A
- Appraise the role of maintenance rituximab in the management of follicular lymphoma .. 4 3 2 1 N/M N/A
- Counsel patients with chronic myelogenous leukemia (CML) about the long-term outcomes associated with the use of tyrosine kinase inhibitors for PDGFR- and c-kit-mediated cellular events ..... 4 3 2 1 N/M N/A
- Formulate therapeutic interventions for patients with imatinib-resistant CML, and delineate strategies for monitoring disease progression ..... 4 3 2 1 N/M N/A
- Recommend primary therapy for patients with chronic lymphocytic leukemia (CLL), considering emerging clinical research on the use of novel chemotherapeutics, monoclonal antibodies and immunomodulatory agents ..... 4 3 2 1 N/M N/A
- Develop an algorithm for the diagnosis, genomic classification and risk-stratified treatment of myelodysplastic syndrome (MDS) ..... 4 3 2 1 N/M N/A
- Devise individualized treatment plans for patients with multiple myeloma (MM), considering baseline eligibility for stem cell transplant and emerging clinical trial data with active novel agents ..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about participation in ongoing clinical research studies ..... 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 editor and faculty for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Bruce D Cheson, MD	4 3 2 1	4 3 2 1
Hagop M Kantarjian, MD	4 3 2 1	4 3 2 1
Sagar Lonial, 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 editor and faculty for this activity:

.....

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Hematologic Oncology™ UPDATE

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Hematologic Oncology™
UPDATE

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